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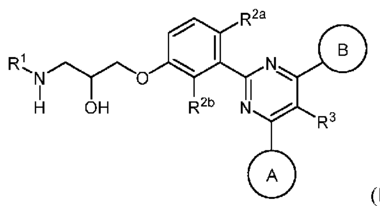

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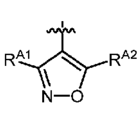

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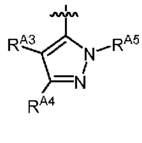

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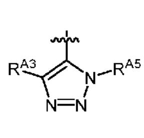

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(57) Abstract: Provided herein are compounds of Formula (I): and pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, wherein R1, R2a, R2b, R3 and Ring B are as defined herein, and Ring A is a group of Formula (A-i), (A-ii), or (A-iii): wherein R, R, R, R, and R are as defined herein. Compounds of the present invention are useful for inhibiting CARMl activity. Methods of using the compounds for treating CARMl -mediated disorders are also described.

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CARM1 INHIBITORS AND USES THEREOF

RELATED APPLICATIONS

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent application, U.S.S.N. 62/051,872, filed September 17, 2014, the entire contents of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

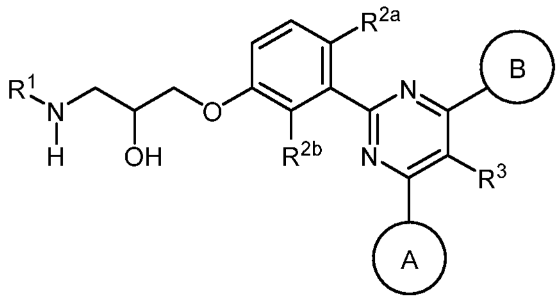
[0002] Epigenetic regulation of gene expression is an important biological determinant of protein production and cellular differentiation and plays a significant pathogenic role in a number of human diseases.

[0003] Epigenetic regulation involves heritable modification of genetic material without changing its nucleotide sequence. Typically, epigenetic regulation is mediated by selective and reversible modification (*e.g.*, methylation) of DNA and proteins (*e.g.*, histones) that control the conformational transition between transcriptionally active and inactive states of chromatin. These covalent modifications can be controlled by enzymes such as methyltransferases (*e.g.,* CARM1 (co-activator-associated arginine methyltransferase 1; PRMT4)), many of which are associated with specific genetic alterations that can cause human disease.

[0004] Disease-associated chromatin-modifying enzymes play a role in diseases such as proliferative disorders, autoimmune disorders, muscular disorders, and neurological disorders. Thus, there is a need for the development of small molecules that are capable of inhibiting the activity of CARM1.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0005] CARM1 is an attractive target for modulation given its role in the regulation of diverse biological processes. It has now been found that compounds described herein, and pharmaceutically acceptable salts and compositions thereof, are effective as inhibitors of CARM1. Such compounds have the general Formula (**I**):



(I)

and pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof; wherein R^1, R^{2a}, R^{2b}, R^3, Ring A and Ring B are as defined herein.

[0006] Pharmaceutical compositions are further provided comprising a compound described herein (*e.g.*, a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof) and, optionally, a pharmaceutically acceptable excipient.

[0007] In certain embodiments, compounds described herein inhibit the activity of CARM1. In certain embodiments, methods of inhibiting CARM1 are provided which comprise contacting CARM1 with an effective amount of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof. The CARM1 may be purified or crude, and may be present in a cell, tissue, or a subject. Thus, such methods encompass inhibition of CARM1 activity both *in vitro* and *in vivo*. In certain embodiments, the CARM1 is wild-type CARM1. In certain embodiments, the CARM1 is overexpressed. In certain embodiments, the CARM1 is a mutant. In certain embodiments, the CARM1 is in a cell. In certain embodiments, the CARM1 is in a tissue. In certain embodiments, the CARM1 is in a biological sample. In certain embodiments, the CARM1 is in an animal, *e.g.*, a human. In some embodiments, the CARM1 is expressed at normal levels in a subject, but the subject would benefit from CARM1 inhibition (*e.g.*, because the subject has one or more mutations in an CARM1 substrate that causes an increase in methylation of the substrate with normal levels of CARM1). In some embodiments, the CARM1 is in a subject known or identified as having abnormal CARM1 activity (*e.g.,* overexpression). In some embodiments, the CARM1 is in a subject known or identified as having aberrant CARM1 activity. In some embodiments, a provided compound is selective for CARM1 over other methyltransferases. In certain embodiments, a provided compound is at least about 10-fold selective, at least about 20-fold selective, at least about 30-fold selective, at least about 40-fold selective, at least about 50-fold selective, at least about 60-fold selective, at least about 70-fold selective, at least about 80-fold selective, at least about 90-fold selective, or at least about 100-fold selective relative to one or more other methyltransferases.

[0008] In certain embodiments, methods of modulating gene expression or activity in a cell are provided which comprise contacting a cell with an effective amount of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the cell is cultured *in vitro*. In certain embodiments, cell is in an animal, *e.g.*, a human.

[0009] In certain embodiments, methods of modulating transcription in a cell are provided which comprise contacting a cell with an effective amount of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the cell is cultured *in vitro*. In certain embodiments, the cell is in an animal, *e.g.*, a human.

[0010] In some embodiments, methods of treating a CARM1-mediated disorder are provided which comprise administering to a subject suffering from a CARM1-mediated disorder an effective amount of a compound described herein (*e.g.*, a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition thereof. In certain embodiments, the CARM1-mediated disorder is a proliferative disorder. In certain embodiments, compounds described herein are useful for treating cancer. In certain embodiments, compounds described herein are useful for treating breast cancer or prostate cancer. In certain embodiments, the CARM1-mediated disorder is a metabolic disorder.

[0011] Compounds described herein are also useful for the study of CARM1 in biological and pathological phenomena, the study of intracellular signal transduction pathways mediated by CARM1, and the comparative evaluation of new CARM1 inhibitors.

[0012] This application refers to various issued patent, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference.

[0013] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0014] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The present disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0015] Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, replacement of ^{19}F with ^{18}F, or the replacement of a carbon by ^{13}C or ^{14}C are within the scope of the disclosure. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[0016] When a range of values is listed, it is intended to encompass each value and sub–range within the range. For example "C_{1-3} alkyl" is intended to encompass, C_1, C_2, C_3, C_{1-3}, C_{1-2}, and C_{2-3} alkyl.

[0017] "Alkyl" refers to a radical of a straight–chain or branched saturated hydrocarbon group having from 1 to 3 carbon atoms ("C_{1-3} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). Examples of C_{1-3} alkyl groups include methyl (C_1), ethyl (C_2), n–propyl (C_3),and isopropyl (C_3). Alkyl groups may be substituted or unsubstituted as described herein.

[0018] "Haloalkyl" refers to an alkyl group, as defined herein, substituted with one or more halogen atoms, *e.g.,* 1, 2, 3, 4, 5, 6, or 7 halogen atoms independently selected from the group consisting of fluoro, bromo, chloro, and iodo. Haloalkyl encompasses perhaloalkyl as defined herein. "Perhaloalkyl" refers to a substituted alkyl group as defined herein wherein all of the hydrogen atoms are independently replaced by a halogen. In some embodiments, at least one of the hydrogen atoms is replaced with fluoro. In some embodiments, at least one of the hydrogen atoms is replaced with chloro. Examples of perhaloalkyl groups include –CF_3, –CF_2CF_3, –$CF_2CF_2CF_3$, –CCl_3, –$CFCl_2$, –CF_2Cl, and the like. Examples of haloalkyl groups include all of the aforementioned perhaloalkyl groups, as well as groups such as –CH_2F, -CHF_2, -CH_2Cl, $CHCl_2$, -CH_2CF_3, -CH_2CHF_2, -CH_2CH_2F, -CH_2CCl_3, -CH_2CHCl_2, -CH_2CH_2Cl, -$CH_2CH_2CF_3$, -$CH_2CH_2CHF_2$, - $CH_2CH_2CH_2F$, - $CH_2CH_2CCl_3$, - $CH_2CH_2CHCl_2$, - $CH_2CH_2CH_2Cl$, -$CH(CH_3)CHF_2$, -$CH(CH_3)CF_3$, and the like.

[0019] "Alkenyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 3 carbon atoms and one carbon-carbon double bond ("$C_{2–3}$ alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). In some embodiments, an alkenyl group has 3 carbon atoms ("C_3 alkenyl"). Examples of $C_{2–3}$ alkenyl groups include ethenyl (C_2), 1–propenyl (C_3), and 2–propenyl (C_3). Alkenyl groups may be substituted or unsubstituted as described herein.

[0020] "Alkynyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 3 carbon atoms and one carbon-carbon triple bond ("$C_{2–3}$ alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). In some embodiments, an alkynyl group has 3 carbon atoms ("C_3 alkynyl"). Examples of $C_{2–3}$ alkynyl groups include, without limitation, ethynyl (C_2), 1–propynyl (C_3), and 2–propynyl (C_3). Alkynyl groups may be substituted or unsubstituted as described herein.

[0021] "Carbocyclyl" or "carbocyclic" refers to a radical of a non–aromatic monocyclic hydrocarbon group having from 3 to 6 ring carbon atoms ("$C_{3–6}$ carbocyclyl") and zero heteroatoms in the non–aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 4 ring carbon atoms ("$C_{3–4}$ carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 5 ring carbon atoms ("$C_{3–5}$ carbocyclyl"). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms ("$C_{4–6}$ carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms ("$C_{5–6}$ carbocyclyl"). Exemplary $C_{3–6}$ carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like.

[0022] "Heterocyclyl" or "heterocyclic" refers to a radical of a 4–6 membered monocyclic non–aromatic ring system having ring carbon atoms and 1, 2, or 3 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("4–6 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. In some embodiments, a heterocyclyl group is a 4–membered monocyclic non–aromatic ring system having ring carbon atoms and 1 ring heteroatom, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("4-membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5- membered monocyclic non–aromatic ring system having ring carbon atoms and 1, 2, or 3 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5– membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 6- membered monocyclic non–aromatic ring system having ring carbon atoms and 1, 2, or 3 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("6- membered heterocyclyl"). Exemplary 4–membered heterocyclyl groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl, and thietanyl. Exemplary 5–membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, pyrrolyl–2,5–dione, and pyrrolidin-2-one. Exemplary 5–membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazinanyl.

[0023] Affixing the suffix "–ene" to a group indicates the group is a divalent moiety, *e.g.*, alkylene is the divalent moiety of alkyl, alkenylene is the divalent moiety of alkenyl, alkynylene is the divalent moiety of alkynyl, as defined herein.

[0024] In general, the term "substituted" means that at least one hydrogen present on a group (*e.g.,* a carbon or nitrogen atom) is replaced with a substituent as defined herein and results in a stable compound, *e.g.,* a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group may have a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent may be the same or different at each position.

[0025] "Halo" or "halogen" refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[0026] "Pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the compounds describe herein include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*–toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, quaternary salts.

[0027] A "subject" to which administration is contemplated includes, but is not limited to, humans (*e.g.,* a male or female of any age group, *e.g.,* a pediatric subject (*e.g,* infant, child, adolescent) or adult subject (*e.g.,* young adult, middle–aged adult or senior adult)) and/or other non–human animals, for example, non-human mammals (*e.g.*, primates (*e.g.,* cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs), birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys), rodents (*e.g.*, rats and/or mice), reptiles, amphibians, and fish. In certain embodiments, the non–human animal is a mammal. The non–human animal may be a male or female at any stage of development. A non–human animal may be a transgenic animal.

[0028] "Condition," "disease," and "disorder" are used interchangeably herein.

[0029] "Treat," "treating" and "treatment" encompasses an action that occurs while a subject is suffering from a condition which reduces the severity of the condition or retards or slows the progression of the condition ("therapeutic treatment"). "Treat," "treating" and "treatment" also encompasses an action that occurs before a subject begins to suffer from the condition and which inhibits or reduces the severity of the condition ("prophylactic treatment").

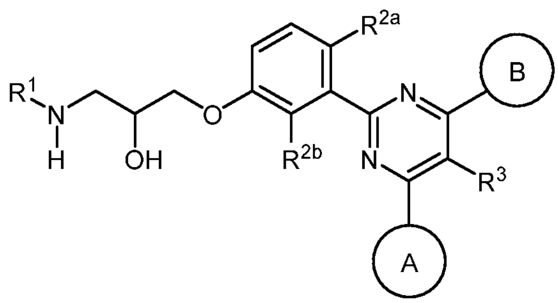
[0030] An "effective amount" of a compound refers to an amount sufficient to elicit the desired biological response, *e.g.*, treat the condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment.

[0031] A "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of the condition, or enhances the therapeutic efficacy of another therapeutic agent.

[0032] A "prophylactically effective amount" of a compound is an amount sufficient to prevent a condition, or one or more symptoms associated with the condition or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[0033] As used herein, the term "methyltransferase" represents transferase class enzymes that are able to transfer a methyl group from a donor molecule to an acceptor molecule, *e.g.*, an amino acid residue of a protein or a nucleic base of a DNA molecule. Methytransferases typically use a reactive methyl group bound to sulfur in S-adenosyl methionine (SAM) as the methyl donor. In some embodiments, a methyltransferase described herein is a protein methyltransferase. In some embodiments, a methyltransferase described herein is a histone methyltransferase. Histone methyltransferases (HMT) are histone-modifying enzymes, (including histone-lysine N-methyltransferase and histone-arginine N-methyltransferase), that catalyze the transfer of one or more methyl groups to lysine and arginine residues of histone proteins. In certain embodiments, a methyltransferase described herein is a histone-arginine N-methyltransferase.

[0034] As generally described above, provided herein are compounds useful as CARM1 inhibitors. In some embodiments, the present disclosure provides a compound of Formula (**I**):



(I)

or pharmaceutically acceptable salt thereof;

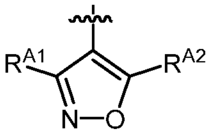
wherein:

R^1 is hydrogen, -CHO, or unsubstituted C_{1-3}alkyl;

each instance of R^{2a} and R^{2b} is independently hydrogen, halogen, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl;

R^3 is unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, or halogen;

Ring A is of formula (A-i), (A-ii), or (A-iii):



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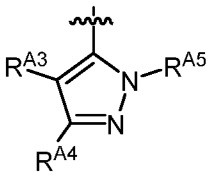

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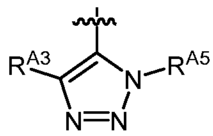


(A-iii)

wherein:

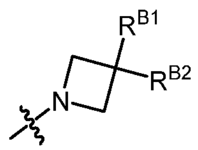
each instance of R^{A1} and R^{A2} is independently unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, or unsubstituted cyclopropyl;

R^{A3} is unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, halogen, or –CN;

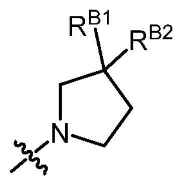
R^{A4} is hydrogen, unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, halogen, or –CN; and

R^{A5} is unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl;

Ring B is any one of formula (i) to (xxviii):



(i)



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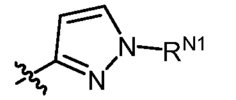
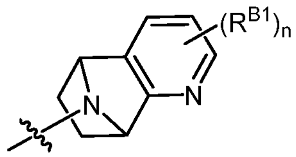


(iii)



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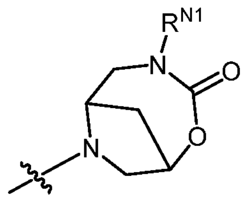

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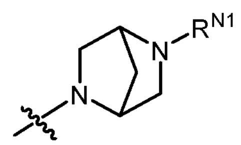

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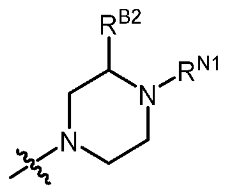

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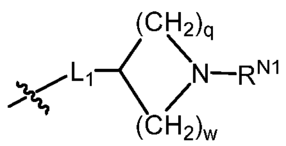

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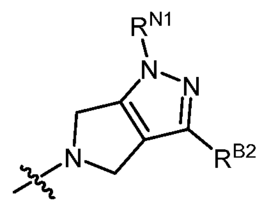

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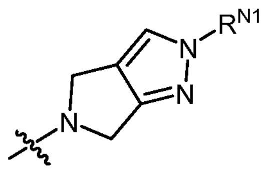

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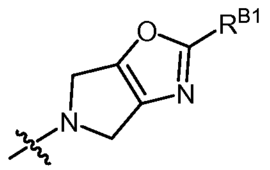

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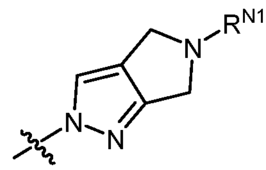

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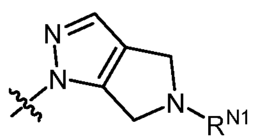

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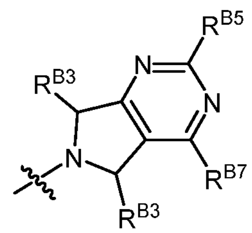

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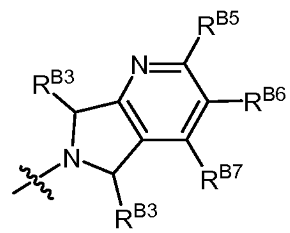

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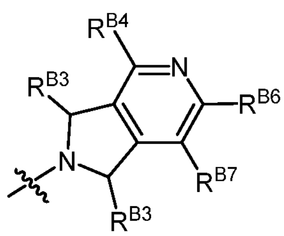

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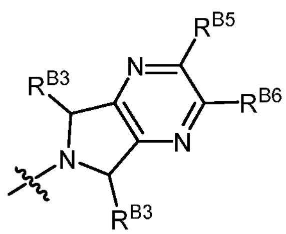

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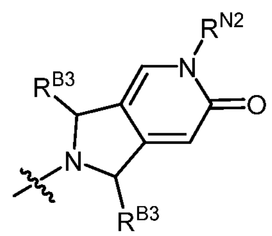

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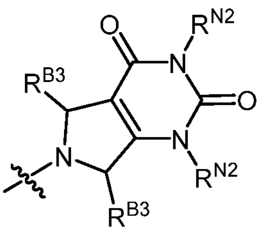

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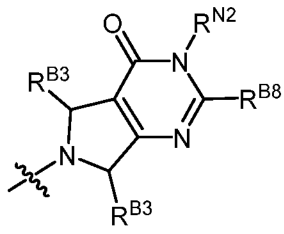

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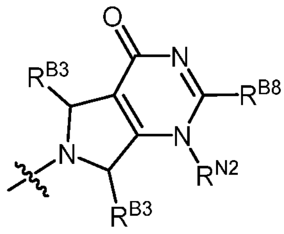

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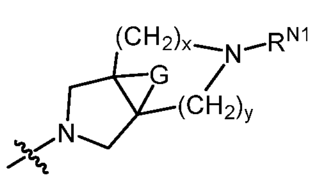

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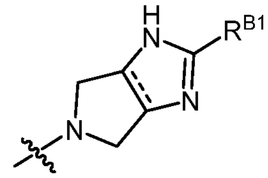

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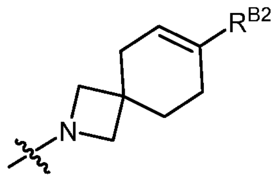

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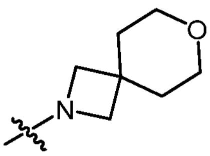

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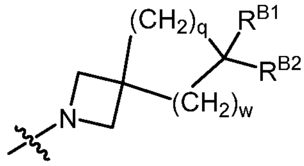

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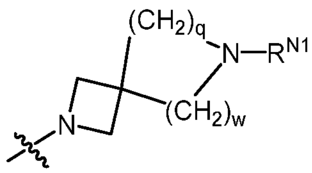

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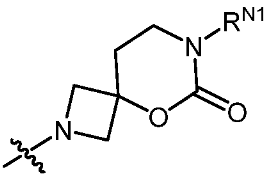

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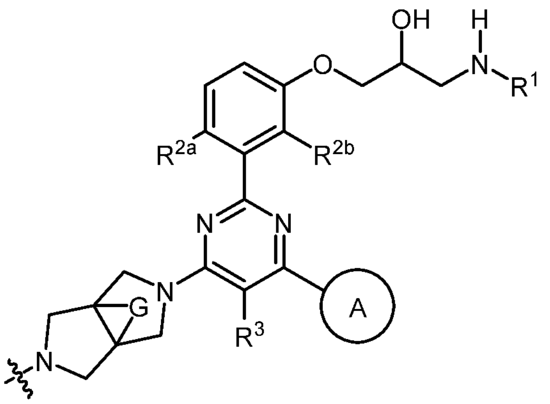


(xxix)

wherein:

q is 1, 2, or 3 and w is 1; or q is 2 and w is 0 or 2;

x is 1 and y is 1 or 2;

n is 0, 1, or 2;

L_1 is –NH–, substituted or unsubstituted C_2alkylene, substituted or unsubstituted C_2alkenylene, or substituted or unsubstituted C_2alkynylene;

R^{N1} is substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted 4- to 6-membered heterocyclyl, $-C(=O)R^{N1A}$, $-C(=O)N(R^{N1A})(R^{N1B})$, $-C(=O)OR^{N1A}$, or $-S(O)_2R^{N1A}$; wherein:

R^{N1A} is substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_{3-6} carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl;

R^{N1B} is hydrogen, substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_{3-6} carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl; or

R^{N1A} and R^{N1B} are joined to form a substituted or unsubstituted 4- to 6-membered heterocyclyl; or

each instance of R^{N2} and R^{B8} is independently substituted or unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl, or R^{N2} and R^{B8} are joined to form a substituted or unsubstituted 5- to 6-membered ring;

R^{B1} is substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, halogen, -CN, $-OR^{B1B}$, $-SR^{B1B}$, $-N(R^{B1A})(R^{B1B})$, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted 4- to 6-membered heterocyclyl, $-C(=O)R^{B1A}$, $-C(=O)N(R^{B1A})(R^{B1B})$, $-C(=O)OR^{B1A}$, $-S(O)_2R^{B1A}$, $-OC(=O)R^{B1A}$, $-OC(=O)N(R^{B1A})(R^{B1B})$, $-OC(=O)OR^{B1A}$, $-NR^{BIB}C(=O)R^{B1A}$, $-NR^{BIB}C(=O)N(R^{B1A})(R^{B1B})$, or $-NR^{BIB}C(=O)OR^{B1A}$;

wherein:

R^{B1A} is substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_{3-6} carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl; and

R^{B1B} is hydrogen, substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_{3-6} carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl; or

R^{B1A} and R^{B1B} are joined to form a substituted or unsubstituted 4- to 6-membered heterocyclyl;

R^{B2} is hydrogen, halogen, $-OR^{B2A}$, substituted or unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl, wherein R^{B2A} is substituted or unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl; or

R^{B1} and R^{B2} are joined to form a substituted or unsubstituted 4- to 6-membered heterocyclyl;

each instance of R^{B3} is independently hydrogen, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl, provided at least one instance of R^{B3} is hydrogen;

each instance of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is independently hydrogen, substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, halogen, -CN, -OR^{B4B}, -SR^{B4B}, -$N(R^{B4A})(R^{B4B})$, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted 4- to 6-membered heterocyclyl, -$C(=O)R^{B4A}$, -$C(=O)N(R^{B4A})(R^{B4B})$, -$C(=O)OR^{B4A}$, -$S(O)_2R^{B4A}$, -$OC(=O)R^{B4A}$, -$OC(=O)N(R^{B4A})(R^{B4B})$, -$OC(=O)OR^{B4A}$, -$NR^{B4B}C(=O)R^{B4A}$, -$NR^{B4B}C(=O)N(R^{B4A})(R^{B4B})$, or -$NR^{B4B}C(=O)OR^{B4A}$;

wherein:

R^{B4A} is substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_{3-6} carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl; and

R^{B4B} is hydrogen, substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_{3-6} carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl; or

R^{B4A} and R^{B4B} are joined to form a substituted or unsubstituted 4- to 6-membered heterocyclyl;

and

wherein ⎓ represents a single or double bond; and

further wherein  represents a single or double bond or G is $-CH_2-$;

wherein each instance of substituted independently refers to substitution with 1, 2, or 3 R^{C1} groups, as valency permits,

and wherein:

each instance of R^{C1} is independently unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, halogen, -CN, -OR^{C1B}, -SR^{C1B}, -$N(R^{C1A})(R^{C1B})$, -$C(=O)R^{C1A}$, -$C(=O)N(R^{C1A})(R^{C1B})$, -$C(=O)OR^{C1A}$, -$S(O)_2R^{C1A}$, -$OC(=O)R^{C1A}$, -$OC(=O)N(R^{C1A})(R^{C1B})$, -$OC(=O)OR^{C1A}$, -$NR^{CIB}C(=O)R^{C1A}$, -$NR^{CIB}C(=O)N(R^{C1A})(R^{C1B})$, or -$NR^{CIB}C(=O)OR^{C1A}$;

wherein:

R^{C1A} is unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups; or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups; and

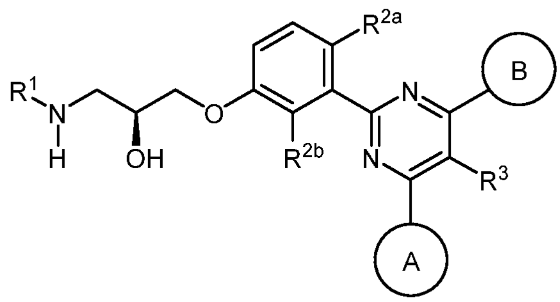
R^{C1B} is hydrogen, unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups; or

R^{C1A} and R^{C1B} are joined to form an 4- to 6- membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups; and

wherein:

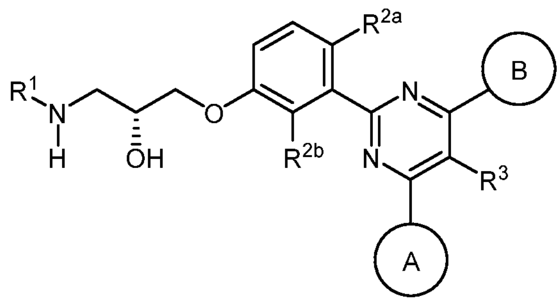
each instance of R^{D1} is independently halogen, -CN, -OR^{D1A}, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl, wherein R^{D1A} is hydrogen, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl.

[0035] In certain embodiments, the compound of Formula (**I**) is a stereoisomer of Formula:



or a pharmaceutically acceptable salt thereof.

[0036] In certain embodiments, the compound of Formula (**I**) is a stereoisomer of Formula:



or a pharmaceutically acceptable salt thereof.

(I) Groups R^1, R^2, and R^3

[0037] As generally defined herein, R^1 is hydrogen, -CHO, or unsubstituted C_{1-3}alkyl.

[0038] In certain embodiments, R^1 is hydrogen. In certain embodiments, R^1 is –CHO. In certain embodiments, R^1 is unsubstituted C_{1-3}alkyl, *i.e.*, unsubstituted C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$).

[0039] Furthermore, as generally defined herein, each instance of R^{2a} and R^{2b} is independently hydrogen, halogen, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl.

[0040] In certain embodiments, at least one instance of R^{2a} and R^{2b} is hydrogen. In certain embodiments, each instance of R^{2a} and R^{2b} is hydrogen.

[0041] In certain embodiments, at least one instance of R^{2a} and R^{2b} is halogen, *i.e.,* at least one instance of R^{2a} and R^{2b} is –F, -Cl, -Br, or -I. In certain embodiments, R^{2a} is halogen and R^{2b} is halogen, *i.e.,* each instance of R^{2a} and R^{2b} is independently –F, -Cl, -Br, or -I. In certain embodiments, at least one instance of R^{2a} and R^{2b} is -F or –Cl. In certain embodiments, R^{2a} is -F or –Cl. In certain embodiments, R^{2b} is -F or –Cl. In certain embodiments, R^{2a} is –Cl and R^{2b} is -Cl. In certain embodiments, R^{2a} is –F and R^{2b} is -F.

[0042] In certain embodiments, at least one instance of R^{2a} and R^{2b} is unsubstituted C_{1-3}alkyl, *i.e.*, unsubstituted C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, at least one instance of R^{2a} and R^{2b} is $-CH_3$.

[0043] In certain embodiments, at least one instance of R^{2a} and R^{2b} is C_{1-3}haloalkyl, *e.g.,* C_1 haloalkyl ($-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, at least one instance of R^{2a} and R^{2b} is $-CF_3$. In certain embodiments, R^{2a} is $-CF_3$. In certain embodiments, R^{2b} is $-CF_3$.

[0044] In certain embodiments, R^{2b} is hydrogen and R^{2a} is halogen, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl. In certain embodiments, R^{2b} is hydrogen and R^{2a} is halogen, *i.e.,* R^{2b} is hydrogen and R^{2a} is –F, -Cl, -Br, or -I. In certain embodiments, R^{2b} is hydrogen and R^{2a} is unsubstituted C_{1-3}alkyl, *i.e.*, unsubstituted C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, R^{2b} is hydrogen and R^{2a} is C_{1-3}haloalkyl, *e.g.,* C_1 haloalkyl ($-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, R^{2b} is hydrogen and R^{2a} is –Cl. In certain embodiments, R^{2b} is hydrogen and R^{2a} is -F. In certain embodiments, R^{2b} is hydrogen and R^{2a} is $-CF_3$.

[0045] In certain embodiments, R^{2a} is hydrogen and R^{2b} is halogen, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl. In certain embodiments, R^{2a} is hydrogen and R^{2b} is halogen, *i.e.,* R^{2a} is hydrogen and R^{2b} is –F, -Cl, -Br, or -I. In certain embodiments, R^{2a} is hydrogen and R^{2b} is unsubstituted C_{1-3}alkyl, *i.e.*, unsubstituted C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, R^{2a} is hydrogen and R^{2b} is C_{1-3}haloalkyl, *e.g.,* C_1 haloalkyl ($-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, R^{2a} is hydrogen and R^{2b} is $-CF_3$.

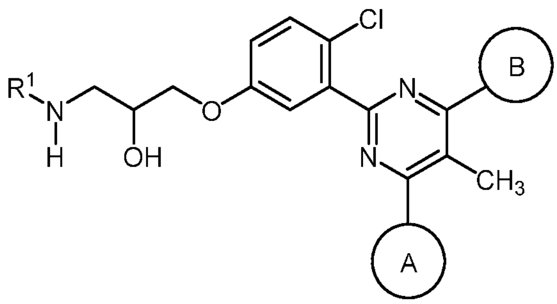
[0046] In certain embodiments, R^{2a} is hydrogen and R^{2b} is $-Cl$. In certain embodiments, R^{2a} is hydrogen and R^{2b} is $-F$. In certain embodiments, R^{2a} is hydrogen and $R^{2b}$is $-CF_3$.

[0047] Furthermore, as generally defined herein, R^3 is unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, or halogen. In certain embodiments, R^3 is unsubstituted C_{1-3}alkyl, *i.e.*, unsubstituted C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, R^3 is C_{1-3}haloalkyl, *e.g.,* C_1 haloalkyl ($-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, R^3 is $-CH_3$. In certain embodiments, R^3 is halogen, *i.e.,* $-F$, $-Cl$, $-Br$, or $-I$. In certain embodiments, $R^3$is $-F$ or $-Cl$.

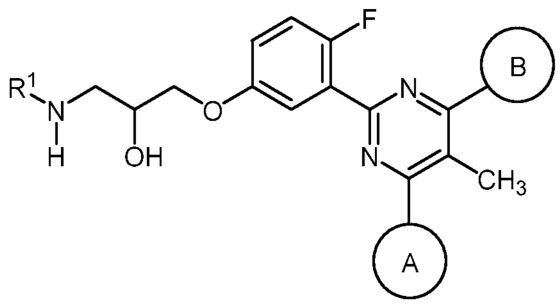
[0048] Various combinations of R^{2a}, R^{2b}, and R^3 are contemplated herein.

[0049] For example, in certain embodiments, each of R^{2a} and R^3 is the same group. In certain embodiments, R^{2a} and R^3 are different groups. In certain embodiments, each of R^{2a} and R^3 is halogen, *e.g.,* R^{2a} is $-Cl$ and R^3 is $-Cl$, or R^{2a} is $-F$ and R^3 is $-F$, or R^{2a} is $-Cl$ and R^3 is $-F$, or R^{2a} is $-F$ and R^3 is $-Cl$. In certain embodiments, R^{2a} is halogen and R^3 is unsubstituted C_{1-3}alkyl, *e.g.,* wherein R^{2a} is $-Cl$ and R^3 is $-CH_3$, or R^{2a} is $-F$ and R^3 is $-CH_3$. In certain embodiments, R^{2a} is C_{1-3}haloalkyl and R^3 is unsubstituted C_{1-3}alkyl, *e.g.,* R^{2a} is $-CF_3$ and R^3 is $-CH_3$. In certain embodiments, R^{2a} is hydrogen and R^3 is unsubstituted C_{1-3}alkyl, *e.g.,* wherein R^{2a} is hydrogen and R^3 is $-CH_3$.

[0050] In certain embodiments, R^{2a} is halogen (*e.g.,* $-F$ or $-Cl$), R^{2b} is hydrogen, and R^3 is unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$). In certain embodiments, R^{2a} is $-Cl$, R^{2b} is hydrogen, and R^3 is $-CH_3$, or R^{2a} is $-F$, R^{2b} is hydrogen, and R^3 is $-CH_3$, to provide a compound of Formulae:

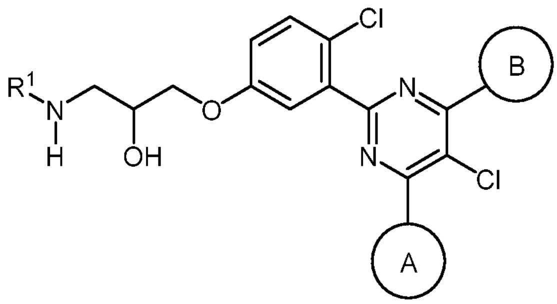


or

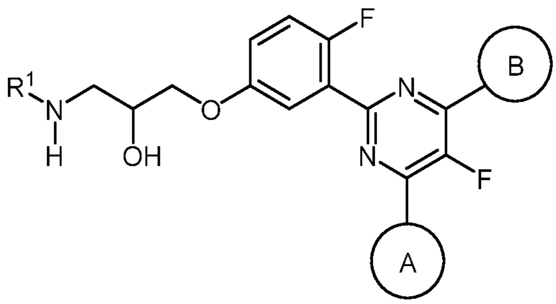


or a pharmaceutically acceptable salt thereof.

[0051] In certain embodiments, R^{2a} is halogen (*e.g.,* -F or –Cl), R^{2b} is hydrogen, and R^3 is halogen (*e.g.,* -F or –Cl). In certain embodiments, R^{2a} is –Cl, R^{2b} is hydrogen, and R^3 is –Cl, or R^{2a} is –F, R^{2b} is hydrogen, and R^3 is –F, to provide a compound of Formulae:

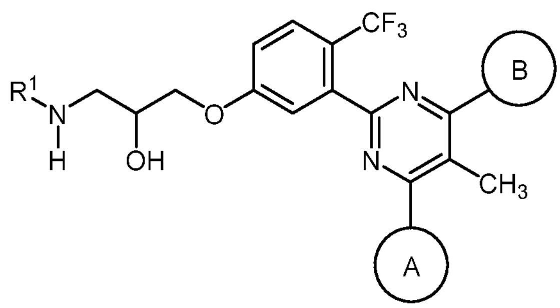


or



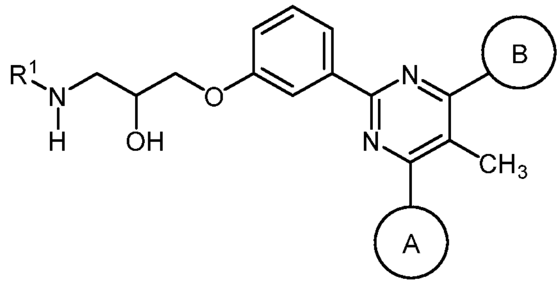
or a pharmaceutically acceptable salt thereof.

[0052] In certain embodiments, R^{2a} is $C_{1\text{-}3}$haloalkyl (*e.g.,* $-CF_3$), R^{2b} is hydrogen, and R^3 is unsubstituted $C_{1\text{-}3}$alkyl (*e.g.,* $-CH_3$). In certain embodiments, R^{2a} is $-CF_3$, R^{2b} is hydrogen, and R^3 is $-CH_3$ to provide a compound of Formula:



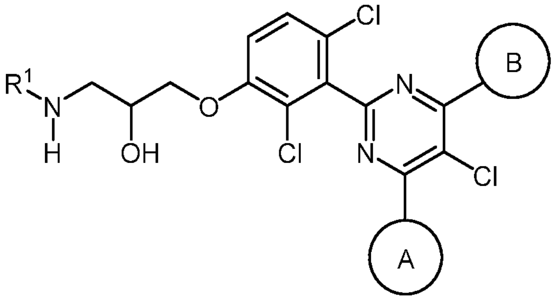
or a pharmaceutically acceptable salt thereof.

[0053] In certain embodiments, each of R^{2a} and R^{2b} is hydrogen, and R^3 is unsubstituted $C_{1\text{-}3}$alkyl (*e.g.,* $-CH_3$). In certain embodiments, R^{2a} is hydrogen, R^{2b} is hydrogen, and R^3 is -CH_3 to provide a compound of Formula:

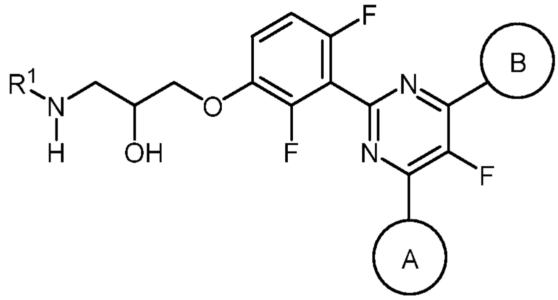


or a pharmaceutically acceptable salt thereof.

[0054] In certain embodiments, each of R^{2a}, R^{2b}, and R^3 is halogen (*e.g.,* -F or –Cl). For example, in certain embodiments, each of R^{2a}, R^{2b}, and R^3 is –Cl, or each of R^{2a}, R^{2b}, and R^3 is –F, to provide a compound ofFormulae:

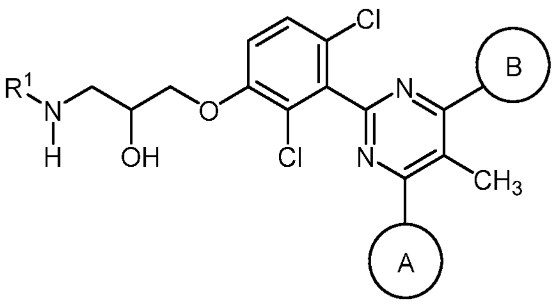


or

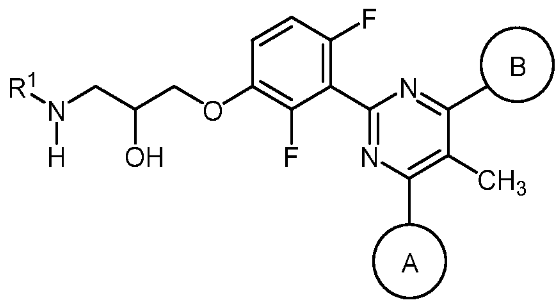


or a pharmaceutically acceptable salt thereof.

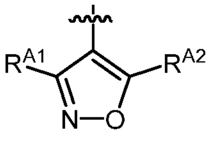
[0055] In certain embodiments, each of R^{2a} and R^{2b} is independently halogen (*e.g.,* -F or –Cl), R^3 is unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$). In certain embodiments, R^{2a} is -Cl, R^{2b} is -Cl, and R^3 is $-CH_3$, or R^{2a} is -F, R^{2b} is -F, and R^3 is $-CH_3$, provide a compound of Formulae:



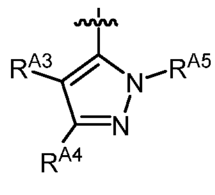
or



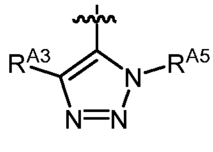
[0056] As generally defined herein, Ring A is of formula (A-i), (A-ii), or (A-iii):



(A-i)



(A-ii)



(A-iii)

wherein:

each instance of R^{A1} and R^{A2} is independently unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl;

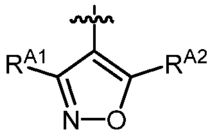
R^{A3} is unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, halogen, or –CN;

R^{A4} is hydrogen, unsubstituted $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$haloalkyl, halogen, or –CN; and

R^{A5} is unsubstituted $C_{1\text{-}3}$alkyl or $C_{1\text{-}3}$haloalkyl.

(II) Ring A

[0057] In certain embodiments, Ring A is of Formula (A-i):



(A-i).

wherein each instance of R^{A1} and R^{A2} is independently unsubstituted $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$haloalkyl, or unsubstituted cyclopropyl.

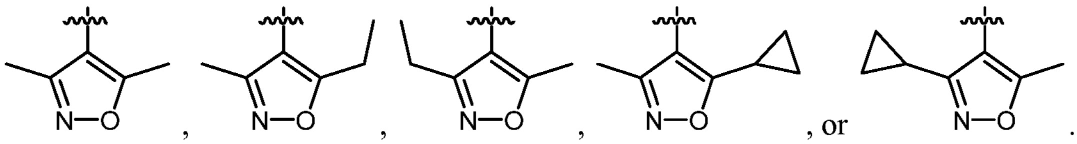
[0058] In certain embodiments, at least one instance of R^{A1} and R^{A2} is unsubstituted $C_{1\text{-}3}$alkyl, *i.e.*, unsubstituted C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, at least one of R^{A1} and R^{A2} is $-CH_3$. In certain embodiments, at least one of R^{A1} and R^{A2} is $-CH_2CH_3$.

[0059] In certain embodiments, at least one instance of R^{A1} and R^{A2} is $C_{1\text{-}3}$haloalkyl, *e.g.,* C_1 haloalkyl ($-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, at least one instance of R^{A1} and R^{A2} $-CF_3$.

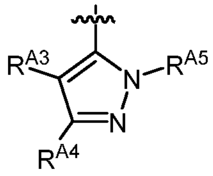
[0060] In certain embodiments, at least one of R^{A1} and R^{A2} is unsubstituted cyclopropyl.

[0061] In certain embodiments, R^{A1} and R^{A2} are the same group, *e.g.,* in certain embodiments, R^{A1} and R^{A2} are each $-CH_3$. However, in certain embodiments, R^{A1} and R^{A2} are different groups, *e.g.,* in certain embodiments, R^{A1} is $-CH_3$ and R^{A2} is $-CH_2CH_3$, or in certain embodiments, R^{A1} is $-CH_2CH_3$ and R^{A2} is $-CH_3$, or in certain embodiments, R^{A1} is unsubstituted cyclopropyl and R^{A2} is $-CH_3$, or in certain embodiments, R^{A2} is unsubstituted cyclopropyl and R^{A1} is $-CH_3$.

[0062] In certain embodiments, Ring A is selected from the group consisting of:



[0063] In certain embodiments, Ring A is of Formula (A-ii):


(A-ii).

[0064] In certain embodiments, R^{A3} is unsubstituted $C_{1\text{-}3}$alkyl, *i.e.*, unsubstituted C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, R^{A3} is $C_{1\text{-}3}$haloalkyl, *e.g.,* C_1 haloalkyl C_1 haloalkyl ($–CF_3$, $–CCl_3$, $–CFCl_2$, $–CF_2Cl$, $–CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($–CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($–CF_2CF_2CF_3$, $–CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-$ $CH_2CH_2CH_2F$, $-$ $CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-$ $CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, R^{A3} is halogen, *i.e.*, -F, -Cl, -Br, or -I. In certain embodiments, R^{A3} is –CN. In certain embodiments, R^{A3} is –CN provided R^{A4} is is not also –CN.

[0065] In certain embodiments, R^{A4} is hydrogen. In certain embodiments, R^{A4} is unsubstituted $C_{1\text{-}3}$alkyl, *i.e.*, unsubstituted C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, R^{A4} is $C_{1\text{-}3}$haloalkyl, *e.g.,* C_1 haloalkyl ($–CF_3$, $–CCl_3$, $–CFCl_2$, $–CF_2Cl$, $–CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($–CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($–CF_2CF_2CF_3$, $–CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-$ $CH_2CH_2CCl_3$, $-$ $CH_2CH_2CHCl_2$, $-$ $CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, R^{A4} is halogen, *i.e.*, -F, -Cl, -Br, or -I. In certain embodiments, R^{A4} is –CN. In certain embodiments, R^{A4} is –CN provided R^{A3} is is not also –CN.

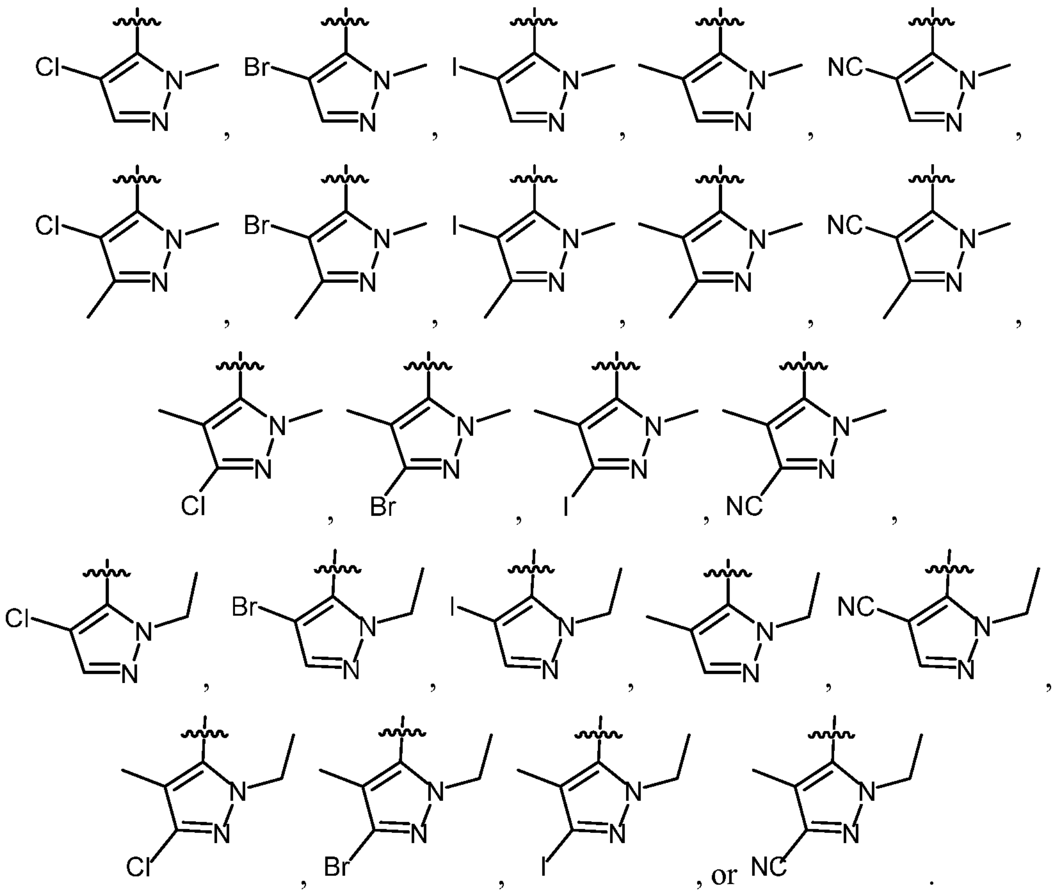
[0066] In certain embodiments, R^{A5} is unsubstituted $C_{1\text{-}3}$alkyl, *i.e.*, unsubstituted C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, R^{A5} is $C_{1\text{-}3}$haloalkyl, *e.g.,* C_1 haloalkyl ($–CF_3$, $–CCl_3$, $–CFCl_2$, $–CF_2Cl$, $–CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($–CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($–CF_2CF_2CF_3$, $–CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-$ $CH_2CH_2CH_2F$, $-$ $CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-$ $CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$).

[0067] Various combinations of R^{A3}, R^{A4}, and R^{A5} are contemplated herein.

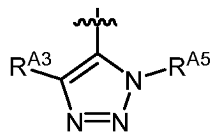
[0068] For example, in certain embodiments, R^{A3} is halogen, -CN, unsubstituted $C_{1\text{-}3}$alkyl, or $C_{1\text{-}3}$haloalkyl, and R^{A4} is hydrogen. In certain embodiments, R^{A3} is halogen (*i.e.,* -F, -Cl, -Br, or –I), and R^{A4} is hydrogen. In certain embodiments, R^{A3} is –CN and R^{A4} is hydrogen. In certain embodiments, R^{A3} is unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$) and R^{A4} is hydrogen. Furthermore, in certain embodiments, in any of the above recited instances, R^{A5} is unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$).

[0069] In certain embodiments, R^{A3} is unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl and R^{A4} is halogen or –CN. In certain embodiments, R^{A4} is unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl and R^{A3} is halogen or –CN. In certain embodiments, R^{A3} is unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$) and R^{A4} is halogen (i.e., -F, -Cl, -Br, or –I). In certain embodiments, R^{A3} is unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$) and R^{A4} is -CN. Furthermore, in certain embodiments, in any of the above recited instances, R^{A5} is unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$).

[0070] In certain embodiments, Ring A is selected from the group consisting of:



[0071] In certain embodiments, Ring A is of Formula (A-ii):



(A-iii).

[0072] In certain embodiments, R^{A3} is unsubstituted C_{1-3}alkyl, *i.e.*, unsubstituted C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or -

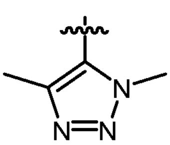
$CH(CH_3)_2$). In certain embodiments, R^{A3} is $C_{1\text{-}3}$haloalkyl, *e.g.,* C_1 haloalkyl ($-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, R^{A3} is halogen, *i.e.*, -F, -Cl, -Br, or -I.

[0073] In certain embodiments, R^{A5} is unsubstituted $C_{1\text{-}3}$alkyl, *i.e.*, unsubstituted C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, R^{A5} is $C_{1\text{-}3}$haloalkyl, *e.g.,* C_1 haloalkyl ($-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$).

[0074] Various combinations of R^{A3} and R^{A5} are contemplated herein.

[0075] For example, in certain embodiments, R^{A3} is halogen, -CN, unsubstituted $C_{1\text{-}3}$alkyl, or $C_{1\text{-}3}$haloalkyl, and R^{A5} is unsubstituted $C_{1\text{-}3}$alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$). In certain embodiments, R^{A3} is halogen (*i.e.,* -F, -Cl, -Br, or –I), and R^{A5} is unsubstituted $C_{1\text{-}3}$alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$). In certain embodiments, R^{A3} is –CN and R^{A5} is unsubstituted $C_{1\text{-}3}$alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$). In certain embodiments, R^{A3} is unsubstituted $C_{1\text{-}3}$alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$) and R^{A5} is unsubstituted $C_{1\text{-}3}$alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$). In certain embodiments, R^{A3} and R^{A5} are the same group. In certain embodiments, R^{A3} and R^{A5} are different groups.

[0076] In certain embodiments, Ring A is: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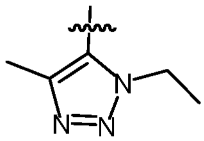
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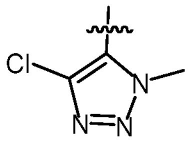
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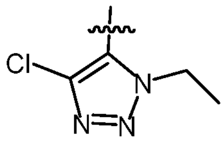
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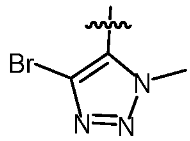
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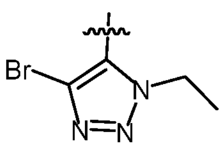
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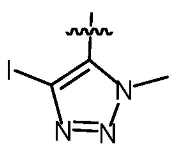
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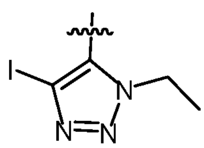
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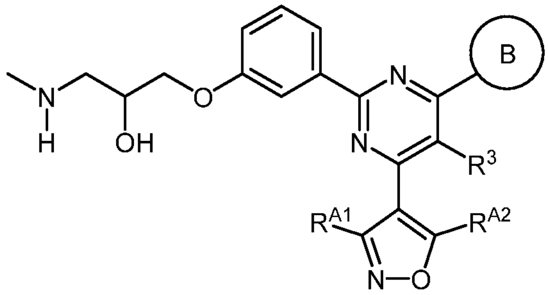
[0077] Various combinations of Ring A, R^1, R^{2a}, and R^{2b}, are contemplated herein.

[0078] For example, in certain embodiments, wherein Ring A is of Formula (A-i), (A-ii), or (A-iii), R^1 is $-CH_3$, and each R^{2a} and R^{2b} is hydrogen, provided is a compound of Formula: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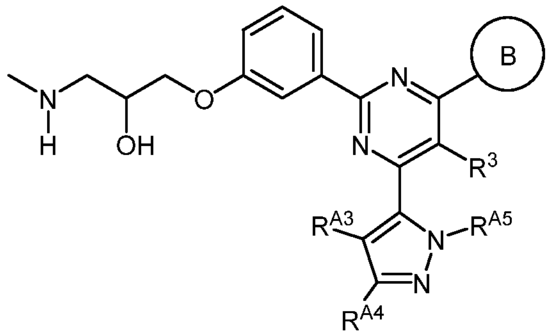
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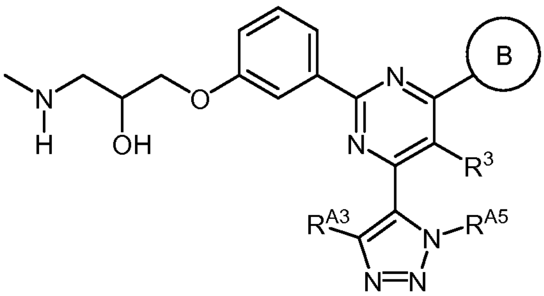
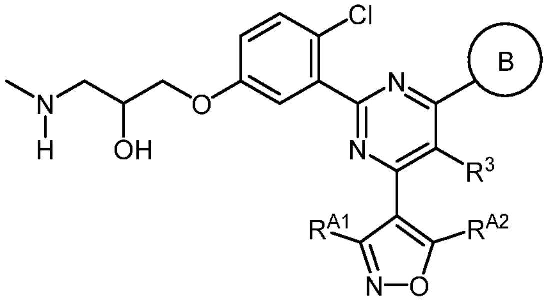


or a pharmaceutically acceptable salt thereof.

[0079] In certain embodiments, wherein Ring A is of Formula (A-i), (A-ii), or (A-iii), R^1 is $-CH_3$, R^{2a} is $-Cl$, and R^{2b} is hydrogen, provided is a compound of Formula: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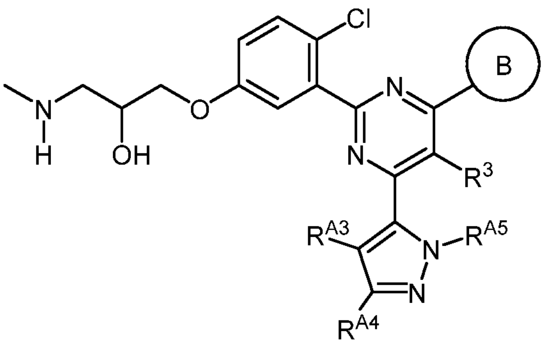
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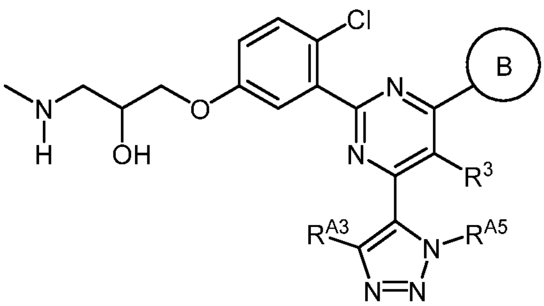
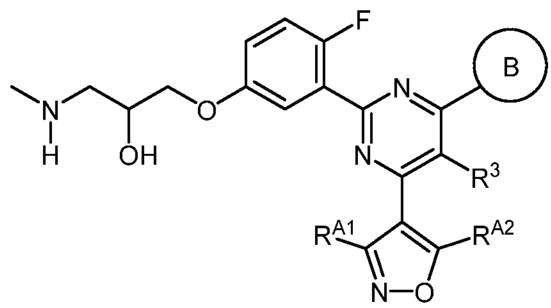
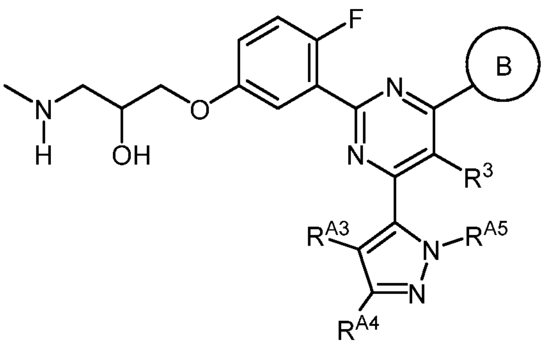


or a pharmaceutically acceptable salt thereof.

[0080] In certain embodiments, wherein Ring A is of Formula (A-i), (A-ii), or (A-iii), R^1 is $-CH_3$, R^{2a} is $-F$, and R^{2b} is hydrogen, provided is a compound of Formulae:

,
,

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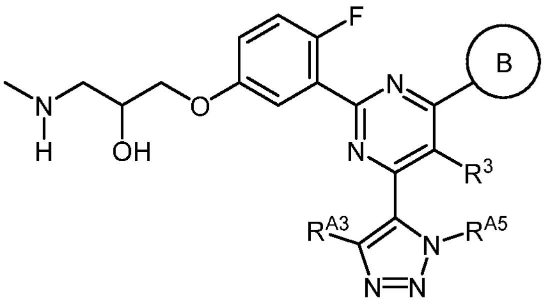
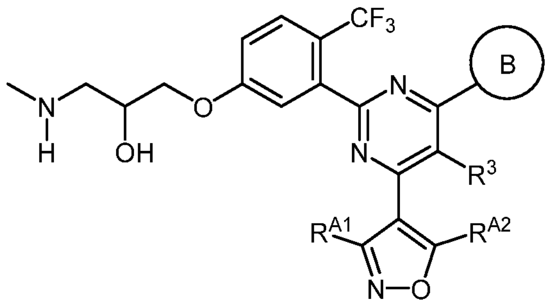
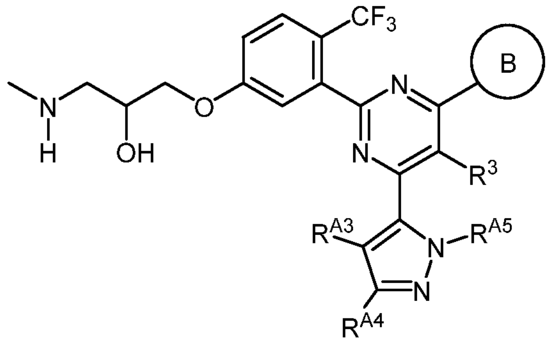


or a pharmaceutically acceptable salt thereof.

[0081] In certain embodiments, wherein Ring A is of Formula (A-i), (A-ii), or (A-iii), R^1 is $-CH_3$, R^{2a} is $-CF_3$, and R^{2b} is hydrogen, provided is a compound of Formulae:

,
,

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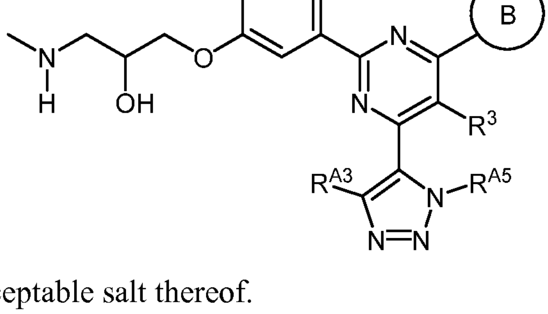
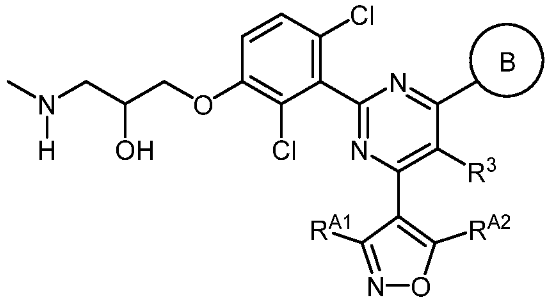


or a pharmaceutically acceptable salt thereof.

[0082] In certain embodiments, wherein Ring A is of Formula (A-i), (A-ii), or (A-iii), R^1 is $-CH_3$, R^{2a} is $-Cl$, and R^{2b} is -Cl, provided is a compound of Formulae: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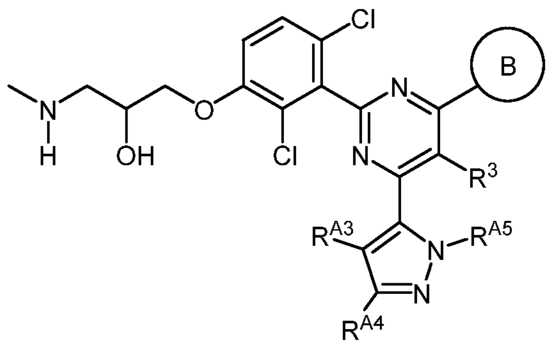
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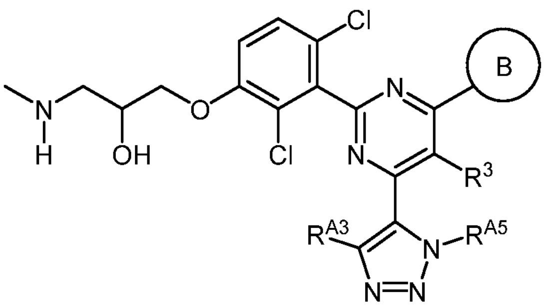
or



or a pharmaceutically acceptable salt thereof.

(III) Ring B Groups: Substitution by R^{C1} and R^{D1}

[0083] It is generally understood, as described herein, that each instance of "substituted" preceding a group refers to a group, *e.g.,* substituted C_2alkylene, substituted C_2alkenylene, or substituted C_2alkynylene in the instance of L_1, and substituted C_{1-3}alkyl, substituted C_{3-6} carbocyclyl, substituted 4- to 6-membered heterocyclyl, and substituted 5- to 6-membered ring, in the instance of various Ring B recitations, refers to a group substituted with 1, 2, or 3 R^{C1} groups, as valency permits. In certain embodiments, such groups are substituted with 1 or 2 R^{C1} groups.

[0084] As generally defined herein, each instance of R^{C1} is independentlyunsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, halogen, -CN, -OR^{C1B}, -SR^{C1B}, -$N(R^{C1A})(R^{C1B})$, -$C(=O)R^{C1A}$, -$C(=O)N(R^{C1A})(R^{C1B})$, -$C(=O)OR^{C1A}$, -$S(O)_2R^{C1A}$, -$OC(=O)R^{C1A}$, -$OC(=O)N(R^{C1A})(R^{C1B})$, -$OC(=O)OR^{C1A}$, -$NR^{CIB}C(=O)R^{C1A}$, -$NR^{CIB}C(=O)N(R^{C1A})(R^{C1B})$, or -$NR^{CIB}C(=O)OR^{C1A}$, wherein R^{C1A} is unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups; and R^{C1B} is hydrogen, unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups; or R^{C1A} and R^{C1B} are joined to form an 4- to 6- membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1}

groups; and wherein each instance of R^{D1} is independently halogen, -CN, -OR^{D1A}, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl, wherein R^{D1A} is hydrogen, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl.

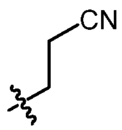
[0085] By way of example, in certain embodiments, substituted C_{1-3}alkyl refers to a C_{1-3}alkyl substituted with 1, 2, or 3 R^{C1} groups, as valency permits, selected from the group consisting of halogen, -CN, -OR^{C1B}, -SR^{C1B}, -$N(R^{C1A})(R^{C1B})$, -$C(=O)R^{C1A}$, -$C(=O)N(R^{C1A})(R^{C1B})$, -$C(=O)OR^{C1A}$, -$S(O)_2R^{C1A}$, -$OC(=O)R^{C1A}$, -$OC(=O)N(R^{C1A})(R^{C1B})$, -$OC(=O)OR^{C1A}$, -$NR^{C1B}C(=O)R^{B1A}$, -$NR^{C1B}C(=O)N(R^{C1A})(R^{C1BB})$, and -$NR^{C1B}C(=O)OR^{C1A}$. In certain embodiments, any recited instance of substituted C_{1-3}alkyl refers to a C_{1-3}alkyl substituted with 1 or 2 R^{C1} groups selected from the group consisting of -CN, -OR^{C1B}, -$N(R^{C1A})(R^{C1B})$, -$C(=O)N(R^{C1A})(R^{C1B})$, and -$C(=O)OR^{C1A}$.

[0086] In certain embodiments, at least one instance of R^{C1} is unsubstituted C_{1-3}alkyl, *i.e.*, unsubstituted C_1 alkyl (-CH_3), unsubstituted C_2 alkyl (-CH_2CH_3), or unsubstituted C_3 alkyl (-$CH_2CH_2CH_3$ or -$CH(CH_3)_2$). Such embodiments are particularly envisioned for substitution on a C_{3-6} carbocyclyl, 4- to 6-membered heterocyclyl, or 5- to 6-membered ring.

[0087] In certain embodiments, at least one instance of R^{C1} is C_{1-3}haloalkyl, *e.g.,* C_1 haloalkyl (–CF_3, –CCl_3, –$CFCl_2$, –CF_2Cl, –CH_2F, -CHF_2, -CH_2Cl, $CHCl_2$), C_2 haloalkyl (–CF_2CF_3, -CH_2CF_3, -CH_2CHF_2, -CH_2CH_2F, -CH_2CCl_3, -CH_2CHCl_2, -CH_2CH_2Cl), or C_3 haloalkyl (–$CF_2CF_2CF_3$, –$CH_2CF_2CF_3$, -$CH_2CH_2CF_3$, -$CH_2CH_2CHF_2$, - $CH_2CH_2CH_2F$, -$CH_2CH_2CCl_3$, - $CH_2CH_2CHCl_2$, - $CH_2CH_2CH_2Cl$, -$CH(CH_3)CHF_2$, or -$CH(CH_3)CF_3$). Such embodiments are also particularly envisioned for substitution on a C_{3-6} carbocyclyl, 4- to 6-membered heterocyclyl, or 5- to 6-membered ring.

[0088] In certain embodiments, at least one instance of R^{C1} is halogen, *i.e.,* -F, -Cl, -Br, or –I. In certain embodiments, at least one instance of R^{C1} is –F or –Cl. Such embodiments are also particularly envisioned for substitution on a C_{3-6} carbocyclyl, 4- to 6-membered heterocyclyl, or 5- to 6-membered ring.

[0089] In certain embodiments, at least one instance of R^{C1} is –CN. For example, in certain embodiments, C_{1-3} alkyl groups are contemplated substituted by –CN. In certain embodiments, C_2 alkyl groups are contemplated substituted by 1 –CN group, *e.g.,* of formula:



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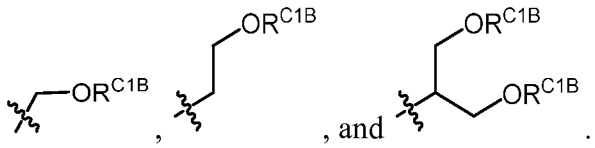
[0090] In certain embodiments, at least one instance of R^{C1} is $-OR^{C1B}$, wherein R^{C1B} is hydrogen, unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups. For example, in certain embodiments, C_{1-3} alkyl groups are contemplated substituted by $-OR^{C1B}$. In certain embodiments, C_{1-3} alkyl groups are contemplated substituted by 1 or 2 $-OR^{C1B}$ groups, *e.g.,* of formula:



[0091] In certain embodiments, R^{C1} is $-OR^{C1B}$, wherein R^{C1B} is hydrogen.

[0092] In certain embodiments, R^{C1} is $-OR^{C1B}$, wherein R^{C1B} is unsubstituted C_{1-3}alkyl, *i.e.*, unsubstituted C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$).

[0093] In certain embodiments, R^{C1} is $-OR^{C1B}$, wherein R^{C1B} is C_{1-3}haloalkyl, *e.g.,* C_1 haloalkyl ($-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, R^{C1} is $-OR^{C1B}$, wherein R^{C1B} is $-CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$.

[0094] In certain embodiments, R^{C1} is $-OR^{C1B}$, wherein R^{C1B} is C_{3-6}carbocylyl or 4-6 membered heterocyclyl , each independently unsubstituted or substituted with 1 or 2 R^{D1} groups, wherein R^{D1} is independently halogen, -CN, $-OR^{D1A}$, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl, and wherein R^{D1A} is hydrogen, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl. In certain embodiments, R^{C1} is $-OR^{C1B}$, wherein R^{C1B} is C_3carbocylyl (*e.g.,* cyclopropyl) unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, R^{C1} is $-OR^{C1B}$, wherein R^{C1B} is 4- membered heterocyclyl (*e.g.,* azetidinyl, oxetanyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, R^{C1} is $-OR^{C1B}$, wherein R^{C1B} is 5-membered heterocyclyl (*e.g.,* tetrahydrofuranyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, R^{C1} is $-OR^{C1B}$, wherein R^{C1B} is 6-membered heterocyclyl (*e.g.,* tetrahydropyranyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, such groups are unsubstituted by R^{D1}. In other embodiments, at least one instance of R^{D1} is halogen (*i.e.,* -F, -Cl, -Br, or –I), -CN, $-OR^{D1A}$ (*e.g.,* -OH, $-OCH_3$), or unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$).

[0095] In certain embodiments, at least one instance of R^{C1} is -SR^{C1B}, wherein R^{C1B} is hydrogen, unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups.

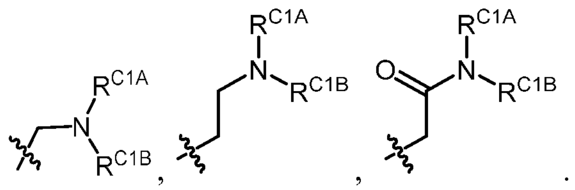
[0096] In certain embodiments, R^{C1} is -SR^{C1B}, wherein R^{C1B} is hydrogen.

[0097] In certain embodiments, R^{C1} is -SR^{C1B}, wherein R^{C1B} is unsubstituted C_{1-3}alkyl, *i.e.*, unsubstituted C_1 alkyl (-CH_3), unsubstituted C_2 alkyl (-CH_2CH_3), or unsubstituted C_3 alkyl (-$CH_2CH_2CH_3$ or -$CH(CH_3)_2$).

[0098] In certain embodiments, R^{C1} is -SR^{C1B}, wherein R^{C1B} is C_{1-3}haloalkyl, *e.g.,* C_1 haloalkyl (–CF_3, –CCl_3, –$CFCl_2$, –CF_2Cl, –CH_2F, -CHF_2, -CH_2Cl, $CHCl_2$), C_2 haloalkyl (–CF_2CF_3, -CH_2CF_3, -CH_2CHF_2, -CH_2CH_2F, -CH_2CCl_3, -CH_2CHCl_2, -CH_2CH_2Cl), or C_3 haloalkyl (–$CF_2CF_2CF_3$, –$CH_2CF_2CF_3$, -$CH_2CH_2CF_3$, -$CH_2CH_2CHF_2$, - $CH_2CH_2CH_2F$, -$CH_2CH_2CCl_3$, - $CH_2CH_2CHCl_2$, - $CH_2CH_2CH_2Cl$, -$CH(CH_3)CHF_2$, or -$CH(CH_3)CF_3$). In certain embodiments, R^{C1} is -SR^{C1B}, wherein R^{C1B} is –CF_3, –CH_2F, -CHF_2, -CH_2Cl, -CH_2CF_3, -CH_2CHF_2, -$CH(CH_3)CHF_2$, or -$CH(CH_3)CF_3$.

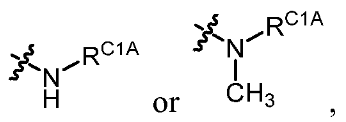
[0099] In certain embodiments, R^{C1} is -SR^{C1B}, wherein R^{C1B} is C_{3-6}carbocylyl or 4-6 membered heterocyclyl , each independently unsubstituted or substituted with 1 or 2 R^{D1} groups, wherein R^{D1} is independently halogen, -CN, -OR^{D1A}, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl, and wherein R^{D1A} is hydrogen, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl. In certain embodiments, R^{C1} is -SR^{C1B}, wherein R^{C1B} is C_3carbocylyl (*e.g.,* cyclopropyl) unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, R^{C1} is -SR^{C1B}, wherein R^{C1B} is 4- membered heterocyclyl (*e.g.,* azetidinyl, oxetanyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, R^{C1} is -SR^{C1B}, wherein R^{C1B} is 5-membered heterocyclyl (*e.g.,* tetrahydrofuranyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, R^{C1} is -SR^{C1B}, wherein R^{C1B} is 6-membered heterocyclyl (*e.g.,* tetrahydropyranyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, such groups are unsubstituted by R^{D1}. In other embodiments, such groups are substituted, *e.g.,* wherein at least one instance of R^{D1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, -OR^{D1A} (*e.g.,* -OH, -OCH_3), or unsubstituted C_{1-3}alkyl (*e.g.,* -CH_3, -CH_2CH_3).

[00100] In certain embodiments, at least one instance of R^{C1} is -$N(R^{C1A})(R^{C1B})$ or -$C(=O)N(R^{C1A})(R^{C1B})$ or -$OC(=O)N(R^{C1A})(R^{C1B})$ or -$NR^{C1B}C(=O)N(R^{C1A})(R^{C1B})$, wherein R^{C1A} is unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups; R^{C1B} is hydrogen, unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups; or R^{C1A} and R^{C1B} are joined to form an 4- to 6- membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups. For example, in certain embodiments, C_{1-3} alkyl groups are contemplated substituted by -N(R^{C1A})(R^{C1B}) or -C(=O)N(R^{C1A})(R^{C1B}). In certain embodiments, C_{1-3} alkyl groups are contemplated substituted by 1 -N(R^{C1A})(R^{C1B}) or -C(=O)N(R^{C1A})(R^{C1B}) group, *e.g.,* of formula:



[00101] In certain embodiments of -N(R^{C1A})(R^{C1B}) or -C(=O)N(R^{C1A})(R^{C1B}) or -OC(=O)N(R^{C1A})(R^{C1B}) or -NR^{CIB}C(=O)N(R^{C1A})(R^{C1B}), R^{C1A} and R^{C1B} do not join to form a cyclic ring structure, such that R^{C1A} is unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups; and R^{C1B} is hydrogen, unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, R^{C1B} is hydrogen or unsubstituted C_{1-3}alkyl (*e.g.,* -CH_3). In certain embodiments, R^{C1A} is unsubstituted C_{1-3}alkyl (*e.g.,* -CH_3), C_{1-3}haloalkyl (*e.g.,* –CF_3, –CH_2F, -CHF_2, -CH_2Cl, -CH_2CF_3, -CH_2CHF_2, -$CH(CH_3)CHF_2$, or -$CH(CH_3)CF_3$), C_3carbocylyl (*e.g.,* cyclopropyl) unsubstituted or substituted with 1 or 2 R^{D1} groups, 4- membered heterocyclyl (*e.g.,* azetidinyl, oxetanyl), unsubstituted or substituted with 1 or 2 R^{D1} groups, 5-membered heterocyclyl (*e.g.,* tetrahydrofuranyl), unsubstituted or substituted with 1 or 2 R^{D1} groups, or 6-membered heterocyclyl (*e.g.,* tetrahydropyranyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, such groups are unsubstituted by R^{D1}. In other embodiments, , such groups are substituted, *e.g.,* wherein at least one instance of R^{D1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, -OR^{D1A} (*e.g.,* -OH, -OCH_3), or unsubstituted C_{1-3}alkyl (*e.g.,* -CH_3, -CH_2CH_3).

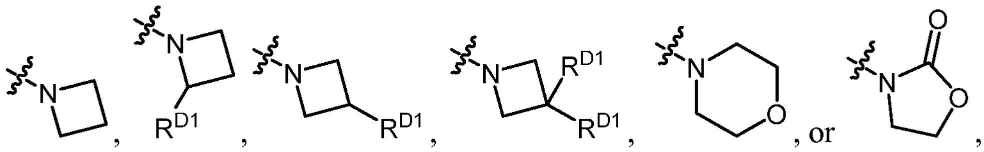
[00102] In certain embodiments of -N(R^{C1A})(R^{C1B}) or -C(=O)N(R^{C1A})(R^{C1B}) or -OC(=O)N(R^{C1A})(R^{C1B}) or -NR^{CIB}C(=O)N(R^{C1A})(R^{C1B}), wherein R^{C1B} is hydrogen or -CH_3, any recited instance of - N(R^{C1A})(R^{C1B}) (*e.g.,* for example, alone or part of a group, such as –C(=O) N(R^{C1A})(R^{C1B}) or -NR^{CIB}C(=O)N(R^{C1A})(R^{C1B}) or -OC(=O)N(R^{C1A})(R^{C1B})) independently refers to a group selected from:



wherein R^{C1A} is as defined herein.

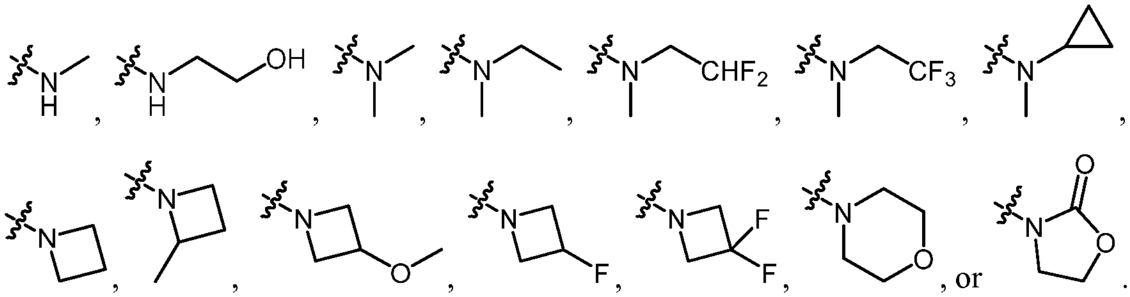
[00103] In certain embodiments of -N(R^{C1A})(R^{C1B}) or -C(=O)N(R^{C1A})(R^{C1B}) or -OC(=O)N(R^{C1A})(R^{C1B}) or -NR^{CIB}C(=O)N(R^{C1A})(R^{C1B}), R^{C1A} and R^{C1B} are joined to form an 4- to 6- membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups, e.g., for example, in certain embodiments, R^{C1A} and R^{C1B} are joined to form an 4- membered heterocyclyl (*e.g.,* azetidinyl), unsubstituted or substituted with 1 or 2 R^{D1} groups, 5-membered heterocyclyl (*e.g.,* pyrrolidinyl, pyrrolidin-2-one, oxazolidin-2-one), unsubstituted or substituted with 1 or 2 R^{D1} groups, or 6-membered heterocyclyl (*e.g.,* morpholinyl, piperidinyl, piperazinyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, such groups are unsubstituted by R^{D1}. In other embodiments, , such groups are substituted, *e.g.,* wherein at least one instance of R^{D1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, -OR^{D1A} (i.e., -OH, -OCH_3), or unsubstituted $C_{1\text{-}3}$alkyl (-CH_3, -CH_2CH_3).

[00104] In certain embodiments of -N(R^{C1A})(R^{C1B}) or -C(=O)N(R^{C1A})(R^{C1B}) or -OC(=O)N(R^{C1A})(R^{C1B}) or -NR^{CIB}C(=O)N(R^{C1A})(R^{C1B}), wherein R^{C1A} and R^{C1B} are joined to form an 4- to 6- membered heterocyclyl, any recited instance of - N(R^{C1A})(R^{C1B}) (*e.g.,* for example, alone or part of a group, such as –C(=O) N(R^{C1A})(R^{C1B}) or -NR^{CIB}C(=O)N(R^{C1A})(R^{C1B}) or -OC(=O)N(R^{C1A})(R^{C1B})) independently refers to a group selected from:

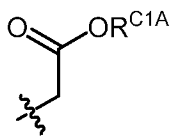


wherein R^{D1} is as defined herein.

[00105] In certain embodiments, any recited instance of - N(R^{C1A})(R^{C1B}) (*e.g.,* for example, alone or part of a group, such as –C(=O) N(R^{C1A})(R^{C1B}) or NR^{CIB}C(=O)N(R^{C1A})(R^{C1B}) or -OC(=O)N(R^{C1A})(R^{C1B})) independently refers to:



[00106] In certain embodiments, at least one instance of R^{C1} is $-C(=O)R^{C1A}$ or $-C(=O)OR^{C1A}$, wherein R^{C1A} is unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups. For example, in certain embodiments, C_{1-3} alkyl groups are contemplated substituted by $-C(=O)R^{C1A}$ or $-C(=O)OR^{C1A}$. In certain embodiments, C_{1-3} alkyl groups are contemplated substituted by one (1) $-C(=O)OR^{C1A}$ group, *e.g.,* of formula:



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[00107] In certain embodiments, at least one instance of R^{C1} is $-C(=O)R^{C1A}$ or $-C(=O)OR^{C1A}$, wherein R^{C1A} is unsubstituted C_{1-3}alkyl, *i.e.*, unsubstituted C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$).

[00108] In certain embodiments, at least one instance of R^{C1} is $-C(=O)R^{C1A}$ or $-C(=O)OR^{C1A}$, wherein R^{C1A} is C_{1-3}haloalkyl, *e.g.,* C_1 haloalkyl ($–CF_3$, $–CCl_3$, $–CFCl_2$, $–CF_2Cl$, $–CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($–CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($–CF_2CF_2CF_3$, $–CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $- CH_2CH_2CH_2F$, $- CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $- CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, $-C(=O)R^{C1A}$ or $-C(=O)OR^{C1A}$, wherein R^{C1A} is $–CF_3$, $–CH_2F$, $-CHF_2$, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$.

[00109] In certain embodiments, at least one instance of R^{C1} is $-C(=O)R^{C1A}$ or $-C(=O)OR^{C1A}$, wherein R^{C1A} is C_{3-6}carbocylyl or 4-6 membered heterocyclyl , each independently unsubstituted or substituted with 1 or 2 R^{D1} groups, wherein R^{D1} is independently halogen, -CN, $-OR^{D1A}$, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl, and wherein R^{D1A} is hydrogen, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl. In certain embodiments, at least one instance of R^{C1} is $-C(=O)R^{C1A}$ or $-C(=O)OR^{C1A}$, wherein R^{C1A} is C_3carbocylyl (*e.g.,* cyclopropyl) unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, at least one instance of R^{C1} is $-C(=O)R^{C1A}$ or $-C(=O)OR^{C1A}$, wherein R^{C1A} is 4- membered heterocyclyl (*e.g.,* azetidinyl, oxetanyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, at least one instance of R^{C1} is $-C(=O)R^{C1A}$ or $-C(=O)OR^{C1A}$, wherein R^{C1A} is 5-membered heterocyclyl (*e.g.,* tetrahydrofuranyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, at least one instance of R^{C1} is $-C(=O)R^{C1A}$ or -

$C(=O)OR^{C1A}$, wherein R^{C1A} is 6-membered heterocyclyl (*e.g.,* tetrahydropyranyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, such groups are unsubstituted by R^{D1}. In other embodiments, , such groups are substituted, *e.g.,* wherein at least one instance of R^{D1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, $-OR^{D1A}$ (*e.g.,* -OH, $-OCH_3$), or unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$).

[00110] In certain embodiments, at least one instance of R^{C1} is $-OC(=O)R^{C1A}$ or $-OC(=O)OR^{C1A}$, wherein R^{C1A} is unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups.

[00111] In certain embodiments, at least one instance of R^{C1} is $-OC(=O)R^{C1A}$ or $-OC(=O)OR^{C1A}$, wherein R^{C1A} is unsubstituted C_{1-3}alkyl, *i.e.*, unsubstituted C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$).

[00112] In certain embodiments, at least one instance of R^{C1} is $-OC(=O)R^{C1A}$ or $-OC(=O)OR^{C1A}$, wherein R^{C1A} is C_{1-3}haloalkyl, *e.g.,* C_1 haloalkyl ($-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, at least one instance of R^{C1} is $-OC(=O)R^{C1A}$ or $-OC(=O)OR^{C1A}$, wherein R^{C1A} is $-CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$.

[00113] In certain embodiments, at least one instance of R^{C1} is $-OC(=O)R^{C1A}$ or $-OC(=O)OR^{C1A}$, wherein R^{C1A} is C_{3-6}carbocylyl or 4-6 membered heterocyclyl , each independently unsubstituted or substituted with 1 or 2 R^{D1} groups, wherein R^{D1} is independently halogen, -CN, $-OR^{D1A}$, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl, and wherein R^{D1A} is hydrogen, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl. In certain embodiments, at least one instance of R^{C1} is $-OC(=O)R^{C1A}$ or $-OC(=O)OR^{C1A}$, wherein R^{C1A} is C_3carbocylyl (*e.g.,* cyclopropyl) unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, at least one instance of R^{C1} is $-OC(=O)R^{C1A}$ or $-OC(=O)OR^{C1A}$, wherein R^{C1A} is 4- membered heterocyclyl (*e.g.,* azetidinyl, oxetanyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, at least one instance of R^{C1} is $-OC(=O)R^{C1A}$ or $-OC(=O)OR^{C1A}$, wherein R^{C1A} is 5-membered heterocyclyl (*e.g.,* tetrahydrofuranyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, at least one instance of R^{C1} is $-OC(=O)R^{C1A}$ or $-OC(=O)OR^{C1A}$, wherein R^{C1A} is 6-membered heterocyclyl (*e.g.,* tetrahydropyranyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, such groups are unsubstituted by R^{D1}. In other embodiments, at least one instance of R^{D1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, $-OR^{D1A}$ (*e.g.,* -OH, $-OCH_3$), or unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$).

[00114] In certain embodiments, at least one instance of R^{C1} is $-S(O)_2R^{C1A}$, wherein R^{C1A} is unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups.

[00115] In certain embodiments, at least one instance of R^{C1} is $-S(O)_2R^{C1A}$, wherein R^{C1A} is unsubstituted C_{1-3}alkyl, *i.e.*, unsubstituted C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$).

[00116] In certain embodiments, at least one instance of R^{C1} is $-S(O)_2R^{C1A}$, wherein R^{C1A} is C_{1-3}haloalkyl, *e.g.,* C_1 haloalkyl ($–CF_3$, $–CCl_3$, $–CFCl_2$, $–CF_2Cl$, $–CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($–CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($–CF_2CF_2CF_3$, $–CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, at least one instance of R^{C1} is $-OC(=O)R^{C1A}$ or $-OC(=O)OR^{C1A}$, wherein R^{C1A} is $–CF_3$, $–CH_2F$, $-CHF_2$, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$.

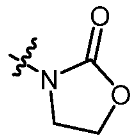
[00117] In certain embodiments, at least one instance of R^{C1} is $-S(O)_2R^{C1A}$, wherein R^{C1A} is C_{3-6}carbocylyl or 4-6 membered heterocyclyl , each independently unsubstituted or substituted with 1 or 2 R^{D1} groups, wherein R^{D1} is independently halogen, -CN, $-OR^{D1A}$, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl, and wherein R^{D1A} is hydrogen, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl. In certain embodiments, at least one instance of R^{C1} is $-S(O)_2R^{C1A}$, wherein R^{C1A} is C_3carbocylyl (*e.g.,* cyclopropyl) unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, at least one instance of R^{C1} is $-S(O)_2R^{C1A}$, wherein R^{C1A} is 4-membered heterocyclyl (*e.g.,* azetidinyl, oxetanyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, at least one instance of R^{C1} is $-S(O)_2R^{C1A}$, wherein R^{C1A} is 5-membered heterocyclyl (*e.g.,* tetrahydrofuranyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, at least one instance of R^{C1} $-S(O)_2R^{C1A}$, wherein R^{C1A} is 6-membered heterocyclyl (*e.g.,* tetrahydropyranyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, such groups are unsubstituted by R^{D1}. In other embodiments, at least one instance of R^{D1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, $-OR^{D1A}$ (*e.g.,* -OH, $-OCH_3$), or unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$).

[00118] In certain embodiments, at least one instance of R^{C1} is $-NR^{CIB}C(=O)R^{C1A}$ or $-NR^{CIB}C(=O)OR^{C1A}$, wherein R^{C1A} is unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups; R^{C1B} is hydrogen, unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups; or R^{C1A} and R^{C1B} are joined to form an 4- to 6- membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups.

[00119] In certain embodiments of $-NR^{CIB}C(=O)R^{C1A}$ or $-NR^{CIB}C(=O)OR^{C1A}$, R^{C1A} and R^{C1B} do not join to form a cyclic ring structure, such that R^{C1A} is unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups, and R^{C1B} is hydrogen, unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, R^{C1B} is hydrogen or unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$). In certain embodiments, R^{C1A} is unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$), C_{1-3}haloalkyl (*e.g.,* $-CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$), C_3carbocylyl (*e.g.,* cyclopropyl) unsubstituted or substituted with 1 or 2 R^{D1} groups, 4-membered heterocyclyl (*e.g.,* azetidinyl, oxetanyl), unsubstituted or substituted with 1 or 2 R^{D1} groups, 5-membered heterocyclyl (*e.g.,* tetrahydrofuranyl), unsubstituted or substituted with 1 or 2 R^{D1} groups, or 6-membered heterocyclyl (*e.g.,* tetrahydropyranyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, such groups are unsubstituted by R^{D1}. In other embodiments, at least one instance of R^{D1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, $-OR^{D1A}$ (i.e., -OH, $-OCH_3$), or unsubstituted C_{1-3}alkyl ($-CH_3$, $-CH_2CH_3$).

[00120] In certain embodiments of $-NR^{CIB}C(=O)R^{C1A}$ or $-NR^{CIB}C(=O)OR^{C1A}$, R^{C1A} and R^{C1B} are joined to form an 4- to 6- membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups, *e.g.,* for example, in certain embodiments, R^{C1A} and R^{C1B} are joined to form an 4- membered heterocyclyl (*e.g.,* azetidinyl), unsubstituted or substituted with 1 or 2 R^{D1} groups, 5-membered heterocyclyl (*e.g.,* pyrrolidinyl, pyrrolidin-2-one, oxazolidin-2-one), unsubstituted or substituted with 1 or 2 R^{D1} groups, or 6-membered heterocyclyl (*e.g.,* morpholinyl, piperidinyl, piperazinyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, such groups are unsubstituted by R^{D1}. In other embodiments, at least one instance of R^{D1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, $-OR^{D1A}$ (*e.g.,* -OH, $-OCH_3$), or unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$).

[00121] In certain embodiments wherein R^{C1A} and R^{C1B} are joined to form an 4- to 6-membered heterocyclyl, any recited instance of -$NR^{CIB}C(=O)OR^{C1A}$ independently refers to the group:



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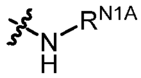
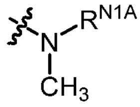
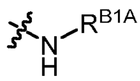
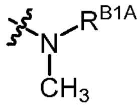
(IV) Ring B Substituents: Groups comprising -N(R^{N1A})(R^{N1B}), -N(R^{B1A})(R^{B1B}), and -N(R^{B4A})(R^{B4B})

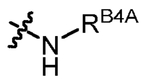
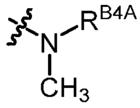
[00122] Various embodiments of Ring B substituents, *e.g.,* wherein R^{N1} is -C(=O)N(R^{N1A})(R^{N1B}), R^{B1} is -N(R^{B1A})(R^{B1B}) (or comprises such a group, such as -C(=O)N(R^{B1A})(R^{B1B}), -OC(=O)N(R^{B1A})(R^{B1B}), or -NR^{BIB}C(=O)N(R^{B1A})(R^{B1B})), and at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is -N(R^{B4A})(R^{B4B}) (or comprises such a group, such as -C(=O)N(R^{B4A})(R^{B4B}), -OC(=O)N(R^{B4A})(R^{B4B}), or -NR^{B4B}C(=O)N(R^{B4A})(R^{B4B})), are contemplated herein.

[00123] For example, in each of the above-recited instances of -C(=O)N(R^{N1A})(R^{N1B}), -N(R^{B1A})(R^{B1B}), or -N(R^{B4A})(R^{B4B}), in certain embodiments the two R groups attached to the amino (N) atom do not join to form a cyclic ring structure, such that R^{N1A} , R^{B1A}, or R^{B4A} is unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups; and R^{N1B}, R^{B1B}, or R^{B4B} is hydrogen, unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-6}carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, R^{N1B}, R^{B1B}, or R^{B4B} is hydrogen or unsubstituted C_{1-3}alkyl (*e.g.,* -CH_3). In certain embodiments, R^{N1A} , R^{B1A}, or R^{B4A} is unsubstituted C_{1-3}alkyl (*e.g.,* -CH_3), C_{1-3}haloalkyl (*e.g.,* –CF_3, –CH_2F, -CHF_2, -CH_2Cl, -CH_2CF_3, -CH_2CHF_2, -$CH(CH_3)CHF_2$, or -$CH(CH_3)CF_3$), C_3carbocylyl (*e.g.,* cyclopropyl) unsubstituted or substituted with 1 or 2 R^{D1} groups, 4-membered heterocyclyl (*e.g.,* azetidinyl, oxetanyl), unsubstituted or substituted with 1 or 2 R^{D1} groups, 5-membered heterocyclyl (*e.g.,* tetrahydrofuranyl), unsubstituted or substituted with 1 or 2 R^{D1} groups, or 6-membered heterocyclyl (*e.g.,* tetrahydropyranyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, such groups are unsubstituted by R^{D1}. In other embodiments, at least one instance of R^{D1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, -OR^{D1A} (*e.g.,* -OH, -OCH_3), or unsubstituted C_{1-3}alkyl (*e.g.,* -CH_3, -CH_2CH_3).

[00124] In certain embodiments of $-C(=O)N(R^{N1A})(R^{N1B})$, $-N(R^{B1A})(R^{B1B})$, or $-N(R^{B4A})(R^{B4B})$, wherein R^{N1B}, R^{B1B}, or R^{B4B} is hydrogen or $-CH_3$, any recited instance of $-N(R^{N1A})(R^{N1B})$, $-N(R^{B1A})(R^{B1B})$, or $-N(R^{B4A})(R^{B4B})$ (*e.g.,* for example, alone or part of a group) independently refers to a group selected from:

 or  for $-N(R^{N1A})(R^{N1B})$;

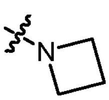
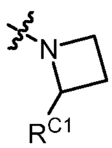
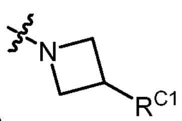
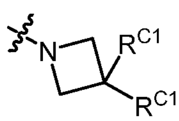
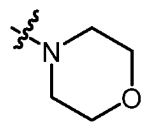
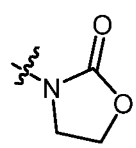
 or  for $-N(R^{B1A})(R^{B1B})$; or

 or  for $N(R^{B4A})(R^{B4B})$.

wherein R^{N1A}, R^{B1A}, and R^{B4A} are as defined herein.

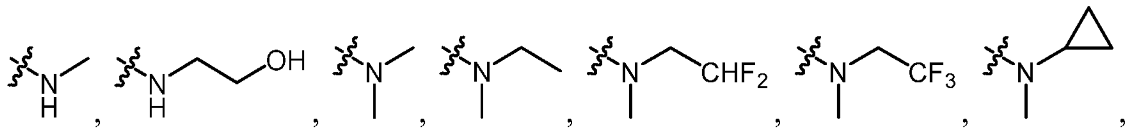
[00125] In certain embodiments of $-C(=O)N(R^{N1A})(R^{N1B})$, $-N(R^{B1A})(R^{B1B})$, or $-N(R^{B4A})(R^{B4B})$, the two R groups attached to the amino (N) atom are joined to form an 4- to 6- membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups, *e.g.,* for example, in certain embodiments, R^{N1A} and R^{N1B} (or R^{B1A} and R^{B1B}, or R^{B4A} and R^{B4B}) are joined to form an 4- membered heterocyclyl (*e.g.,* azetidinyl), unsubstituted or substituted with 1 or 2 R^{D1} groups, 5-membered heterocyclyl (*e.g.,* pyrrolidinyl, pyrrolidin-2-one, oxazolidin-2-one), unsubstituted or substituted with 1 or 2 R^{D1} groups, or 6-membered heterocyclyl (*e.g.,* morpholinyl, piperidinyl, piperazinyl), unsubstituted or substituted with 1 or 2 R^{D1} groups. In certain embodiments, such groups are unsubstituted by R^{D1}. In other embodiments, at least one instance of R^{D1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, $-OR^{D1A}$ (i.e., -OH, $-OCH_3$), or unsubstituted C_{1-3}alkyl ($-CH_3$, $-CH_2CH_3$).

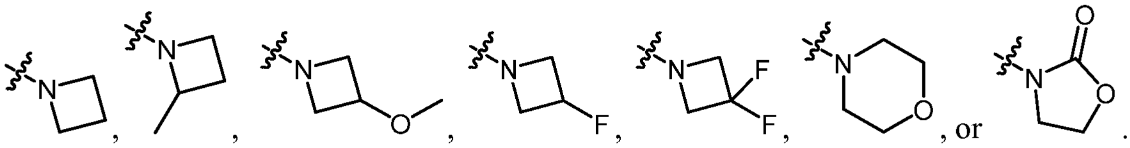
[00126] In certain embodiments of $-C(=O)N(R^{N1A})(R^{N1B})$, $-N(R^{B1A})(R^{B1B})$, or $-N(R^{B4A})(R^{B4B})$, wherein R^{N1A} and R^{N1B}, or R^{B1A} and R^{B1B}, or R^{B4A} and R^{B4B}, are joined to form an 4- to 6- membered heterocyclyl, any recited instance of $-N(R^{N1A})(R^{N1B})$, $-N(R^{B1A})(R^{B1B})$, or $-N(R^{B4A})(R^{B4B})$ (*e.g.,* for example, alone or part of a group) independently refers to a group selected from:

, , , , , or ,

wherein R^{C1} is as defined herein.

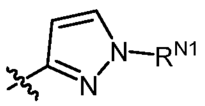
[00127] In certain embodiments, any recited instance of -C(=O)N(R^{N1A})(R^{N1B}), -N(R^{B1A})(R^{B1B}), or -N(R^{B4A})(R^{B4B}) (*e.g.,* for example, alone or part of a group) independently refers to:



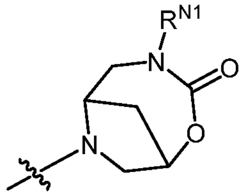


(V) Ring B Groups comprising R^{N1}, R^{B2}, and L_1

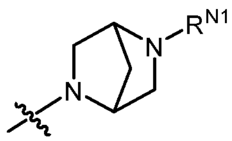
[00128] Groups R^{N1}, R^{B2} and/or L_1, are present in Ring B groups of formula (iii), (v), (vi), (vii), (viii), (ix), (x), (xii), (xiii), (xxii), (xxvii), (xxviii), and (xxiv):



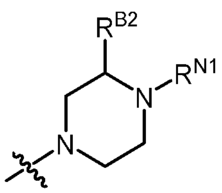
(iii)



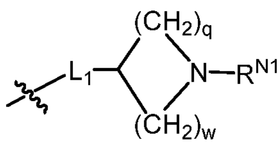
(v)



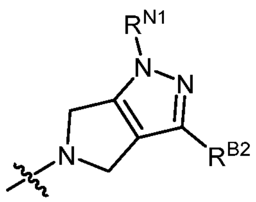
(vi)



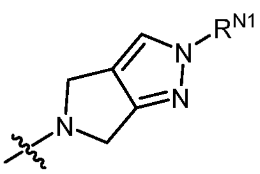
(vii)



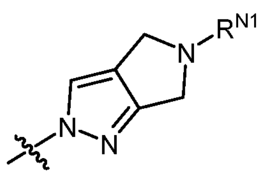
(viii)



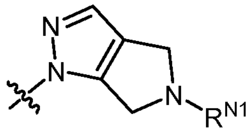
(ix)



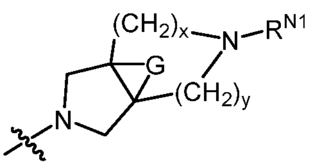
(x)



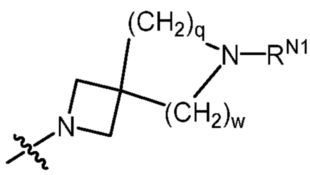
(xii)



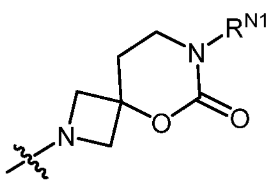
(xiii)



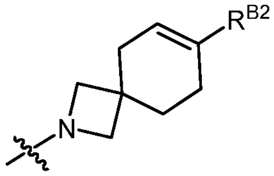
(xxii)



(xxvii)



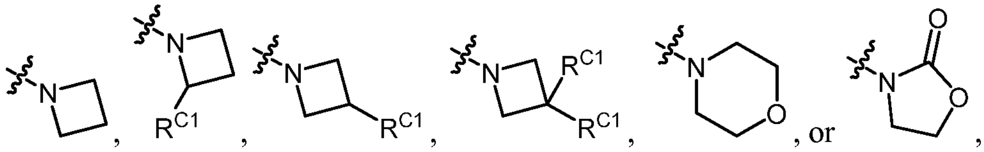
(xxviii)



(xxiv).

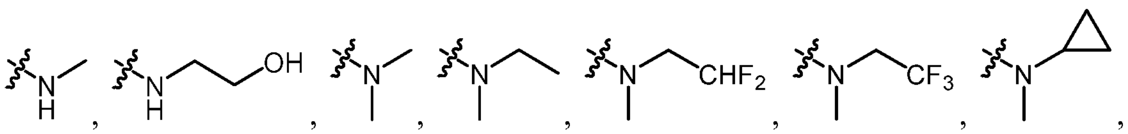
[00129] Various embodiments of R^{N1}, R^{B2} and L^1 are further contemplated herein. In particular, embodiments wherein R^{N1} is substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted 4- to 6-membered heterocyclyl, $-C(=O)R^{N1A}$, $-C(=O)OR^{N1A}$, or $-S(O)_2R^{N1A}$, is further contemplated herein.

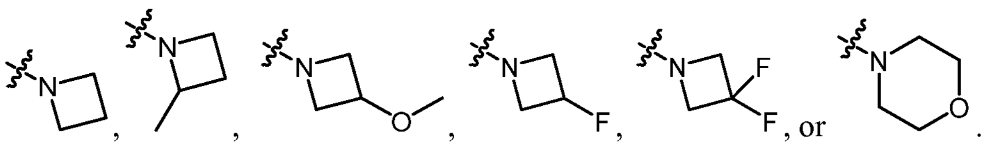
[00130] Embodiments wherein R^{N1} is $-C(=O)N(R^{N1A})(R^{N1B})$ is contemplated in a preceding section. For example, in certain embodiments, R^{N1} is $-C(=O)N(R^{N1A})(R^{N1B})$, wherein R^{N1A} and R^{N1B} are as defined herein. In certain embodiments, R^{N1} is $-C(=O)N(R^{N1A})(R^{N1B})$, wherein the group $-N(R^{N1A})(R^{N1B})$ is of the formula:



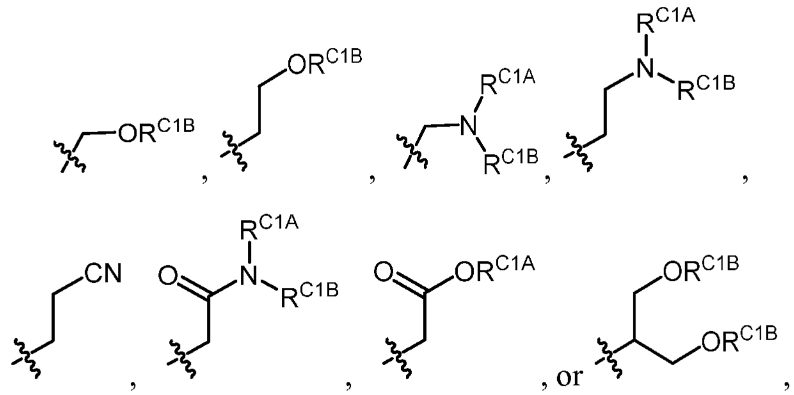
wherein R^{C1} is as defined herein.

[00131] In certain embodiments, R^{N1} is $-C(=O)N(R^{N1A})(R^{N1B})$, wherein the group -$N(R^{N1A})(R^{N1B})$ is of the formula:





[00132] In certain embodiments, R^{N1} is substituted or unsubstituted C_{1-3}alkyl, *i.e.*, a C_{1-3}alkyl substituted by 1, 2, or 3 R^{C1} groups as previously described herein, or an unsubstituted C_{1-3}alkyl. In certain embodiments, R^{N1} is unsubstituted C_{1-3}alkyl, *i.e.,* C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, R^{N1} is unsubstituted C_{1-3}alkyl of formula $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$. In certain embodiments, R^{N1} is substituted C_{1-3}alkyl, *e.g.,* of formula:



wherein R^{C1A} and R^{C1B} are as defined herein.

[00133] In certain embodiments, R^{N1} is $C_{1\text{-}3}$haloalkyl, *e.g.,* C_1 haloalkyl ($-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, R^{N1} is $-CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$.

[00134] In certain embodiments, R^{N1} is substituted or unsubstituted $C_{3\text{-}6}$carbocylyl. In certain embodiments, R^{N1} is substituted or unsubstituted C_3carbocylyl (*e.g.,* substituted or unsubstituted cyclopropyl). In certain embodiments, such groups are unsubstituted by R^{C1}. In other embodiments, such groups are substituted, *e.g.,* wherein at least one instance of R^{C1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, $-OR^{C1A}$ (*e.g.,* -OH, $-OCH_3$), or unsubstituted $C_{1\text{-}3}$alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$).

[00135] In certain embodiments, R^{N1} is substituted or unsubstituted 4-6 membered heterocyclyl. In certain embodiments, R^{N1} is a substituted or unsubstituted 4- membered heterocyclyl (*e.g.,* azetidinyl), substituted or unsubstituted 5-membered heterocyclyl (*e.g.,* pyrrolidinyl, pyrrolidin-2-one, oxazolidin-2-one), or substituted or unsubstituted 6-membered heterocyclyl (*e.g.,* morpholinyl, piperidinyl, piperazinyl). In certain embodiments, such groups are unsubstituted by R^{C1}. In other embodiments, such groups are substituted, *e.g.,* wherein at least one instance of R^{C1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, $-OR^{C1A}$ (*e.g.,* -OH, $-OCH_3$), or unsubstituted $C_{1\text{-}3}$alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$).

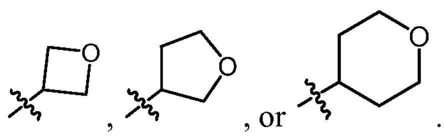
[00136] In certain embodiments, R^{N1} is $-C(=O)R^{N1A}$, $-C(=O)OR^{N1A}$, or $-S(O)_2R^{N1A}$ wherein R^{N1A} is substituted or unsubstituted $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$haloalkyl, substituted or unsubstituted $C_{3\text{-}6}$ carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl.

[00137] In certain embodiments, R^{N1} is $-C(=O)R^{N1A}$, $-C(=O)OR^{N1A}$, or $-S(O)_2R^{N1A}$ wherein R^{N1A} is unsubstituted C_{1-3}alkyl, *i.e.*, unsubstituted C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$).

[00138] In certain embodiments, R^{N1} is $-C(=O)R^{N1A}$, $-C(=O)OR^{N1A}$, or $-S(O)_2R^{N1A}$ wherein R^{N1A} is C_{1-3}haloalkyl, *e.g.,* C_1 haloalkyl ($-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, R^{N1} is $-C(=O)R^{N1A}$, $-C(=O)OR^{N1A}$, or $-S(O)_2R^{N1A}$ wherein R^{N1A} is $-CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$.

[00139] In certain embodiments, R^{N1} is $-C(=O)R^{N1A}$, $-C(=O)OR^{N1A}$, or $-S(O)_2R^{N1A}$ wherein R^{N1A} is substituted or unsubstituted C_{3-6}carbocylyl or substituted or unsubstituted 4-6 membered heterocyclyl. In certain embodiments, R^{N1} is $-C(=O)R^{N1A}$, $-C(=O)OR^{N1A}$, or $-S(O)_2R^{N1A}$ wherein R^{N1A} is substituted or unsubstituted C_3carbocylyl (*e.g.,* cyclopropyl). In certain embodiments, R^{N1} is $-C(=O)R^{N1A}$, $-C(=O)OR^{N1A}$, or $-S(O)_2R^{N1A}$ wherein R^{N1A} is substituted or unsubstituted 4- membered heterocyclyl (*e.g.,* azetidinyl, oxetanyl). In certain embodiments, R^{N1} is $-C(=O)R^{N1A}$, $-C(=O)OR^{N1A}$, or $-S(O)_2R^{N1A}$ wherein R^{N1A} is substituted or unsubstituted 5-membered heterocyclyl (*e.g.,* tetrahydrofuranyl). In certain embodiments, R^{N1} is $-C(=O)R^{N1A}$, $-C(=O)OR^{N1A}$, or $-S(O)_2R^{N1A}$ wherein R^{N1A} is substituted or unsubstituted 6-membered heterocyclyl (*e.g.,* tetrahydropyranyl). In certain embodiments, such groups are unsubstituted by R^{C1}. In other embodiments, such groups are substituted, *e.g.,* wherein at least one instance of R^{C1} is halogen (*i.e.,* -F, -Cl, -Br, or –I), -CN, $-OR^{C1A}$ (*e.g.,* -OH, $-OCH_3$), or unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$).

[00140] For example, in certain embodiments, R^{N1} is a substituted or unsubstituted 4- to 6-membered heterocyclyl comprising one oxygen ring heteroatom. In certain embodiments, R^{N1} is:



[00141] In certain embodiments, R^{N1} is:

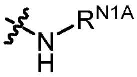
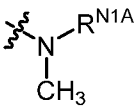
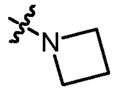
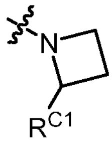
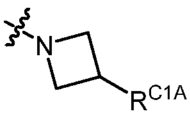
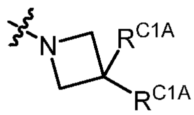
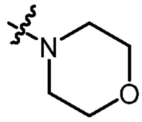
(a) substituted or unsubstituted C_{1-3}alkyl ($-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$);

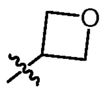
(b) $C_{1\text{-}3}$haloalkyl ($-CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$);

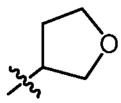
(c) substituted or unsubstituted C_3 carbocyclyl (*e.g.,* );

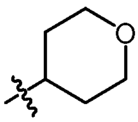
(d) $-C(=O)R^{N1A}$, $-C(=O)OR^{N1A}$, or $-S(O)_2R^{N1A}$, wherein R^{N1A} is $-CH_3$, CH_2CH_3, $-CH(CH_3)_2$, $-CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$;

(e) $-C(=O)N(R^{N1A})(R^{N1B})$, as previously contemplated, *e.g.,* wherein $N(R^{N1A})(R^{N1B})$ is:

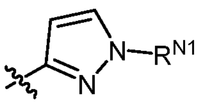
, , , , , , or ;

(f) substituted or unsubstituted 4- membered heterocyclyl (*e.g.,* );

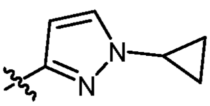
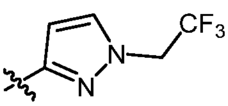
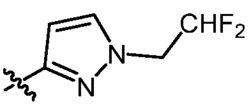
(g) substituted or unsubstituted 5- membered heterocyclyl (*e.g.,* ); or

(h) substituted or unsubstituted 6-membered heterocyclyl (*e.g.,* ).

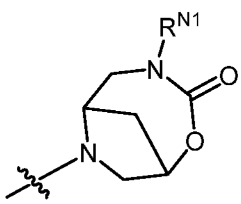
[00142] In certain embodiments, wherein Ring B is of formula:

 (iii).

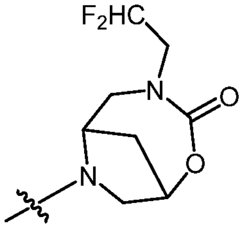
[00143] In certain embodiments of formula (iii), wherein Ring B is of formula:

, , or .

[00144] In certain embodiments, Ring B is of formula:

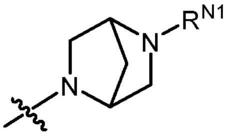
 (v).

[00145] In certain embodiments of formula (v), Ring B is of formula:



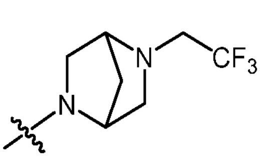
.

[00146] In certain embodiments, Ring B is of formula:

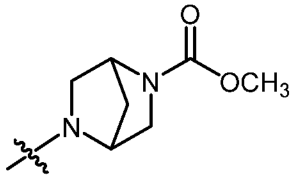


(vi).

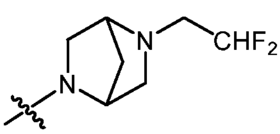
[00147] In certain embodiments of formula (vi), Ring B is of formula:



,

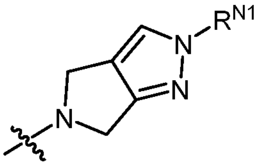


, or



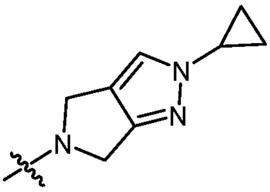
.

[00148] In certain embodiments, Ring B is of formula:

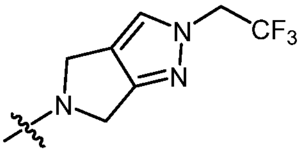


(x).

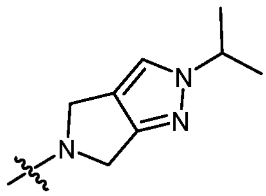
[00149] In certain embodiments of formula (x), Ring B is of formula:



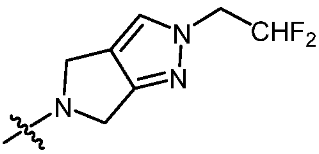
,



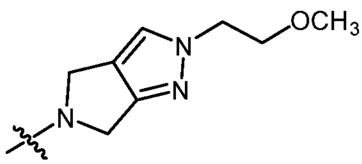
,



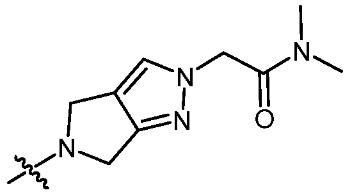
,



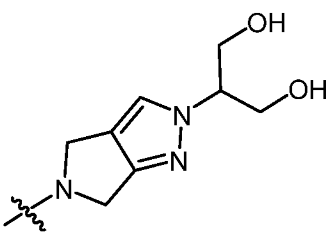
,



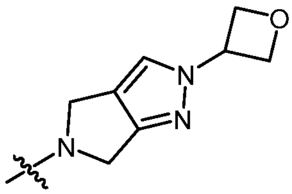
,



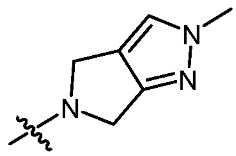
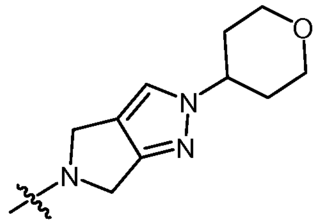
,



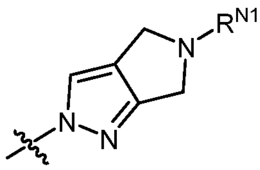
,



,

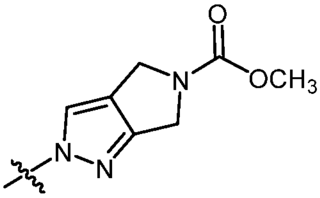
, or .

[00150] In certain embodiments, Ring B is of formula:



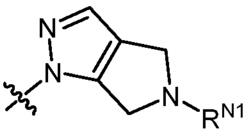
(xii).

[00151] In certain embodiments of formula (xii), Ring B is of formula:



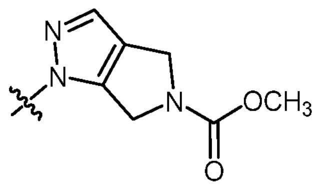
.

[00152] In certain embodiments, Ring B is of formula:



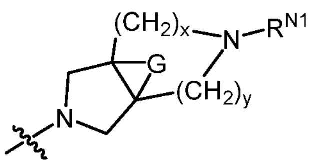
(xiii).

[00153] In certain embodiments of formula (xiii), Ring B is of formula:



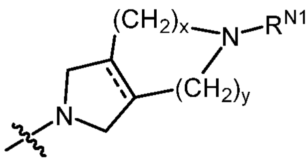
.

[00154] In certain embodiments, Ring B is of formula:



(xxii).

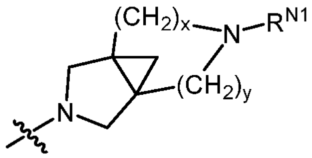
[00155] In certain embodiments of formula (xxii),  represents a single or double bond (*e.g.,* represented by) to provide Ring B of formula:



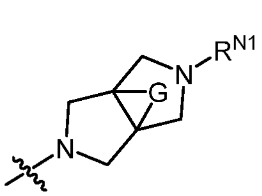
.

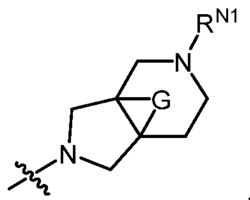
[00156] In certain embodiments of formula (xxii), ==== represents a single bond. In certain embodiments of formula (xxii), ==== represents a single bond, and the ring fusion is in the *trans* configuration. In certain embodiments of formula (xxii), ==== represents a single bond, and the ring fusion is in the *cis* configuration. In certain embodiments of formula (xxii), ==== represents a double bond.

[00157] In certain embodiments of formula (xxii), G of  is $-CH_2-$ to provide a cyclopropanated Ring B of formula:



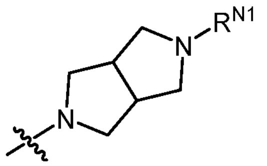
[00158] In certain embodiments of formula (xxii), x is 1 and y is 1. In certain embodiments of formula (xxii), x is 1 and y is 2. For example, in certain embodiments of formula (xxii), Ring B is of formula:

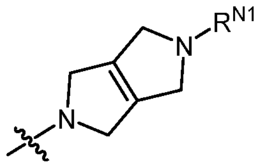


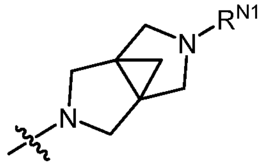
or 

.

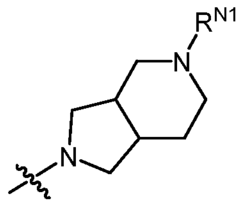
[00159] In certain embodiments of formula (xxii), Ring B is of formula:

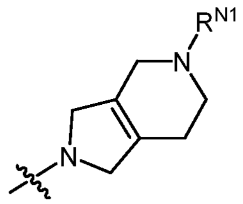


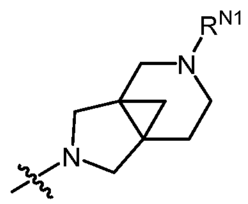
, 

, 

,

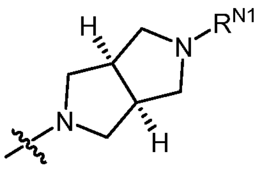


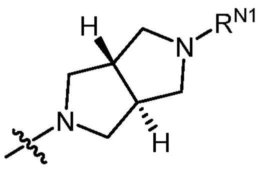
, 

, or 

.

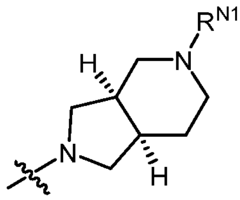
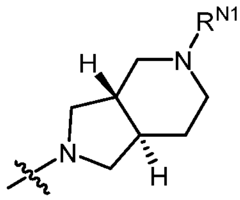
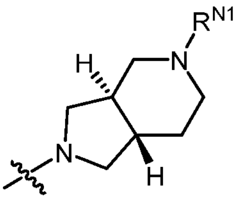
[00160] In certain embodiments of formula (xxii), Ring B is of formula:



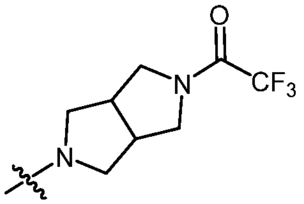
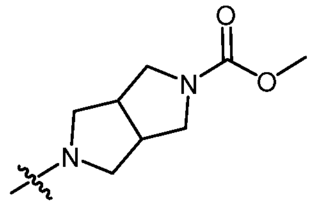
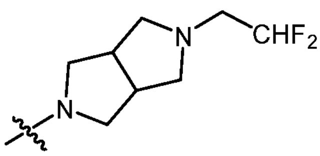
or 

.

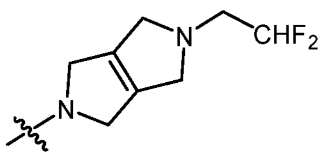
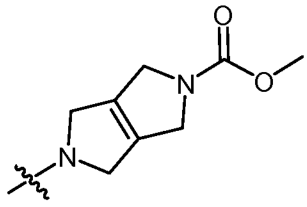
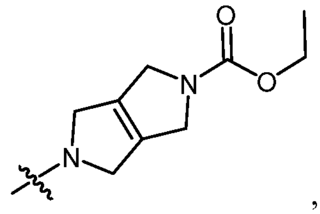
[00161] In certain embodiments of formula (xxii), Ring B is of formula:

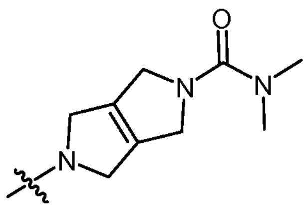
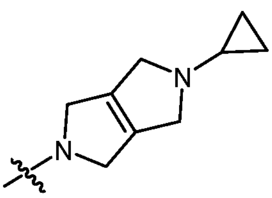
, , or .

[00162] In certain embodiments of formula (xxii), Ring B is of formula:

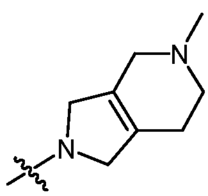
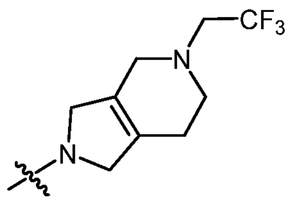
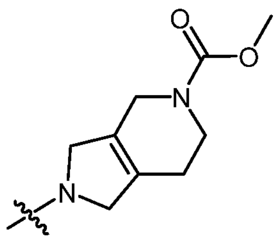
, , or .

[00163] In certain embodiments of formula (xxii), Ring B is of formula:

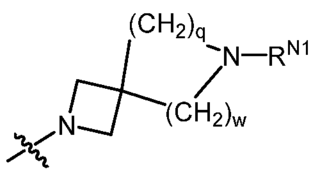
, , ,

, or .

[00164] In certain embodiments of formula (xxii), Ring B is of formula:

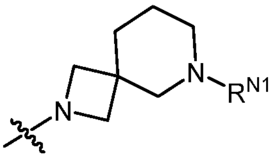
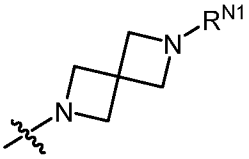
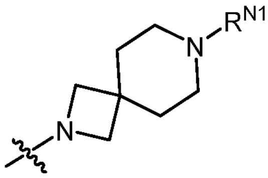
, , or .

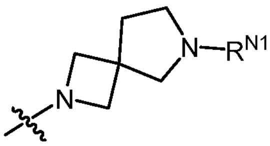
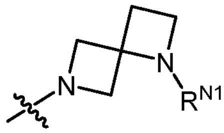
[00165] In certain embodiments, Ring B is of formula:



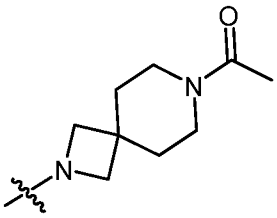
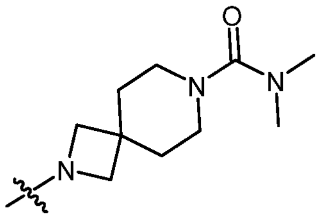
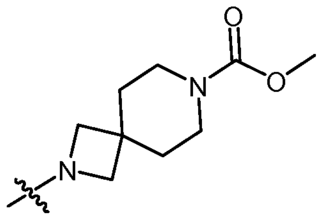
(xxvii).

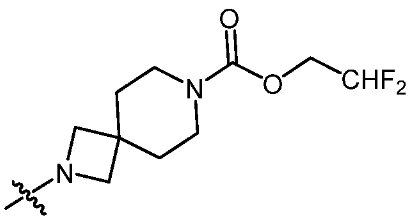
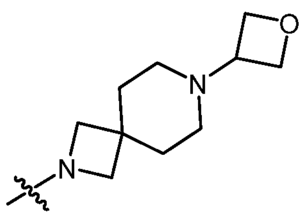
[00166] In certain embodiments of formula (xxvii), q is 1, 2, or 3 and w is 1. In certain embodiments of formula (xxvii), q is 2 and w is 0 or 2. For example, in certain embodiments of formula (xxvii), Ring B is of formula:

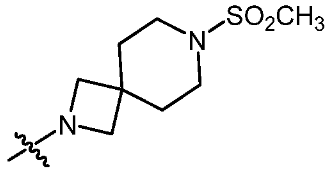
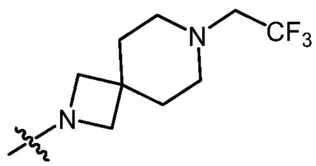
, , ,

, or .

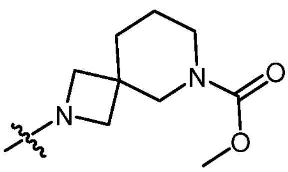
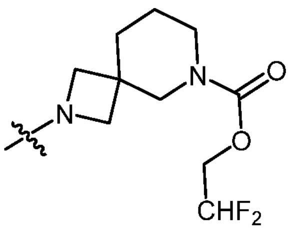
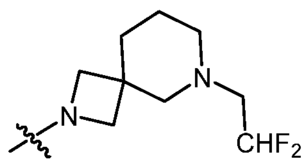
[00167] In certain embodiments of formula (xxvii), Ring B is of formula:

 , ,

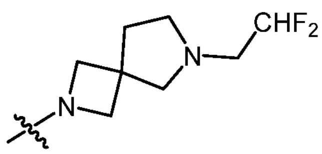
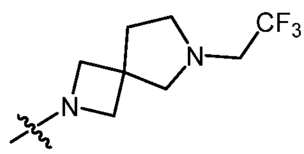
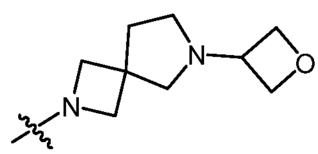
, ,

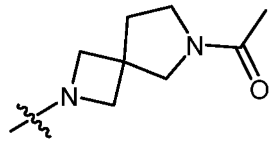
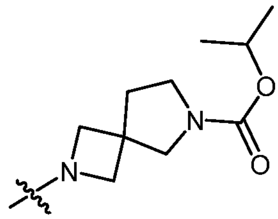
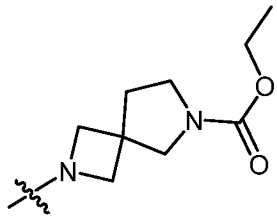
, or .

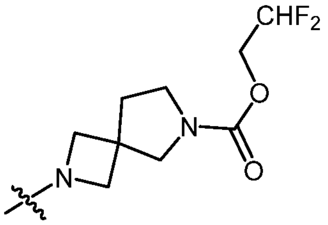
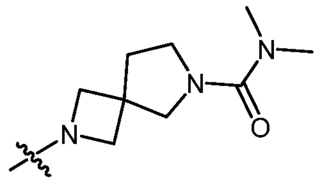
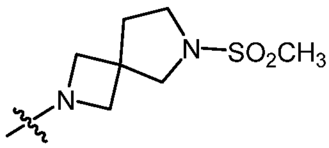
[00168] In certain embodiments of formula (xxvii), Ring B is of formula:

, , or .

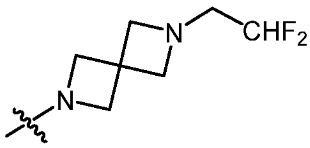
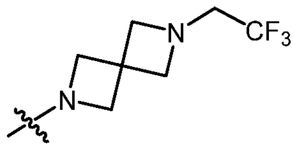
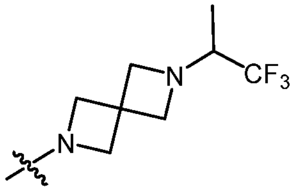
[00169] In certain embodiments of formula (xxvii), Ring B is of formula:

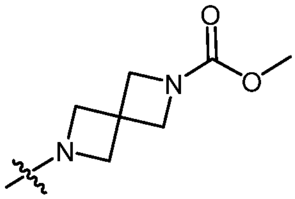
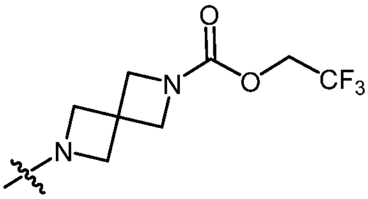
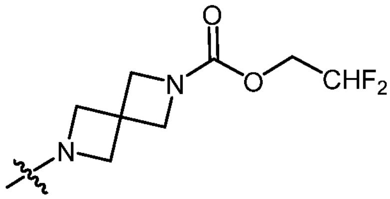
, , ,

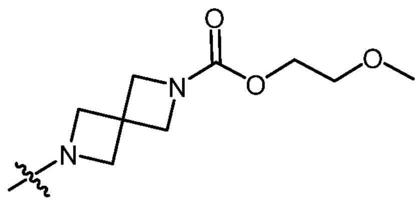
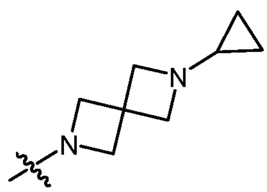
, , ,

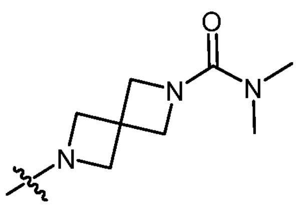
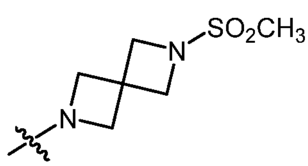
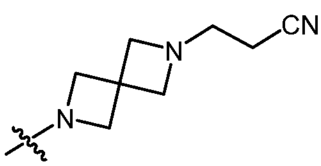
, , or .

[00170] In certain embodiments of formula (xxvii), Ring B is of formula:

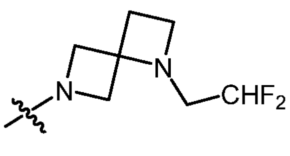
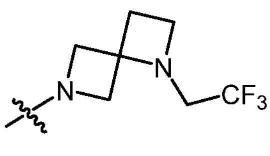
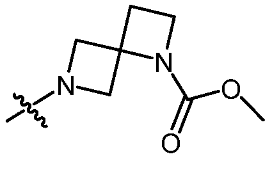
, , ,

. , ,

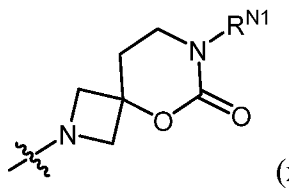
, ,

, , or .

[00171] In certain embodiments of formula (xxvii), Ring B is of formula:

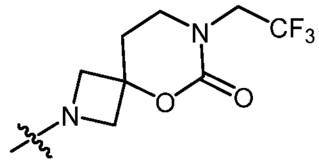
, , or .

[00172] In certain embodiments, Ring B is of formula:



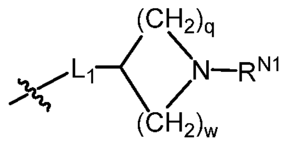
(xxviii).

[00173] In certain embodiments of formula (xxviii), Ring B is of formula:



.

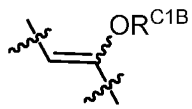
[00174] In certain embodiments, Ring B is of formula:



(viii),

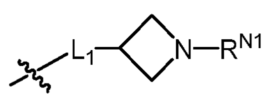
wherein L_1 is –NH–, substituted or unsubstituted C_2alkylene, substituted or unsubstituted C_2alkenylene, or substituted or unsubstituted C_2alkynylene.

[00175] In certain embodiments of formula (viii), L_1 is –NH–. In certain embodiments of formula (viii), L_1 is substituted or unsubstituted C_2alkylene. In certain embodiments of formula (viii), L_1 is substituted or unsubstituted C_2alkenylene. In certain embodiments of formula (viii), L_1 is substituted or unsubstituted C_2alkynylene. In certain embodiments of formula (viii), L_1 is an unsubstituted C_2alkylene, unsubstituted C_2alkenylene, or unsubstituted C_2alkynylene group. However, in certain embodiments of formula (viii), L_1 is a substituted C_2alkylene, substituted C_2alkenylene, or substituted C_2alkynylene group, *e.g.,* substituted with 1 R^{C1} group such as $-OR^{C1B}$ (*e.g.,* $-OCH_3$). Exemplary substituted L^1 groups include:

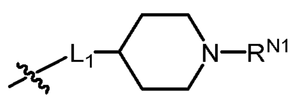


wherein R^{C1B} is as defined herein, excluding hydrogen.

[00176] Furthermore, in certain embodiments of formula (viii), q is 1, 2, or 3 and w is 1. In certain embodiments of formula (viii), q is 2 and w is 0 or 2. For example, in certain embodiments of formula (viii), Ring B is of formula:

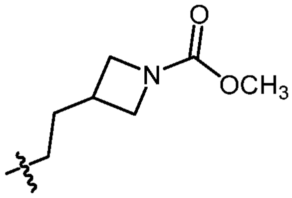
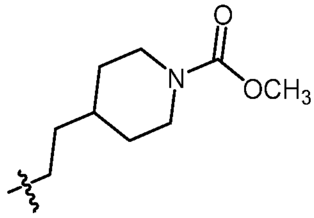
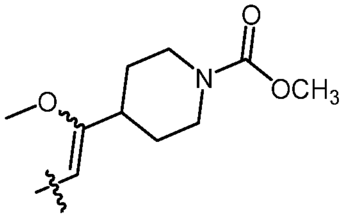


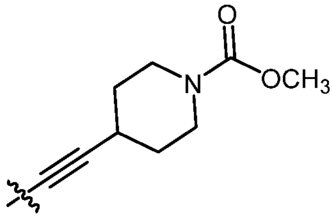
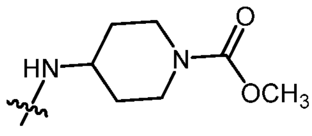
or



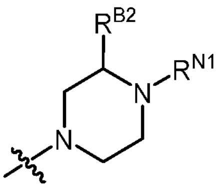
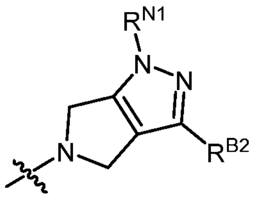
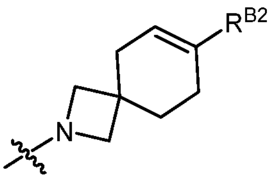
.

[00177] In certain embodiments of formula (viii), Ring B is of formula:

, , ,

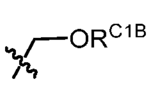
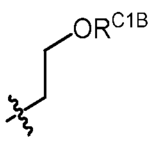
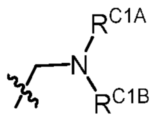
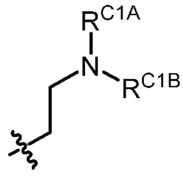
, or .

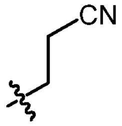
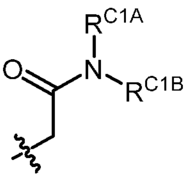
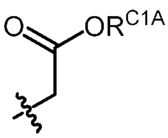
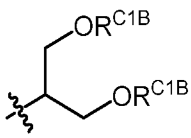
[00178] In certain embodiments, Ring B is of formula:

 (vii),  (ix), or  (xxiv),

wherein R^{B2} is hydrogen, halogen, -OR^{B2A}, substituted or unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl, and wherein R^{B2A} is substituted or unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl.

[00179] In certain embodiments, R^{B2} is hydrogen. In certain embodiments, R^{B2} is halogen, *e.g.,* -F, -Cl, -Br, or –I. In certain embodiments, R^{B2} is substituted or unsubstituted C_{1-3}alkyl, *i.e.*, a C_{1-3}alkyl substituted by 1, 2, or 3 R^{C1} groups as previously described herein, or an unsubstituted C_{1-3}alkyl. In certain embodiments, R^{B2} is unsubstituted C_{1-3}alkyl, *i.e.,* C_1 alkyl (-CH_3), unsubstituted C_2 alkyl (-CH_2CH_3), or unsubstituted C_3 alkyl (-$CH_2CH_2CH_3$ or -$CH(CH_3)_2$). In certain embodiments, R^{B2} is unsubstituted C_{1-3}alkyl of formula -CH_3, -CH_2CH_3, or -$CH(CH_3)_2$. In certain embodiments, R^{B2} is substituted C_{1-3}alkyl, *e.g.,* of formula:

, , , ,

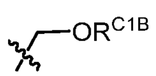
, , , or ,

wherein R^{C1A} and R^{C1B} are as defined herein.

[00180] In certain embodiments, R^{B2} is C_{1-3}haloalkyl, *e.g.,* C_1 haloalkyl (–CF_3, –CCl_3, –$CFCl_2$, –CF_2Cl, –CH_2F, -CHF_2, -CH_2Cl, $CHCl_2$), C_2 haloalkyl (–CF_2CF_3, -CH_2CF_3, -

CH_2CHF_2, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, R^{B2} is $-CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$.

[00181] In certain embodiments, R^{B2} is $-OR^{B2A}$, wherein R^{B2A} is substituted or unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl. In certain embodiments, R^{B2A} is substituted or unsubstituted C_{1-3}alkyl, *i.e.*, a C_{1-3}alkyl substituted by 1, 2, or 3 R^{C1} groups as previously described herein, or an unsubstituted C_{1-3}alkyl. In certain embodiments, R^{B2A} is unsubstituted C_{1-3}alkyl, *i.e.,* C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, R^{B2A} is unsubstituted C_{1-3}alkyl of formula $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$. In certain embodiments, R^{B2A} is substituted C_{1-3}alkyl, *e.g.,* of formula:



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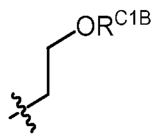

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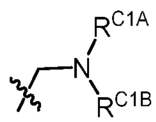

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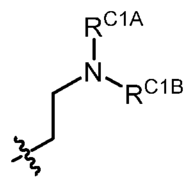

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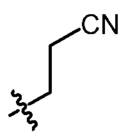

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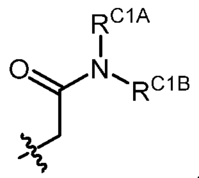

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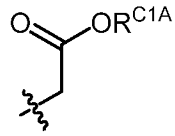
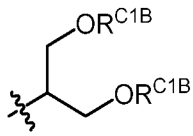


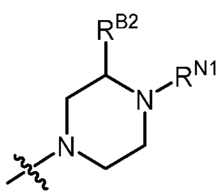
, or


,

wherein R^{C1A} and R^{C1B} are as defined herein.

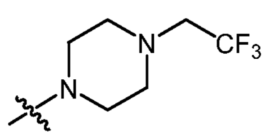
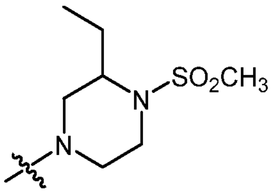
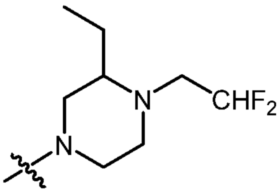
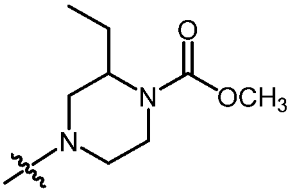
[00182] In certain embodiments, R^{B2} is hydrogen, $-OR^{B2A}$, $-F$, unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, or C_{1-3} alkyl substituted with $-OR^{C1B}$.

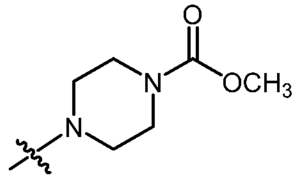
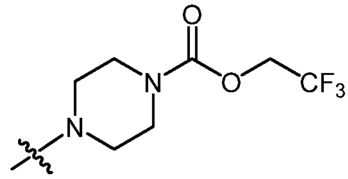
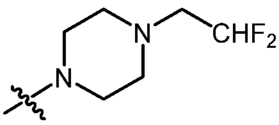
[00183] In certain embodiments, Ring B is of formula:



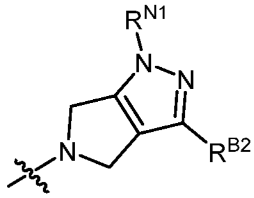
(vii).

[00184] In certain embodiments of formula (vii), R^{B2} is hydrogen or $-CH_3CH_3$. For example, in certain embodiments of formula (vii), Ring B is of formula:

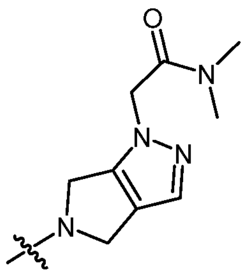
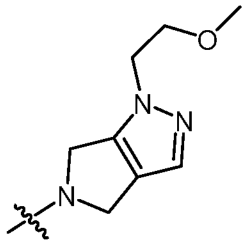
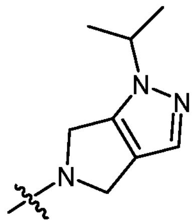
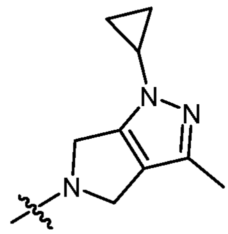
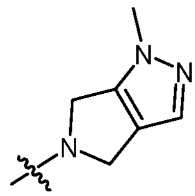
, , , 

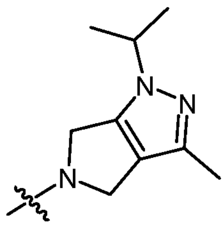
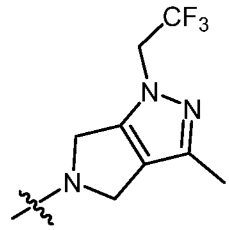
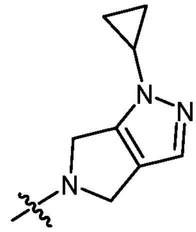
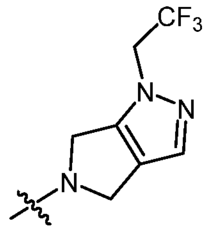
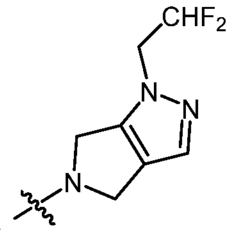
, , or .

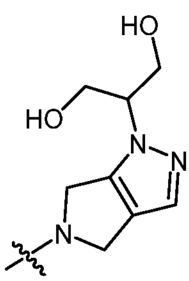
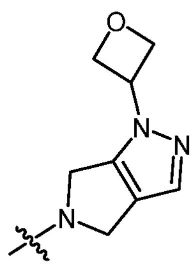
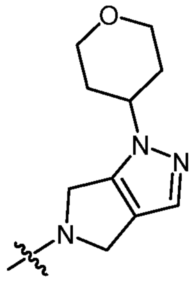
[00185] In certain embodiments, Ring B is of formula:

 (ix).

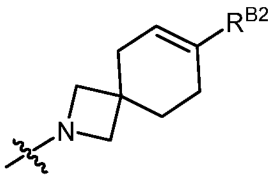
[00186] In certain embodiments of formula (ix), R^{B2} is hydrogen or $-CH_3$. For example, in certain embodiments of formula (ix), Ring B is of formula:

, , , , ,

, , , , ,

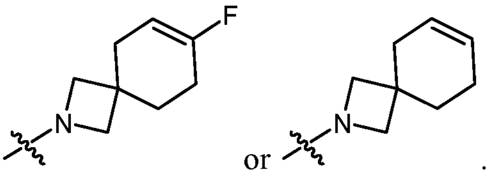
, , or .

[00187] In certain embodiments, Ring B is of formula:



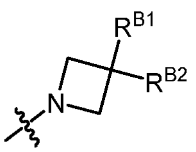
(xxiv).

[00188] In certain embodiments of formula (xxiv), R^{B2} is hydrogen or halogen (e.g., -F, -Cl, -Br, or –I). In certain embodiments of formula (xxiv), Ring B is of formula:

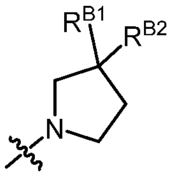


(VI) Ring B Groups comprising R^{B1} and optionally R^{B2}

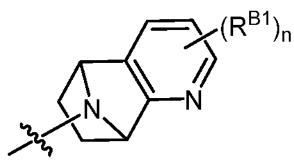
[00189] Group R^{B1}, and optionally group R^{B2}, are present in Ring B groups of formula (i), (ii), (iv), (xi), (xxiii), and (xxvi):



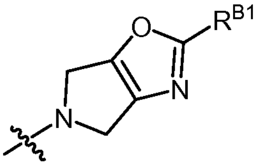
(i)



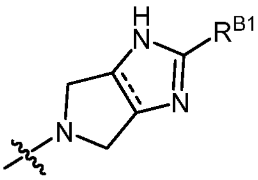
(ii)



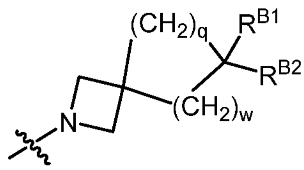
(iv)



(xi)



(xxiii)

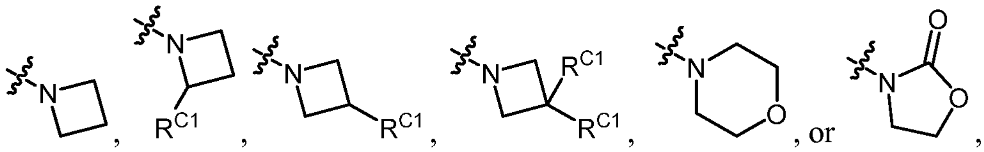


(xxvi)

[00190] Various embodiments of R^{B1} are contemplated herein. In particular, embodiments wherein R^{B1} is substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, halogen, -CN, -OR^{B1B}, -SR^{B1B}, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted 4- to 6-membered heterocyclyl, -C(=O)R^{B1A}, -C(=O)OR^{B1A}, -$S(O)_2R^{B1A}$, -OC(=O)R^{B1A}, -OC(=O)N(R^{B1A})(R^{B1B}), -OC(=O)OR^{B1A}, -NR^{BIB}C(=O)R^{B1A}, and -NR^{BIB}C(=O)OR^{B1A}, embodiments wherein R^{B2} is hydrogen, halogen, -OR^{B2A}, substituted or unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl, wherein R^{B2A} is substituted or unsubstituted C_{1-3}alkyl or C_{1-}

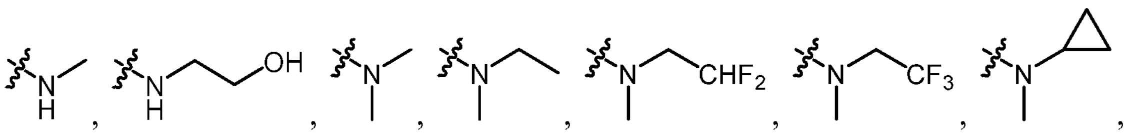
$_{3}$haloalkyl; or R^{B1} and R^{B2} are joined to form a substituted or unsubstituted 4- to 6-membered heterocyclyl, are contemplated herein.

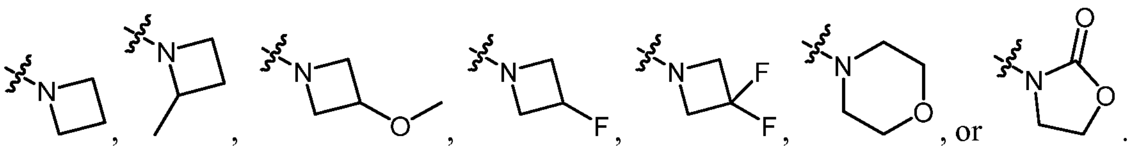
[00191] Embodiments wherein R^{B1} is -N(R^{B1A})(R^{B1B}), -C(=O)N(R^{B1A})(R^{B1B}), -OC(=O)N(R^{B1A})(R^{B1B}), or -NR^{BIB}C(=O)N(R^{B1A})(R^{B1B}) are contemplated in a preceding section. In certain embodiments, R^{B1} is -N(R^{B1A})(R^{B1B}), wherein R^{B1A} and R^{B1B} are as defined herein. In certain embodiments, R^{B1} is -C(=O)N(R^{B1A})(R^{B1B}), wherein R^{B1A} and R^{B1B} are as defined herein. In certain embodiments, R^{B1} is -OC(=O)N(R^{B1A})(R^{B1B}), or -NR^{BIB}C(=O)N(R^{B1A})(R^{B1B}) , wherein R^{B1A} and R^{B1B} are as defined herein. For example, in certain embodiments, R^{B1} is -N(R^{B1A})(R^{B1B}), -C(=O)N(R^{B1A})(R^{B1B}), -OC(=O)N(R^{B1A})(R^{B1B}), or -NR^{BIB}C(=O)N(R^{B1A})(R^{B1B}), wherein the group -N(R^{B1A})(R^{B1B}) is of the formula:



wherein R^{C1} is as defined herein.

[00192] In certain embodiments, R^{B1} is -N(R^{B1A})(R^{B1B}), -C(=O)N(R^{B1A})(R^{B1B}), -OC(=O)N(R^{B1A})(R^{B1B}), or -NR^{BIB}C(=O)N(R^{B1A})(R^{B1B}), wherein the group -N(R^{B1A})(R^{B1B}) is of the formula:



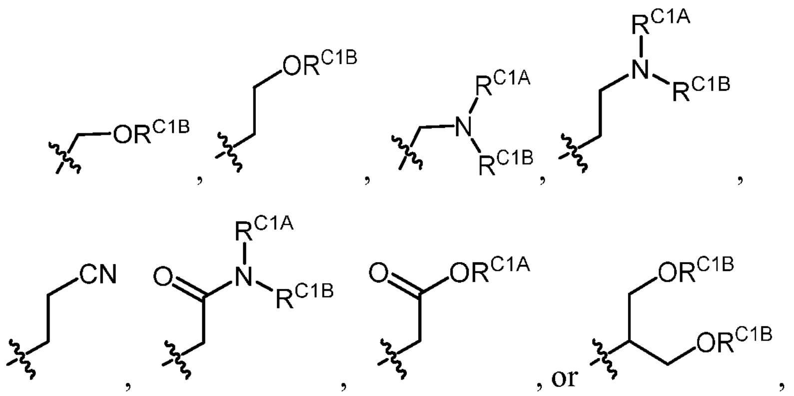


[00193] In certain embodiments, R^{B1} is halogen, i.e., -F, -Cl, -Br, or –I.

[00194] In certain embodiments, R^{B1} is –CN.

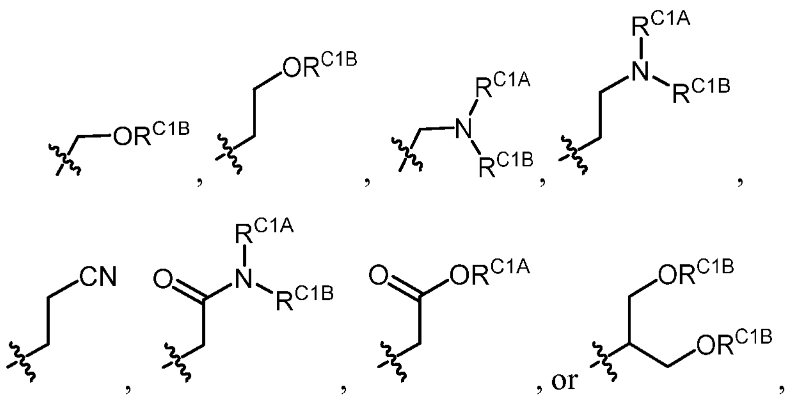
[00195] In certain embodiments, R^{B1} is -OR^{B1B} or -SR^{B1B}, wherein R^{B1B} is hydrogen, substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_{3-6} carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl. In certain embodiments, R^{B1} is -OR^{B1B} or -SR^{B1B}, wherein R^{B1B} is substituted or unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl. In certain embodiments, R^{B1} is -OR^{B1B} or -SR^{B1B}, wherein R^{B1B} is substituted or unsubstituted C_{1-3}alkyl, *i.e.*, a C_{1-3}alkyl substituted by 1, 2, or 3 R^{C1} groups as previously described herein, or an unsubstituted C_{1-3}alkyl. In certain embodiments, R^{B1} is -OR^{B1B} or -SR^{B1B}, wherein R^{B1B} is unsubstituted C_{1-3}alkyl, *i.e.,* C_1 alkyl (-CH_3), unsubstituted

C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, R^{B1} is $-OR^{B1B}$ or $-SR^{B1B}$, wherein R^{B1B} is unsubstituted $C_{1\text{-}3}$alkyl of formula $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$. In certain embodiments, R^{B1} is $-OR^{B1B}$ or $-SR^{B1B}$, wherein R^{B1B} is substituted $C_{1\text{-}3}$alkyl, *e.g.,* of formula:



wherein R^{C1A} and R^{C1B} are as defined herein.

[00196] In certain embodiments, R^{B1} is substituted or unsubstituted $C_{1\text{-}3}$alkyl, *i.e.*, a $C_{1\text{-}3}$alkyl substituted by 1, 2, or 3 R^{C1} groups as previously described herein, or an unsubstituted $C_{1\text{-}3}$alkyl. In certain embodiments, R^{B1} is unsubstituted $C_{1\text{-}3}$alkyl, *i.e.,* C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, R^{B1} is unsubstituted $C_{1\text{-}3}$alkyl of formula $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$. In certain embodiments, R^{B1} is substituted $C_{1\text{-}3}$alkyl, *e.g.,* of formula:



wherein R^{C1A} and R^{C1B} are as defined herein.

[00197] In certain embodiments, R^{B1} is $C_{1\text{-}3}$haloalkyl, *e.g.,* C_1 haloalkyl ($-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, R^{B1} is $-CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$.

[00198] In certain embodiments, R^{B1} is substituted or unsubstituted C_{3-6}carbocylyl. In certain embodiments, R^{B1} is substituted or unsubstituted C_3carbocylyl (*e.g.,* substituted or unsubstituted cyclopropyl). In certain embodiments, such groups are unsubstituted by R^{C1}. In other embodiments, such groups are substituted, *e.g.,* wherein at least one instance of R^{C1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, -OR^{C1A} (*e.g.,* -OH, -OCH_3), or unsubstituted C_{1-3}alkyl (*e.g.,* -CH_3, -CH_2CH_3).

[00199] In certain embodiments, R^{B1} is substituted or unsubstituted 4-6 membered heterocyclyl. In certain embodiments, R^{B1} is a substituted or unsubstituted 4- membered heterocyclyl (*e.g.,* azetidinyl), substituted or unsubstituted 5-membered heterocyclyl (*e.g.,* pyrrolidinyl, pyrrolidin-2-one, oxazolidin-2-one), or substituted or unsubstituted 6-membered heterocyclyl (*e.g.,* morpholinyl, piperidinyl, piperazinyl). In certain embodiments, such groups are unsubstituted by R^{C1}. In other embodiments, such groups are substituted, *e.g.,* wherein at least one instance of R^{C1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, -OR^{C1A} (*e.g.,* -OH, -OCH_3), or unsubstituted C_{1-3}alkyl (*e.g.,* -CH_3, -CH_2CH_3).

[00200] In certain embodiments, R^{B1} is -C(=O)R^{B1A}, -C(=O)OR^{B1A}, -OC(=O)R^{B1A}, -OC(=O)OR^{B1A}, -NR^{B1B}C(=O)R^{B1A}, -NR^{B1B}C(=O)OR^{B1A}, or -$S(O)_2R^{B1A}$, wherein R^{B1A} is substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_{3-6} carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl, and R^{B1B} is as defined herein.

[00201] In certain embodiments, R^{B1} is -C(=O)R^{B1A}, -C(=O)OR^{B1A}, -OC(=O)R^{B1A}, -OC(=O)OR^{B1A}, -NR^{B1B}C(=O)R^{B1A}, -NR^{B1B}C(=O)OR^{B1A}, or -$S(O)_2R^{B1A}$ wherein R^{B1A} is unsubstituted C_{1-3}alkyl, *i.e.*, unsubstituted C_1 alkyl (-CH_3), unsubstituted C_2 alkyl (-CH_2CH_3), or unsubstituted C_3 alkyl (-$CH_2CH_2CH_3$ or -$CH(CH_3)_2$).

[00202] In certain embodiments, R^{B1} is C(=O)R^{B1A}, -C(=O)OR^{B1A}, -OC(=O)R^{B1A}, -OC(=O)OR^{B1A}, -NR^{B1B}C(=O)R^{B1A}, -NR^{B1B}C(=O)OR^{B1A}, or -$S(O)_2R^{B1A}$ wherein R^{B1A} is C_{1-3}haloalkyl, *e.g.,* C_1 haloalkyl (–CF_3, –CCl_3, –$CFCl_2$, –CF_2Cl, –CH_2F, -CHF_2, -CH_2Cl, $CHCl_2$), C_2 haloalkyl (–CF_2CF_3, -CH_2CF_3, -CH_2CHF_2, -CH_2CH_2F, -CH_2CCl_3, -CH_2CHCl_2, -CH_2CH_2Cl), or C_3 haloalkyl (–$CF_2CF_2CF_3$, –$CH_2CF_2CF_3$, -$CH_2CH_2CF_3$, -$CH_2CH_2CHF_2$, -$CH_2CH_2CH_2F$, - $CH_2CH_2CCl_3$, - $CH_2CH_2CHCl_2$, - $CH_2CH_2CH_2Cl$, -$CH(CH_3)CHF_2$, or -$CH(CH_3)CF_3$). In certain embodiments, R^{B1} is C(=O)R^{B1A}, -C(=O)OR^{B1A}, -OC(=O)R^{B1A}, -OC(=O)OR^{B1A}, -NR^{B1B}C(=O)R^{B1A}, -NR^{B1B}C(=O)OR^{B1A}, or -$S(O)_2R^{B1A}$ wherein R^{B1A} is –CF_3, –CH_2F, -CHF_2, -CH_2Cl, -CH_2CF_3, -CH_2CHF_2, -$CH(CH_3)CHF_2$, or -$CH(CH_3)CF_3$.

[00203] In certain embodiments, R^{B1} is C(=O)R^{B1A}, -C(=O)OR^{B1A}, -OC(=O)R^{B1A}, -OC(=O)OR^{B1A}, -NR^{B1B}C(=O)R^{B1A}, -NR^{B1B}C(=O)OR^{B1A}, or -$S(O)_2R^{B1A}$ wherein R^{B1A} is substituted or unsubstituted C_{3-6}carbocylyl or substituted or unsubstituted 4-6 membered heterocyclyl. In certain embodiments, R^{B1} $C(=O)R^{B1A}$, $-C(=O)OR^{B1A}$, $-OC(=O)R^{B1A}$, $-OC(=O)OR^{B1A}$, $-NR^{B1B}C(=O)R^{B1A}$, $-NR^{B1B}C(=O)OR^{B1A}$, or $-S(O)_2R^{B1A}$ wherein R^{B1A} is substituted or unsubstituted C_3carbocylyl (*e.g.,* cyclopropyl). In certain embodiments, R^{B1} is $C(=O)R^{B1A}$, $-C(=O)OR^{B1A}$, $-OC(=O)R^{B1A}$, $-OC(=O)OR^{B1A}$, $-NR^{B1B}C(=O)R^{B1A}$, $-NR^{B1B}C(=O)OR^{B1A}$, or $-S(O)_2R^{B1A}$ wherein R^{B1A} is substituted or unsubstituted 4- membered heterocyclyl (*e.g.,* azetidinyl, oxetanyl). In certain embodiments, R^{B1} is $C(=O)R^{B1A}$, $-C(=O)OR^{B1A}$, $-OC(=O)R^{B1A}$, $-OC(=O)OR^{B1A}$, $-NR^{B1B}C(=O)R^{B1A}$, $-NR^{B1B}C(=O)OR^{B1A}$, or $-S(O)_2R^{B1A}$ wherein R^{B1A} is substituted or unsubstituted 5-membered heterocyclyl (*e.g.,* tetrahydrofuranyl). In certain embodiments, R^{B1} is $C(=O)R^{B1A}$, $-C(=O)OR^{B1A}$, $-OC(=O)R^{B1A}$, $-OC(=O)OR^{B1A}$, $-NR^{B1B}C(=O)R^{B1A}$, $-NR^{B1B}C(=O)OR^{B1A}$, or $-S(O)_2R^{B1A}$ wherein R^{B1A} is substituted or unsubstituted 6-membered heterocyclyl (*e.g.,* tetrahydropyranyl). In certain embodiments, such groups are unsubstituted by R^{C1}. In other embodiments, such groups are substituted, *e.g.,* wherein at least one instance of R^{C1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, $-OR^{C1A}$ (*e.g.,* -OH, $-OCH_3$), or unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$).

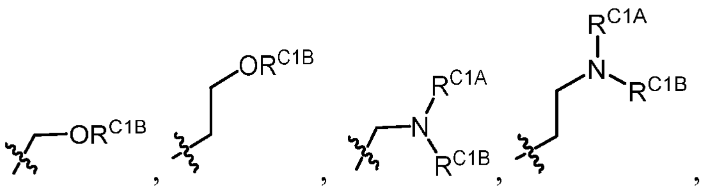
[00204] In certain embodiments, R^{B1} is unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, C_{1-3} alkyl substituted with $-OR^{C1B}$, C_{1-3} alkyl substituted with $-N(R^{C1A})(R^{C1B})$, C_{1-3}alkyl substituted with –CN, C_{1-3} alkyl substituted with $-C(=O)N(R^{C1A})(R^{C1B})$, C_{1-3} alkyl substituted with $-C(=O)OR^{C1A}$, $-C(=O)N(R^{B1A})(R^{B1B})$, $-OC(=O)OR^{B1A}$, $-N(R^{B1A})(R^{B1B})$, $-OR^{B1B}$, $-SR^{B1B}$, $-S(O)_2R^{B1A}$, -F, -Cl, –CN, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl.

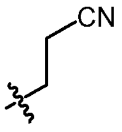
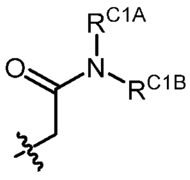
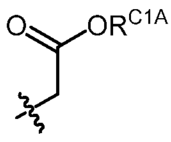
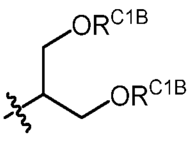
[00205] In certain embodiments, R^{B1} is:

(a) unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$); or

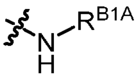
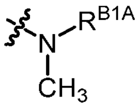
(b) C_{1-3}haloalkyl (*e.g.,* $-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$, $-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$, $-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, $-CH(CH_3)CF_3$); or

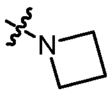
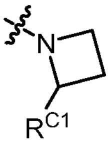
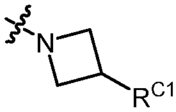
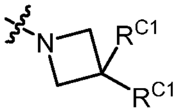
(c) substituted C_{1-3} alkyl, *e.g.,*

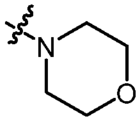
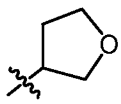
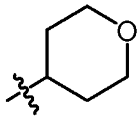
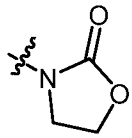


, , , or ; or

(d) $-N(R^{B1A})(R^{B1B})$, as previously contemplated, *e.g.*,

, ,

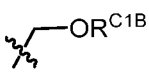
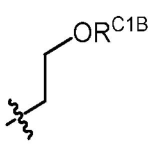
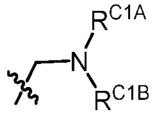
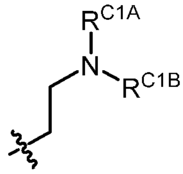
, , , ,

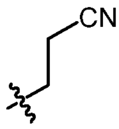
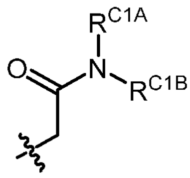
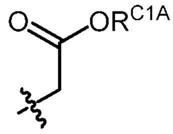
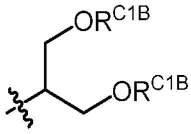
, , , , or ; or

(e) substituted or unsubstituted C_3 carbocyclyl (*e.g.*, );

[00206] Furthermore, as generally defined herein, in certain embodiments, R^{B2} is hydrogen, halogen, $-OR^{B2A}$, substituted or unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl, wherein R^{B2A} is substituted or unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl.

[00207] In certain embodiments, R^{B2} is hydrogen. In certain embodiments, R^{B2} is halogen, *e.g.*, -F, -Cl, -Br, or –I. In certain embodiments, R^{B2} is substituted or unsubstituted C_{1-3}alkyl, *i.e.*, a C_{1-3}alkyl substituted by 1, 2, or 3 R^{C1} groups as previously described herein, or an unsubstituted C_{1-3}alkyl. In certain embodiments, R^{B2} is unsubstituted C_{1-3}alkyl, *i.e.*, C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, R^{B2} is unsubstituted C_{1-3}alkyl of formula $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$. In certain embodiments, R^{B2} is substituted C_{1-3}alkyl, *e.g.*, of formula:

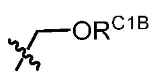
, , , ,

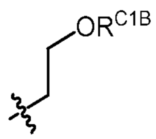
, , , or ,

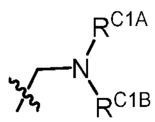
wherein R^{C1A} and R^{C1B} are as defined herein.

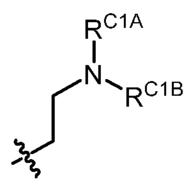
[00208] In certain embodiments, R^{B2} is $C_{1\text{-}3}$haloalkyl, *e.g.,* C_1 haloalkyl ($-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, R^{B2} is $-CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$.

[00209] In certain embodiments, R^{B2} is $-OR^{B2A}$, wherein R^{B2A} is substituted or unsubstituted $C_{1\text{-}3}$alkyl or $C_{1\text{-}3}$haloalkyl. In certain embodiments, R^{B2A} is substituted or unsubstituted $C_{1\text{-}3}$alkyl, *i.e.*, a $C_{1\text{-}3}$alkyl substituted by 1, 2, or 3 R^{C1} groups as previously described herein, or an unsubstituted $C_{1\text{-}3}$alkyl. In certain embodiments, R^{B2A} is unsubstituted $C_{1\text{-}3}$alkyl, *i.e.,* C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, R^{B2A} is unsubstituted $C_{1\text{-}3}$alkyl of formula $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$. In certain embodiments, R^{B2A} is substituted $C_{1\text{-}3}$alkyl, *e.g.,* of formula:



, 

, 

, 

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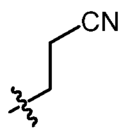
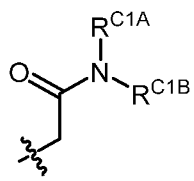
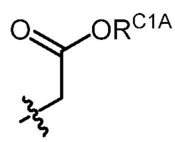
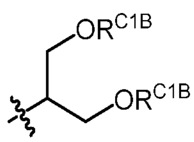


, 

, 

, or 

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wherein R^{C1A} and R^{C1B} are as defined herein.

[00210] In certain embodiments, R^{B2} is hydrogen, $-OR^{B2A}$, $-F$, unsubstituted $C_{1\text{-}3}$ alkyl, $C_{1\text{-}3}$haloalkyl, or $C_{1\text{-}3}$ alkyl substituted with $-OR^{C1B}$.

[00211] In certain embodiments, wherein R^{B1} and R^{B2} are each present on Ring B, such as Ring B of formula (i), (ii), or (xxvi), various combinations of R^{B1} and R^{B2} are contemplated herein. For example, in certain embodiments, the following R^{B1} and R^{B2} combinations are specifically contemplated:

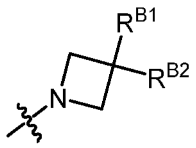
a. R^{B1} is $-N(R^{B1A})(R^{B1B})$, $-OR^{B1B}$, $-SR^{B1B}$, $-S(O)_2R^{B1A}$, -F, -Cl, $-CN$, $-OC(=O)OR^{B1A}$, $-C(=O)N(R^{B1A})(R^{B1B})$, and R^{B2} is hydrogen; or
b. R^{B1} is -F and R^{B2} is $-F$; or

c. R^{B1} is -OR^{B1B}, -C(=O)N(R^{B1A})(R^{B1B}), –CN , or C_{1-3} alkyl substituted with -OR^{C1B}, C_{1-3} alkyl substituted with -N(R^{C1A})(R^{C1B}), and R^{B2} is substituted or unsubstituted C_{1-3} alkyl or C_{1-3}haloalkyl; or

d. R^{B1} is -OR^{B1B} and R^{B2} is -OR^{B2A}, and each instance of R^{B1B} and R^{B2A} is independently substituted or unsubstituted C_{1-3} alkyl or C_{1-3}haloalkyl.

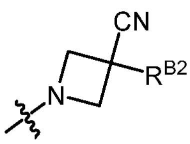
[00212] Furthermore, as generally defined herein, in certain embodiments, R^{B1} and R^{B2} are joined to form a substituted or unsubstituted 4- to 6-membered heterocyclyl, *e.g.,* a substituted or unsubstituted 4-membered heterocyclyl, a substituted or unsubstituted 5-membered heterocyclyl, or a substituted or unsubstituted 6-membered heterocyclyl. For example, in certain embodiments, wherein R^{B1} is -OR^{B1B} and R^{B2} is -OR^{B2A}, R^{B1B} and R^{B2A} are joined to form a substituted or unsubstituted 5- membered heterocyclyl (*e.g.,* dioxolanyl) or substituted or unsubstituted 6- membered heterocyclyl (*e.g.,* dioxanyl).

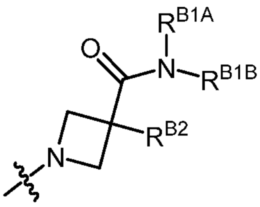
[00213] In certain embodiments, Ring B is of formula:

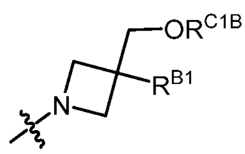


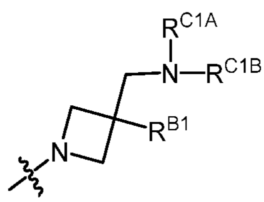
(i).

[00214] In certain embodiments of formula (i), Ring B is of formula:



, 

, 

, or 

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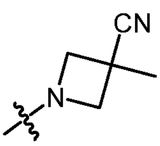
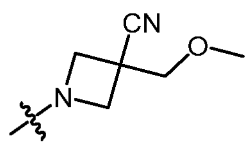
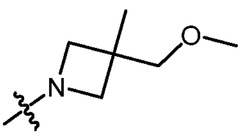
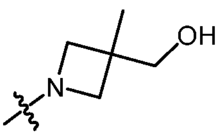
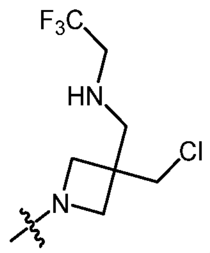
[00215] In certain embodiments of formula (i), Ring B is of formula:



, 

, 

, 

, 

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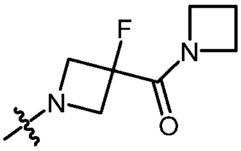
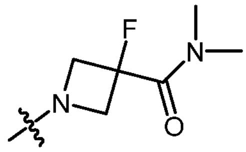
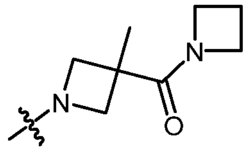
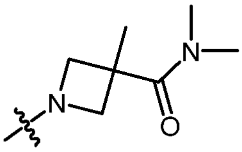


, 

, 

, 

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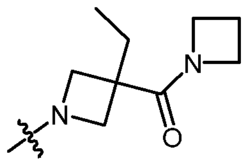
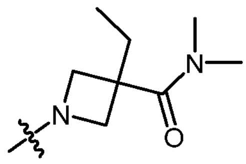
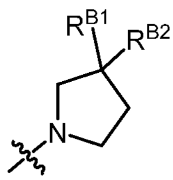
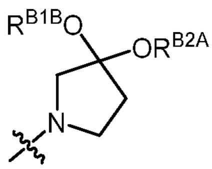
, or  .

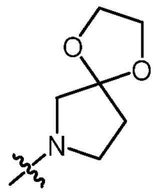
[00216] In certain embodiments, Ring B is of formula:


(ii).

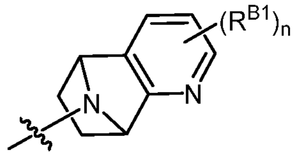
[00217] In certain embodiments of formula (ii), Ring B is of formula:


.

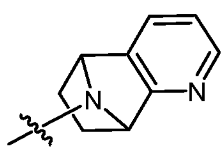
[00218] In certain embodiments of formula (ii), Ring B is of formula:


.

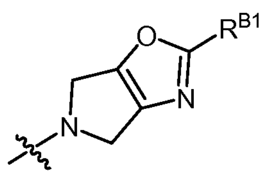
[00219] In certain embodiments, Ring B is of formula:


(iv).

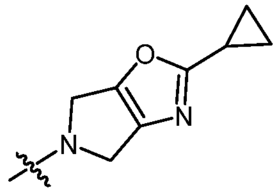
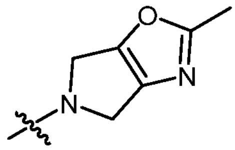
[00220] In certain embodiments of formula (iv), Ring B is of formula:


.

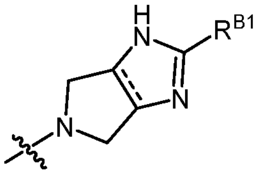
[00221] In certain embodiments, Ring B is of formula:


(xi).

[00222] In certain embodiments of formula (xi), Ring B is of formula:

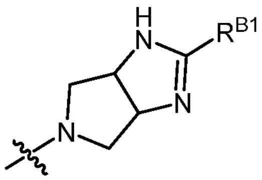
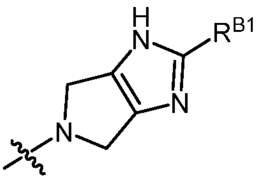
 or  .

[00223] In certain embodiments, Ring B is of formula:

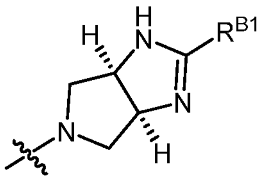
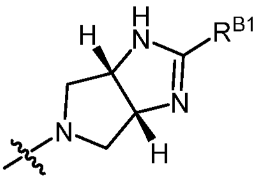
 (xxiii).

[00224] In certain embodiments of formula (xxiii), $=\!=\!=$ represents a single bond. In certain embodiments of formula (xxiii), $=\!=\!=$ represents a single bond, and the ring fusion is in the *trans* configuration. In certain embodiments of formula (xxiii), $=\!=\!=$ represents a single bond, and the ring fusion is in the *cis* configuration. In certain embodiments of formula (xxiii), $=\!=\!=$ represents a double bond.

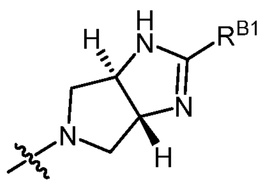
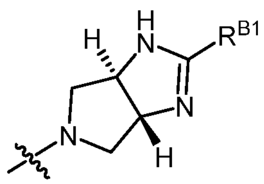
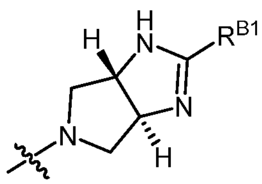
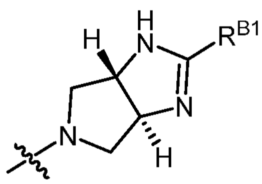
[00225] In certain embodiments, Ring B is of formula:

 or  .

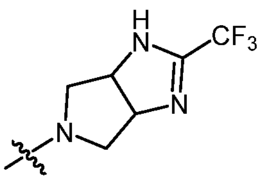
[00226] In certain embodiments, Ring B is of formula:

 or  .

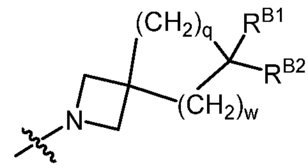
[00227] In certain embodiments, Ring B is of formula:

 ,  ,  , or  .

[00228] In certain embodiments of formula (xxiii), Ring B is of formula:

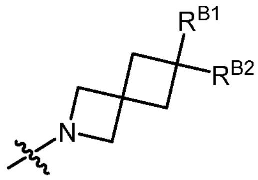
 .

[00229] In certain embodiments, Ring B is of formula:

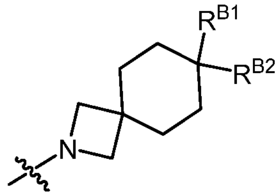


(xxvi).

[00230] In certain embodiments of formula (xxvii), q is 1, 2, or 3 and w is 1. In certain embodiments of formula (xxvii), q is 2 and w is 0 or 2. For example, in certain embodiments of formula (xxvii), Ring B is of formula:



,



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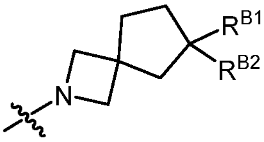
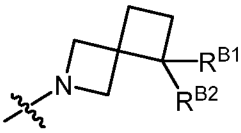
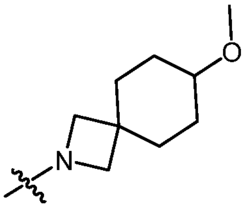


, or



.

[00231] In certain embodiments of formula (xxvii), Ring B is of formula:



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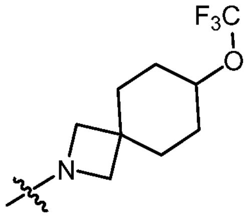

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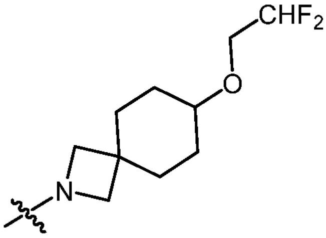

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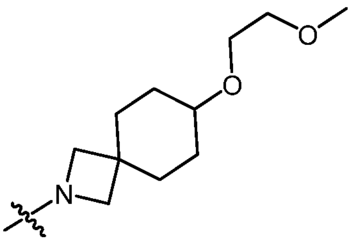

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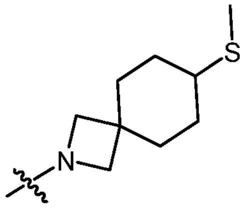

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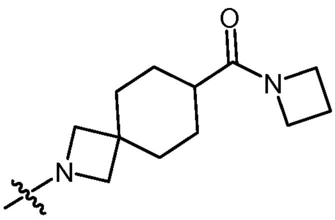

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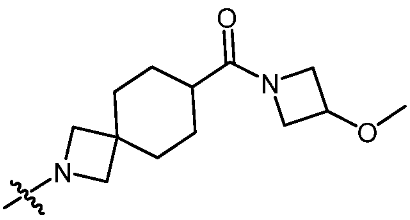

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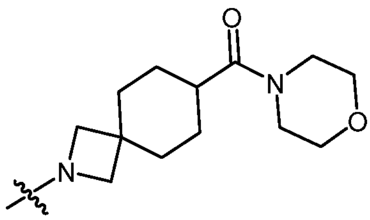

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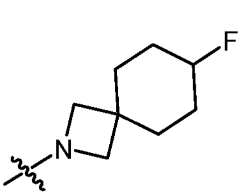

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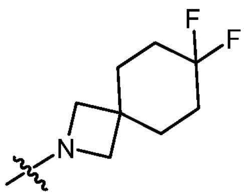

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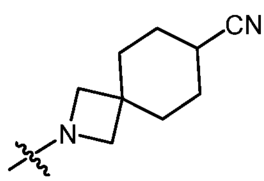

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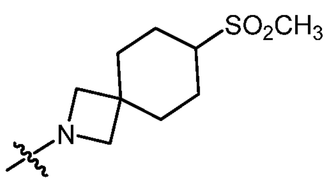
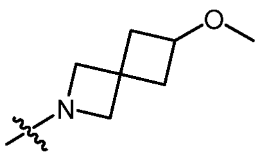
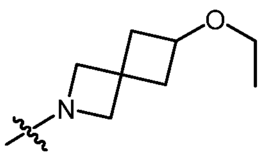
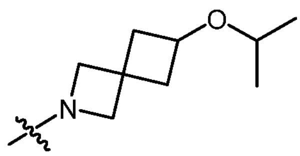
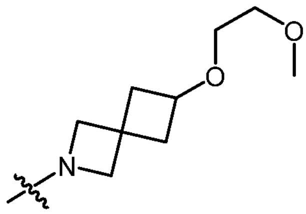
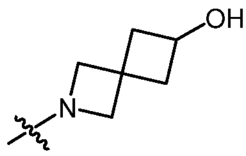
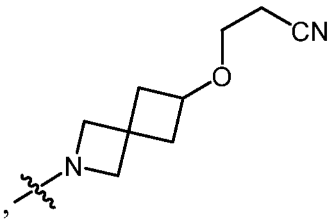
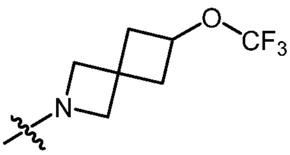
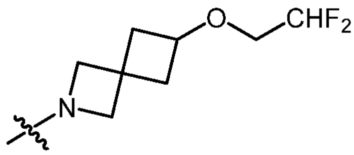
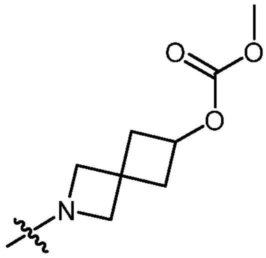


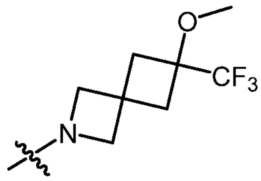
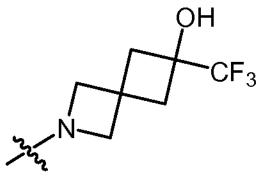
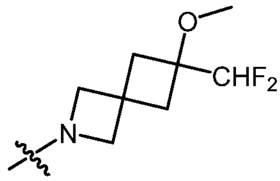
.

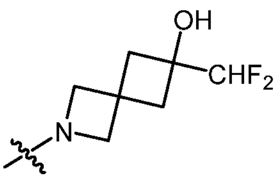
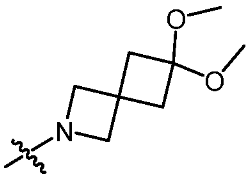
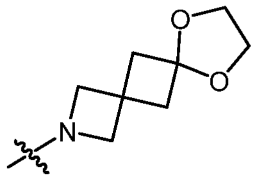
[00232] In certain embodiments of formula (xxvii), Ring B is of formula:

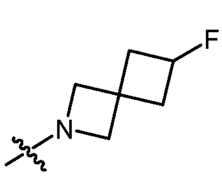
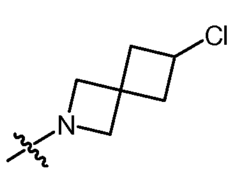
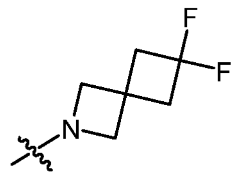
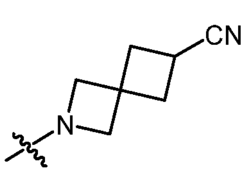
, , ,

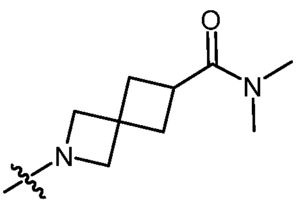
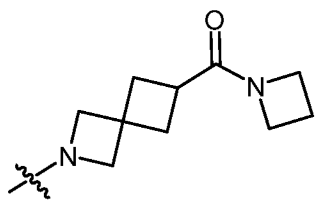
, , ,

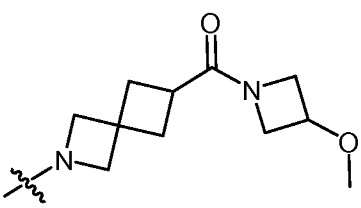
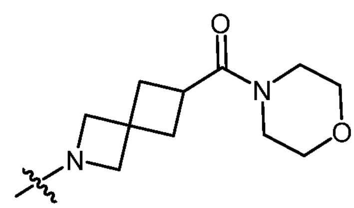
, , ,

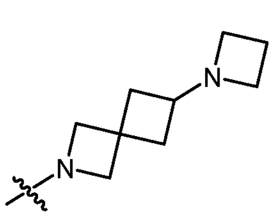
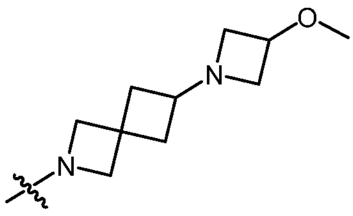
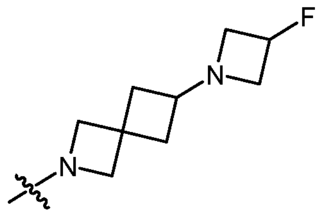
, , ,

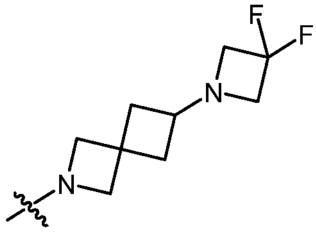
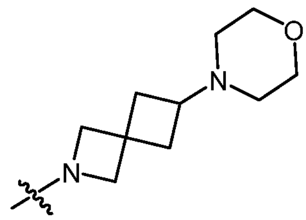
, , ,

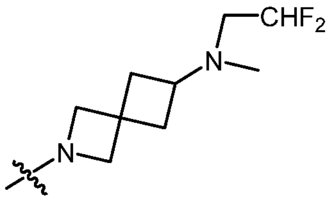
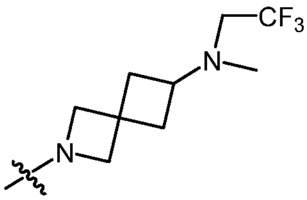
, , , ,

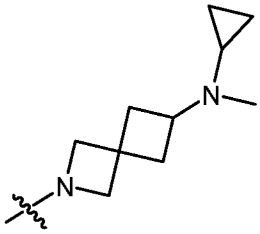
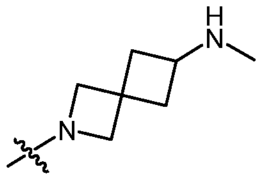
, ,

, ,

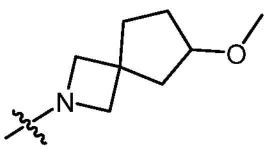
 ,  ,  ,

 ,  ,

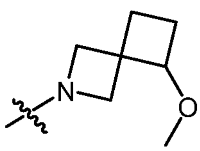
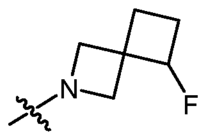
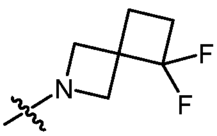
 ,  ,

 , or  .

[00233] In certain embodiments of formula (xxvii), Ring B is of formula:

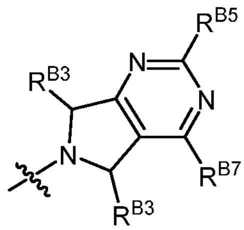
 .

[00234] In certain embodiments of formula (xxvii), Ring B is of formula:

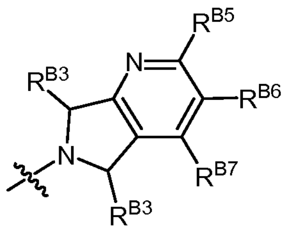
 ,  , or  .

(VII) Ring B: Groups comprising R^{N2}, R^{B3}, R^{B4}, R^{B5}, R^{B6}, and/or R^{B7}

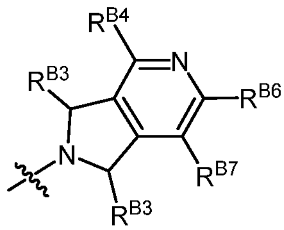
[00235] Groups R^{N2}, R^{B3}, R^{B4}, R^{B5}, R^{B6}, and/or $R^{B7}$are provided in Ring B groups of formula (xiv), (xv), (xvi), (xvii), (xviii), (xix), (xx), and (xxi):



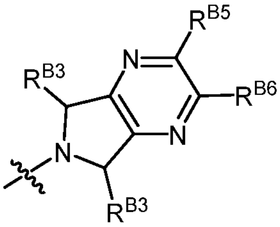
(xiv)



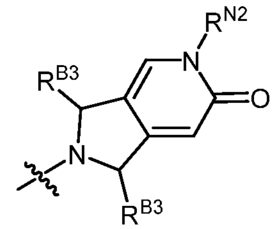
(xv)



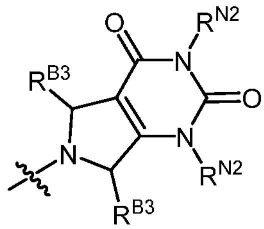
(xvi)



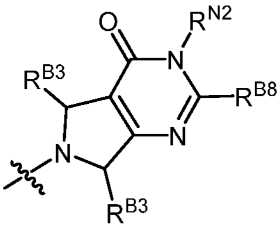
(xvii)



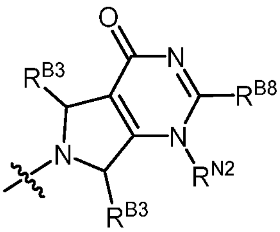
(xviii)



(xix)



(xx)

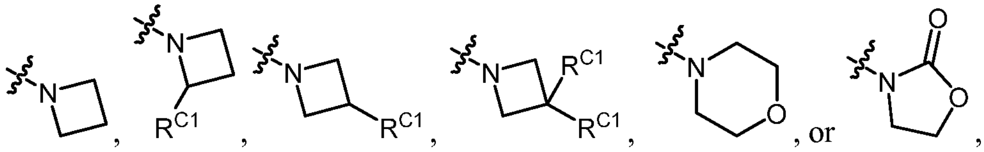


(xxi)

[00236] Various embodiments of R^{B4}, R^{B5}, R^{B6}, and $R^{B7}$are contemplated herein. In particular, embodiments wherein at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is hydrogen, substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, halogen, -CN, -OR^{B4B}, -SR^{B4B}, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted 4- to 6-membered heterocyclyl, -C(=O)R^{B4A}, -C(=O)OR^{B4A}, -S(O)$_2R^{B4A}$, -OC(=O)R^{B4A}, -OC(=O)N(R^{B4A})(R^{B4B}), -OC(=O)OR^{B4A}, -NR^{B4B}C(=O)R^{B4A}, and -NR^{B4B}C(=O)OR^{B4A}.

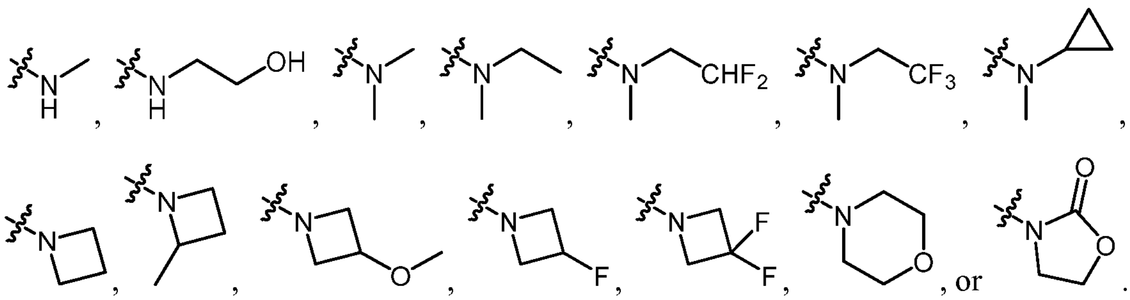
[00237] Embodiments wherein R^{B4}, R^{B5}, R^{B6}, or R^{B7} is -N(R^{B4A})(R^{B4B}), -C(=O)N(R^{B4A})(R^{B4B}), -OC(=O)N(R^{B4A})(R^{B4B}), or -NR^{B4B}C(=O)N(R^{B4A})(R^{B4B}) are contemplated in a preceding section. In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is -N(R^{B4A})(R^{B4B}), wherein R^{B4A} and R^{B4B} are as defined herein. In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is -C(=O)N(R^{B4A})(R^{B4B}), wherein R^{B4A} and R^{B4B} are as defined herein. In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is-OC(=O)N(R^{B4A})(R^{B4B}), or -NR^{B4B}C(=O)N(R^{B4A})(R^{B4B}) , wherein R^{B4A} and R^{B4B} are as defined herein. For example, in certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7}

is -N(R^{B4A})(R^{B4B}), -C(=O)N(R^{B4A})(R^{B4B}), -OC(=O)N(R^{B4A})(R^{B4B}), or -NR^{B4B}C(=O)N(R^{B4A})(R^{B4B}), wherein the group -N(R^{B4A})(R^{B4B}) is of the formula:



wherein R^{C1} is as defined herein.

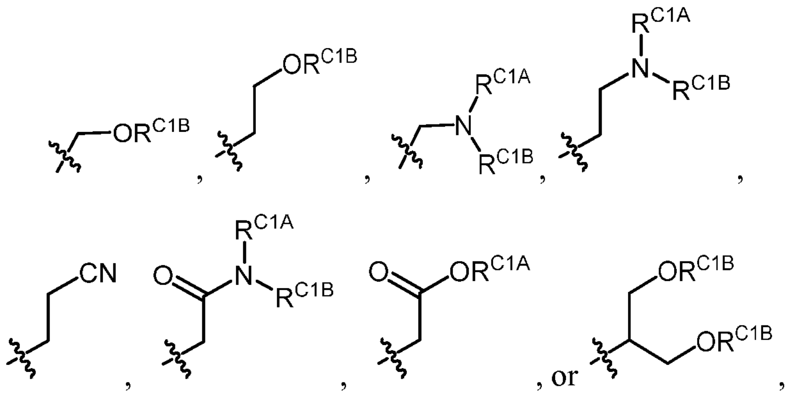
[00238] In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is -N(R^{B4A})(R^{B4B}), -C(=O)N(R^{B4A})(R^{B4B}), -OC(=O)N(R^{B4A})(R^{B4B}), or -NR^{B4B}C(=O)N(R^{B4A})(R^{B4B}), wherein the group -N(R^{B4A})(R^{B4B}) is of the formula:



[00239] In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is hydrogen. In certain embodiments, two of R^{B4}, R^{B5}, R^{B6}, and R^{B7} are hydrogen. In certain embodiments, each of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is hydrogen.

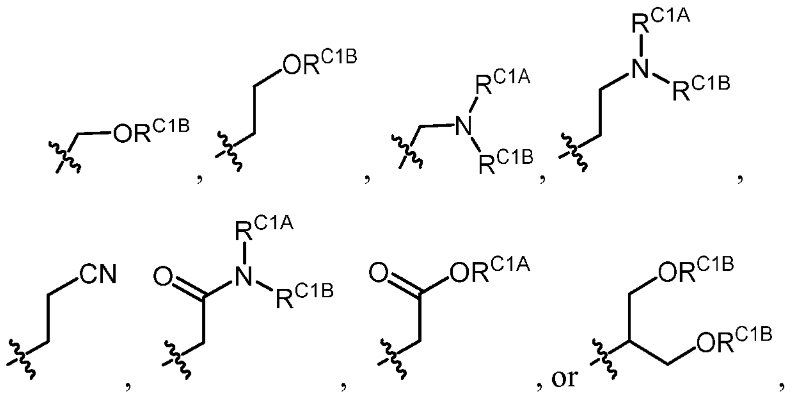
[00240] In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is halogen, *i.e.,* -F, -Cl, -Br, or –I. In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is –CN.

[00241] In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is -OR^{B4B} or -SR^{B4B}, wherein R^{B4B} is hydrogen, substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_{3-6} carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl. In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is -OR^{B4B} or -SR^{B4B}, wherein R^{B4B} is substituted or unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is -OR^{B4B} or -SR^{B4B}, wherein R^{B4B} is substituted or unsubstituted C_{1-3}alkyl, *i.e.*, a C_{1-3}alkyl substituted by 1, 2, or 3 R^{C1} groups as previously described herein, or an unsubstituted C_{1-3}alkyl. In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is -OR^{B4B} or -SR^{B4B}, wherein R^{B4B} is unsubstituted C_{1-3}alkyl, *i.e.,* C_1 alkyl (-CH_3), unsubstituted C_2 alkyl (-CH_2CH_3), or unsubstituted C_3 alkyl (-$CH_2CH_2CH_3$ or -$CH(CH_3)_2$). In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is -OR^{B4B} or -SR^{B4B}, wherein R^{B4B} is unsubstituted C_{1-3}alkyl of formula -CH_3, -CH_2CH_3, or -$CH(CH_3)_2$. In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is -OR^{B4B} or -SR^{B4B}, wherein R^{B4B} is substituted C_{1-3}alkyl, *e.g.,* of formula:



wherein R^{C1A} and R^{C1B} are as defined herein.

[00242] In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is substituted or unsubstituted $C_{1\text{-}3}$alkyl, *i.e.*, a $C_{1\text{-}3}$alkyl substituted by 1, 2, or 3 R^{C1} groups as previously described herein, or an unsubstituted $C_{1\text{-}3}$alkyl. In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is unsubstituted $C_{1\text{-}3}$alkyl, *i.e.,* C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is unsubstituted $C_{1\text{-}3}$alkyl of formula $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$. In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is substituted $C_{1\text{-}3}$alkyl, *e.g.,* of formula:



wherein R^{C1A} and R^{C1B} are as defined herein.

[00243] In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is $C_{1\text{-}3}$haloalkyl, *e.g.,* C_1 haloalkyl ($-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is $-CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$.

[00244] In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is substituted or unsubstituted $C_{3\text{-}6}$carbocylyl. In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7}

is substituted or unsubstituted C_3carbocylyl (*e.g.,* substituted or unsubstituted cyclopropyl). In certain embodiments, such groups are unsubstituted by R^{C1}. In other embodiments, such groups are substituted, *e.g.,* wherein at least one instance of R^{C1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, -OR^{C1A} (*e.g.,* -OH, -OCH_3), or unsubstituted C_{1-3}alkyl (*e.g.,* -CH_3, -CH_2CH_3).

[00245] In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is substituted or unsubstituted 4-6 membered heterocyclyl. In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is a substituted or unsubstituted 4- membered heterocyclyl (*e.g.,* azetidinyl), substituted or unsubstituted 5-membered heterocyclyl (*e.g.,* pyrrolidinyl, pyrrolidin-2-one, oxazolidin-2-one), or substituted or unsubstituted 6-membered heterocyclyl (*e.g.,* morpholinyl, piperidinyl, piperazinyl). In certain embodiments, such groups are unsubstituted by R^{C1}. In other embodiments, such groups are substituted, *e.g.,* wherein at least one instance of R^{C1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, -OR^{C1A} (*e.g.,* -OH, -OCH_3), or unsubstituted C_{1-3}alkyl (*e.g.,* -CH_3, -CH_2CH_3).

[00246] In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is -$C(=O)R^{B4A}$, -$C(=O)OR^{B4A}$, -$OC(=O)R^{B4A}$, -$OC(=O)OR^{B4A}$, -$NR^{B4B}C(=O)R^{B4A}$, -$NR^{B4B}C(=O)OR^{B4A}$, or -$S(O)_2R^{B4A}$, wherein R^{B4A} is substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_{3-6} carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl, and R^{B4B} is as defined herein.

[00247] In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is -$C(=O)R^{B4A}$, -$C(=O)OR^{B4A}$, -$OC(=O)R^{B4A}$, -$OC(=O)OR^{B4A}$, -$NR^{B4B}C(=O)R^{B4A}$, -$NR^{B4B}C(=O)OR^{B4A}$, or -$S(O)_2R^{B4A}$, wherein R^{B4A} is unsubstituted C_{1-3}alkyl, *i.e.*, unsubstituted C_1 alkyl (-CH_3), unsubstituted C_2 alkyl (-CH_2CH_3), or unsubstituted C_3 alkyl (-$CH_2CH_2CH_3$ or -$CH(CH_3)_2$).

[00248] In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is -$C(=O)R^{B4A}$, -$C(=O)OR^{B4A}$, -$OC(=O)R^{B4A}$, -$OC(=O)OR^{B4A}$, -$NR^{B4B}C(=O)R^{B4A}$, -$NR^{B4B}C(=O)OR^{B4A}$, or -$S(O)_2R^{B4A}$, wherein R^{B4A} is C_{1-3}haloalkyl, *e.g.,* C_1 haloalkyl (–CF_3, –CCl_3, –$CFCl_2$, –CF_2Cl, –CH_2F, -CHF_2, -CH_2Cl, $CHCl_2$), C_2 haloalkyl (–CF_2CF_3, -CH_2CF_3, -CH_2CHF_2, -CH_2CH_2F, -CH_2CCl_3, -CH_2CHCl_2, -CH_2CH_2Cl), or C_3 haloalkyl (–$CF_2CF_2CF_3$, –$CH_2CF_2CF_3$, -$CH_2CH_2CF_3$, -$CH_2CH_2CHF_2$, - $CH_2CH_2CH_2F$, - $CH_2CH_2CCl_3$, - $CH_2CH_2CHCl_2$, -$CH_2CH_2CH_2Cl$, -$CH(CH_3)CHF_2$, or -$CH(CH_3)CF_3$). In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is -$C(=O)R^{B4A}$, -$C(=O)OR^{B4A}$, -$OC(=O)R^{B4A}$, -$OC(=O)OR^{B4A}$, -$NR^{B4B}C(=O)R^{B4A}$, -$NR^{B4B}C(=O)OR^{B4A}$, or -$S(O)_2R^{B4A}$, wherein R^{B4A} is –CF_3, –CH_2F, -CHF_2, -CH_2Cl, -CH_2CF_3, -CH_2CHF_2, -$CH(CH_3)CHF_2$, or -$CH(CH_3)CF_3$.

[00249] In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is -$C(=O)R^{B4A}$, -$C(=O)OR^{B4A}$, -$OC(=O)R^{B4A}$, -$OC(=O)OR^{B4A}$, -$NR^{B4B}C(=O)R^{B4A}$, -$NR^{B4B}C(=O)OR^{B4A}$, or -

$S(O)_2R^{B4A}$, wherein R^{B4A} is substituted or unsubstituted C_{3-6}carbocylyl or substituted or unsubstituted 4-6 membered heterocyclyl. In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is $-C(=O)R^{B4A}$, $-C(=O)OR^{B4A}$, $-OC(=O)R^{B4A}$, $-OC(=O)OR^{B4A}$, $-NR^{B4B}C(=O)R^{B4A}$, $-NR^{B4B}C(=O)OR^{B4A}$, or $-S(O)_2R^{B4A}$, wherein R^{B4A} is substituted or unsubstituted C_3carbocylyl (*e.g.,* cyclopropyl). In certain embodiments, at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is $-C(=O)R^{B4A}$, $-C(=O)OR^{B4A}$, $-OC(=O)R^{B4A}$, $-OC(=O)OR^{B4A}$, $-NR^{B4B}C(=O)R^{B4A}$, $-NR^{B4B}C(=O)OR^{B4A}$, or $-S(O)_2R^{B4A}$, wherein R^{B4A} is substituted or unsubstituted 4- membered heterocyclyl (*e.g.,* azetidinyl, oxetanyl). at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is $-C(=O)R^{B4A}$, $-C(=O)OR^{B4A}$, $-OC(=O)R^{B4A}$, $-OC(=O)OR^{B4A}$, $-NR^{B4B}C(=O)R^{B4A}$, $-NR^{B4B}C(=O)OR^{B4A}$, or $-S(O)_2R^{B4A}$, wherein R^{B4A} is substituted or unsubstituted 5-membered heterocyclyl (*e.g.,* tetrahydrofuranyl). at least one of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is $-C(=O)R^{B4A}$, $-C(=O)OR^{B4A}$, $-OC(=O)R^{B4A}$, $-OC(=O)OR^{B4A}$, $-NR^{B4B}C(=O)R^{B4A}$, $-NR^{B4B}C(=O)OR^{B4A}$, or $-S(O)_2R^{B4A}$, wherein R^{B4A} is substituted or unsubstituted 6-membered heterocyclyl (*e.g.,* tetrahydropyranyl). In certain embodiments, such groups are unsubstituted by R^{C1}. In other embodiments, such groups are substituted, *e.g.,* wherein at least one instance of R^{C1} is halogen *(i.e.,* -F, -Cl, -Br, or –I), -CN, $-OR^{C1A}$ (*e.g.,* -OH, $-OCH_3$), or unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$, $-CH_2CH_3$).

[00250] In certain embodiments, at least one instance of R^{B4}, R^{B5}, R^{B6}, and R^{B7}, is C_{1-3} alkyl, C_{1-3}haloalkyl, C_{1-3} alkyl substituted with $-OR^{C1B}$, C_{1-3} alkyl substituted with $-N(R^{C1A})(R^{C1B})$, C_{1-3}alkyl substituted with –CN, C_{1-3} alkyl substituted with $-C(=O)N(R^{C1A})(R^{C1B})$, C_{1-3} alkyl substituted with $-C(=O)OR^{C1A}$, $-C(=O)N(R^{B4A})(R^{B4B})$, $-OC(=O)OR^{B1A}$, $-N(R^{B4A})(R^{B4B})$, $-OR^{B4B}$, $-SR^{B4B}$, $-S(O)_2R^{B4A}$, -F, -Cl, –CN, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl.

[00251] Various combination s of the above described embodiemnts of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is further contemplated herein.

[00252] For example, in certain embodiments, wherein Ring B is of formula (xiv), various combinations of R^{B5} and R^{B7} are contemplated, *e.g.,* wherein:

a. each instance of R^{B5} and R^{B7} is hydrogen; or
b. each instance of R^{B5} and R^{B7} is independently $-OR^{B4B}$; or
c. R^{B5} is $-N(R^{B4A})(R^{B4B})$, $-OR^{B4B}$, $-SR^{B4B}$, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl; and R^{B7} is hydrogen; or

d. R^{B5} is hydrogen and R^{B7} is $-N(R^{B4A})(R^{B4B})$, $-OR^{B4B}$, $-SR^{B4B}$, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, or substituted or unsubstituted C_3 carbocyclyl.

[00253] In certain embodiments, wherein Ring B is of formula (xv), various combinations of R^{B5}, R^{B6}, and R^{B7} are contemplated, *e.g.,* wherein:

a. each instance of R^{B5}, R^{B6}, and R^{B7} is hydrogen; or

b. $R^{B5}$is $-N(R^{B4A})(R^{B4B})$, $-OR^{B4B}$, $-SR^{B4B}$, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B6} and R^{B7} are hydrogen; or

c. $R^{B6}$is $-N(R^{B4A})(R^{B4B})$, $-OR^{B4B}$, $-SR^{B4B}$, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B5} and R^{B7} are hydrogen; or

d. $R^{B7}$is $-N(R^{B4A})(R^{B4B})$, $-OR^{B4B}$, $-SR^{B4B}$, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B5} and R^{B6} are hydrogen.

[00254] In certain embodiments, wherein Ring B is of formula (xvi), various combinations of R^{B4}, R^{B6} and R^{B7} are contemplated, *e.g.,* wherein:

a. $R^{B4}$is $-N(R^{B4A})(R^{B4B})$, $-OR^{B4B}$, $-SR^{B4B}$, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B6} and R^{B7} are hydrogen; or

b. $R^{B6}$is $-N(R^{B4A})(R^{B4B})$, $-OR^{B4B}$, $-SR^{B4B}$, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B5} and R^{B7} are hydrogen; or

c. $R^{B7}$is $-N(R^{B4A})(R^{B4B})$, $-OR^{B4B}$, $-SR^{B4B}$, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B5} and R^{B6} are hydrogen; or

d. $R^{B4}$and $R^{B6}$are$-N(R^{B4A})(R^{B4B})$, $-OR^{B4B}$, $-SR^{B4B}$, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3

carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B7} is hydrogen.

[00255] In certain embodiments, wherein Ring B is of formula (xvii), various combinations of R^{B5} and R^{B6} are contemplated, *e.g.,* wherein:

a. $R^{B5}$is $-N(R^{B4A})(R^{B4B})$, $-OR^{B4B}$, $-SR^{B4B}$, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B6} is hydrogen; or

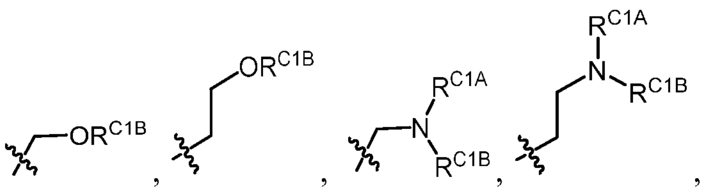
b. $R^{B6}$is $-N(R^{B4A})(R^{B4B})$, $-OR^{B4B}$, $-SR^{B4B}$, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B5} is hydrogen.

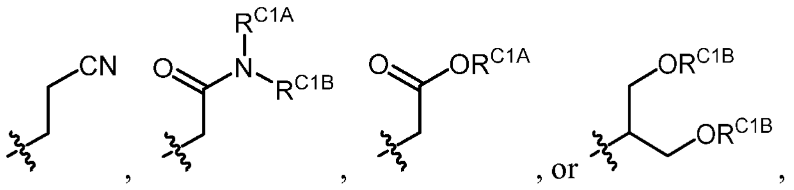
[00256] Furthermore, as generally defined herein, in certain embodiments, each instance of R^{B3} is independently hydrogen, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl, provided at least one instance of R^{B3} is hydrogen. In certain embodiments, each instance of R^{B3} is hydrogen. In certain embodiments, one instance of R^{B3} is unsubstituted C_{1-3}alkyl (*e.g.,* $-CH_3$) or C_{1-3}haloalkyl (*e.g.,* $-CF_3$). R^{B3} is hydrogen or $-CH_3$, provided at least one instance of R^{B3} is hydrogen.

[00257] Furthermore, as generally defined herein, in certain embodiments, each instance of R^{N2} and R^{B8} is independently substituted or unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl, or R^{N2} and R^{B8} are joined to form a substituted or unsubstituted 5- to 6-membered ring.

[00258] In certain embodiments, each instance of R^{N2} and R^{B8} is independently substituted or unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl.

[00259] In certain embodiments, at least one of R^{N2} and R^{B8} is substituted or unsubstituted C_{1-3}alkyl, *i.e.*, a C_{1-3}alkyl substituted by 1, 2, or 3 R^{C1} groups as previously described herein, or an unsubstituted C_{1-3}alkyl. In certain embodiments, at least one of R^{N2} and R^{B8} is unsubstituted C_{1-3}alkyl, *i.e.,* C_1 alkyl ($-CH_3$), unsubstituted C_2 alkyl ($-CH_2CH_3$), or unsubstituted C_3 alkyl ($-CH_2CH_2CH_3$ or $-CH(CH_3)_2$). In certain embodiments, at least one of R^{N2} and R^{B8} is unsubstituted C_{1-3}alkyl of formula $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$. In certain embodiments, at least one of R^{N2} and R^{B8} is substituted C_{1-3}alkyl, *e.g.,* of formula:





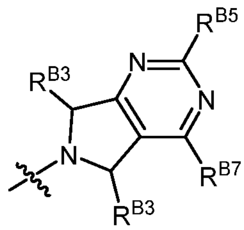
wherein R^{C1A} and R^{C1B} are as defined herein.

[00260] In certain embodiments, at least one of R^{N2} and R^{B8} is $C_{1\text{-}3}$haloalkyl, *e.g.,* C_1 haloalkyl ($-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$), C_2 haloalkyl ($-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$), or C_3 haloalkyl ($-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$). In certain embodiments, at least one of R^{N2} and R^{B8} is $-CF_3$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$.

[00261] Alternatively, in certain embodiments, R^{N2} and R^{B8} are joined to form a substituted or unsubstituted 5- to 6-membered ring. In certain embodiments, R^{N2} and R^{B8} are joined to form a substituted or unsubstituted 5-membered ring. In certain embodiments, R^{N2} and R^{B8} are joined to form a substituted or unsubstituted 6-membered ring. In certain embodiments, R^{N2} and R^{B8} are joined to form an unsubstituted ring.

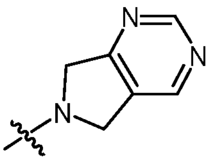
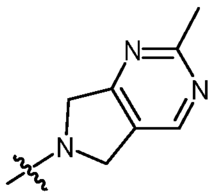
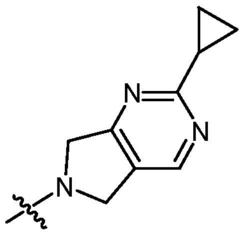
[00262] In certain embodiments, each instance of R^{B8} and R^{N2} is independently $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$, $-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$, $-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$; or R^{N2} and R^{B8} are joined to form an unsubstituted 5-membered ring.

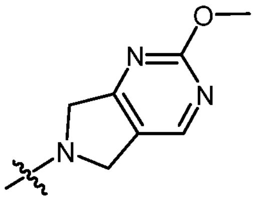
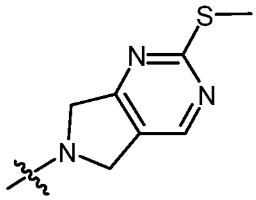
[00263] In certain embodiments, Ring B is of formula:

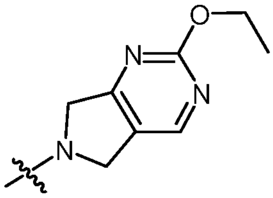
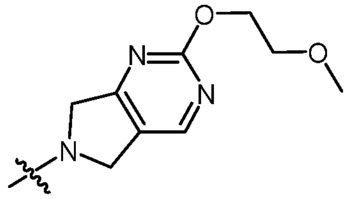
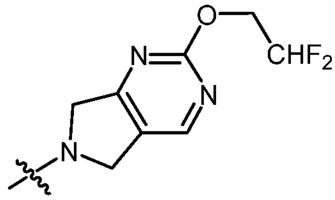


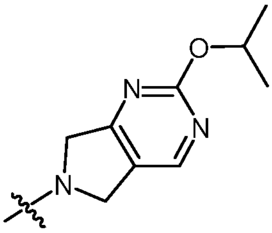
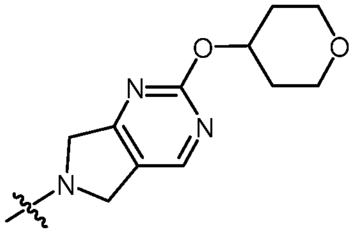
(xiv).

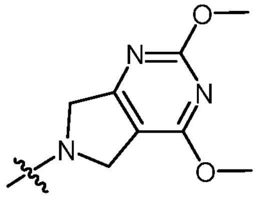
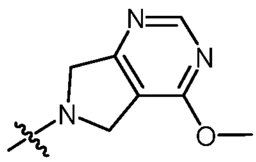
[00264] In certain embodiments of formula (xiv), Ring B is of formula:

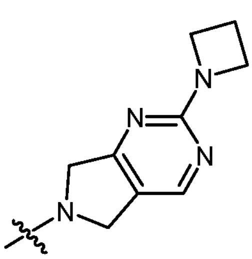
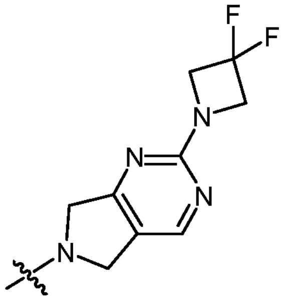
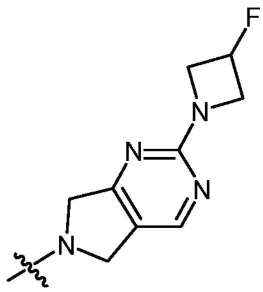
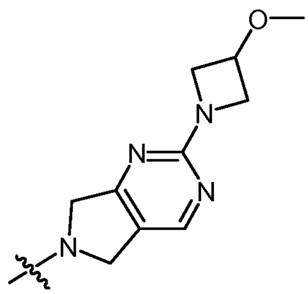
, , ,

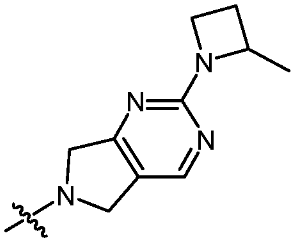
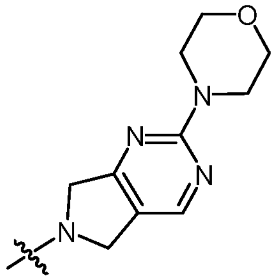
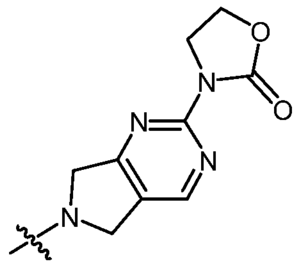
, ,

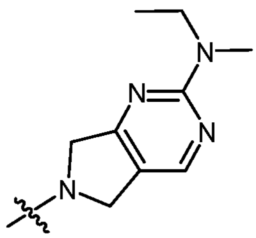
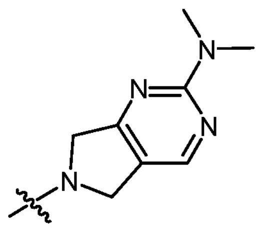
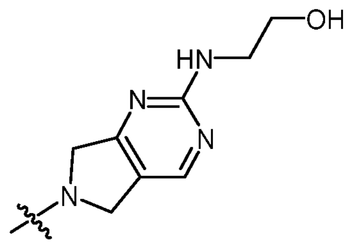
, , ,

, ,

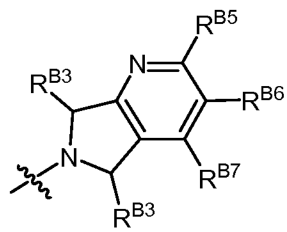
, , ,

, , , ,

 ,  ,  ,

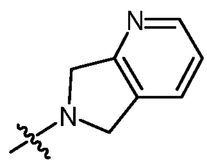
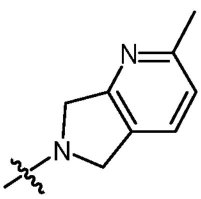
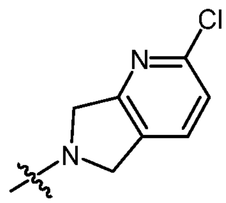
 ,  , or  .

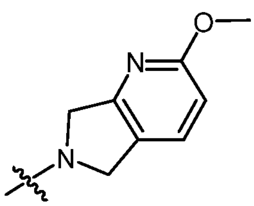
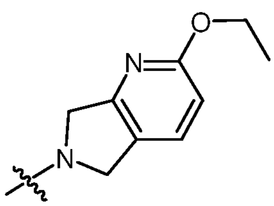
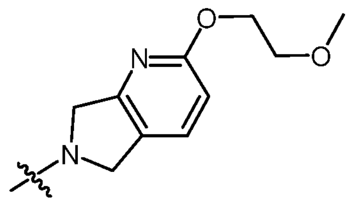
[00265] In certain embodiments, Ring B is of formula:

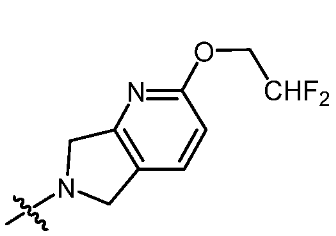
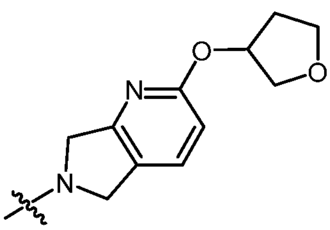


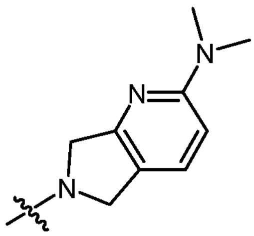
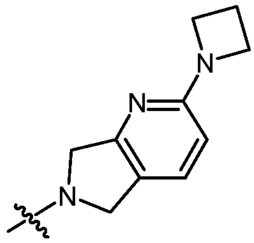
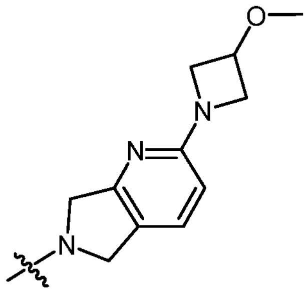
(xv).

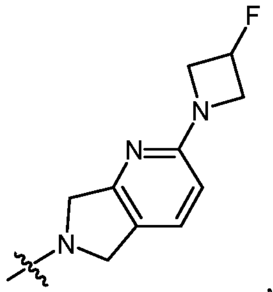
[00266] In certain embodiments of formula (xv), Ring B is of formula:

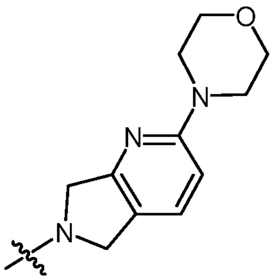
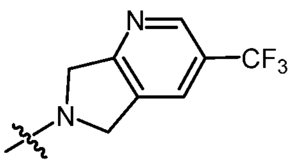
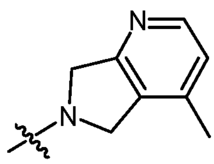
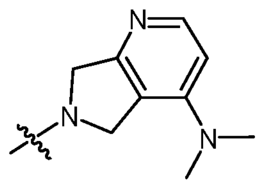
 ,  ,  ,

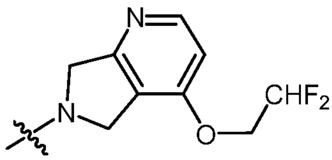
 ,  ,  ,

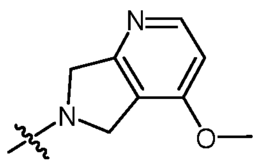
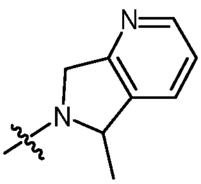
 ,  ,

 ,  ,  ,

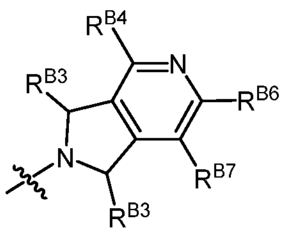
 ,

 ,  ,  ,  ,

 ,

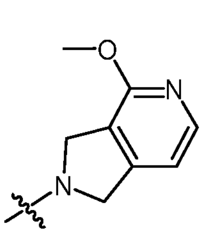
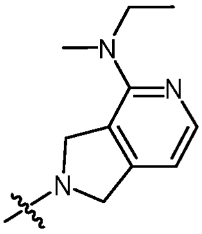
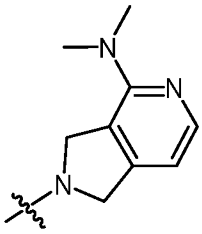
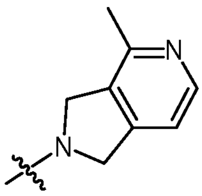
 , or  .

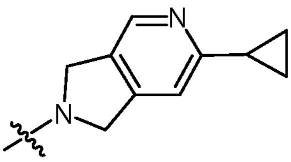
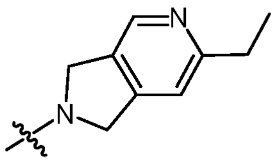
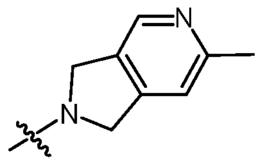
[00267] In certain embodiments, Ring B is of formula:

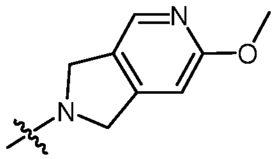
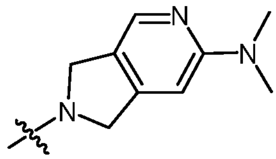


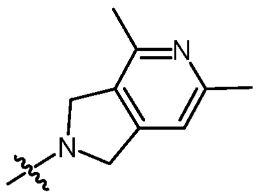
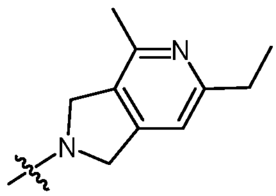
(xvi).

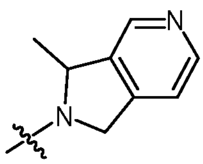
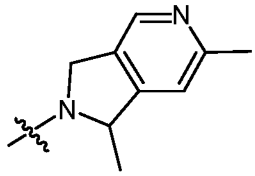
[00268] In certain embodiments of formula (xvi), Ring B is of formula:

, , , ,

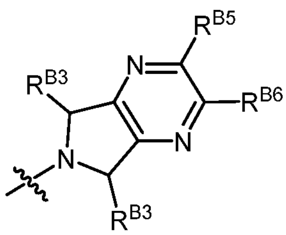
, , ,

, ,

, ,

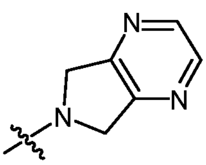
, or .

[00269] In certain embodiments, Ring B is of formula:

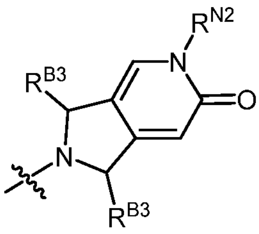


(xvii).

[00270] In certain embodiments of formula (xvii), Ring B is of formula:

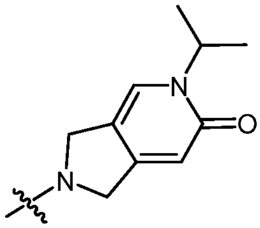
.

[00271] In certain embodiments, Ring B is of formula:



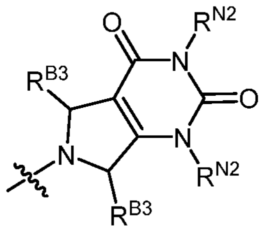
(xviii).

[00272] In certain embodiments of formula (xviii), Ring B is of formula:



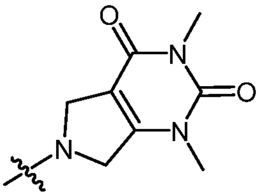
.

[00273] In certain embodiments, Ring B is of formula:

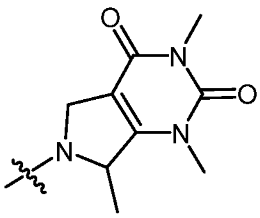


(xix).

[00274] In certain embodiments of formula (xix), Ring B is of formula:

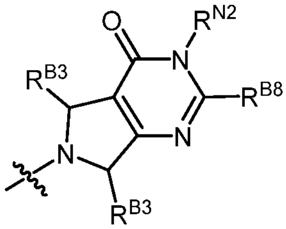


or



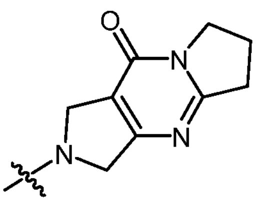
.

[00275] In certain embodiments, Ring B is of formula:

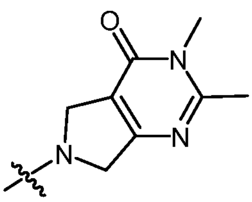


(xx).

[00276] In certain embodiments of formula (xx), Ring B is of formula:

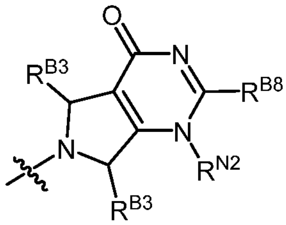


or



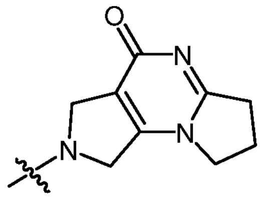
.

[00277] In certain embodiments, Ring B is of formula:



(xxi).

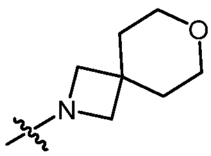
[00278] In certain embodiments of formula (xxi), Ring B is of formula:



.

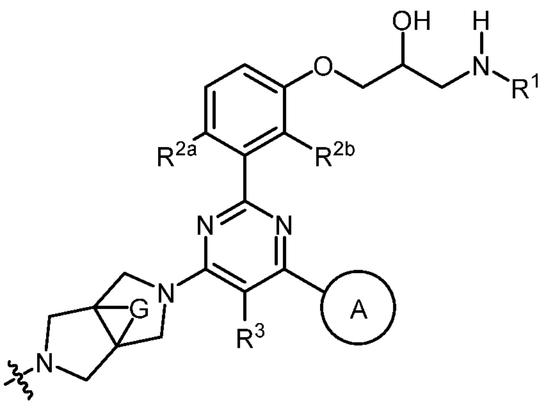
(VIII) Other Ring B groups

[00279] Other Ring B groups contemplated herein include Ring B groups of formula (xxv) and (xxix). For example, in certain embodiments, Ring B is of formula:



(xxv).

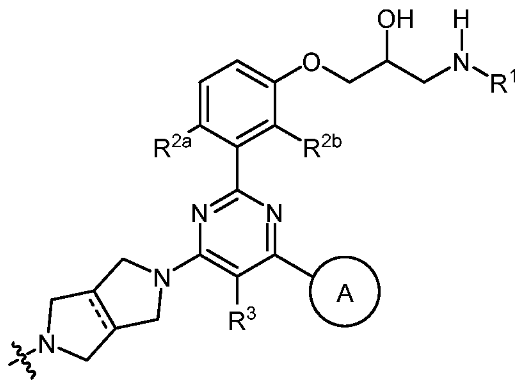
[00280] In certain embodiments, Ring B is of formula:



(xxix)

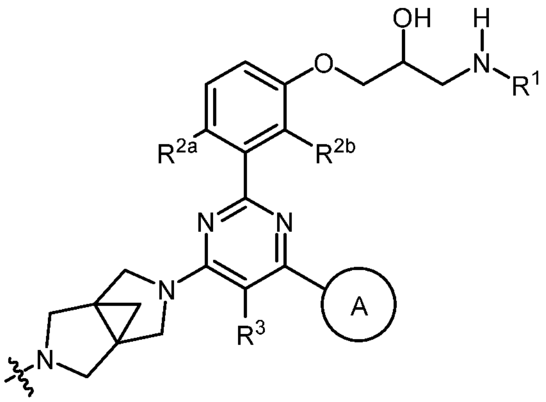
wherein R^1, R^{2a}, R^{2b}, R^3, Ring A, and ---- are as defined herein.

[00281] In certain embodiments,  represents a double or single bond (*e.g.,* represented by ----) to provide a Ring B of formula:

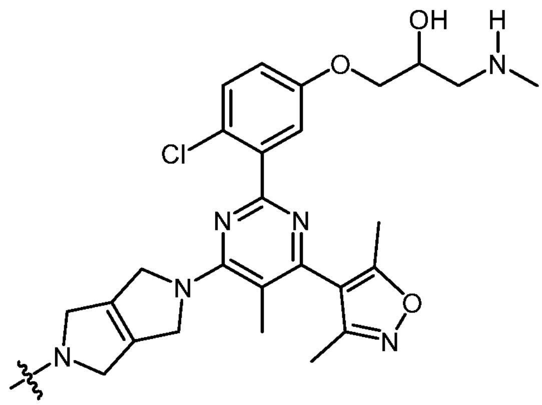


[00282] In certain embodiments of formula (xxix), ==== represents a single bond. In certain embodiments of formula (xxix), ==== represents a single bond, and the ring fusion is in the *trans* configuration. In certain embodiments of formula (xxix), ==== represents a single bond, and the ring fusion is in the *cis* configuration. In certain embodiments of formula (xxix), ==== represents a double bond.

[00283] In certain embodiments of formula (xxix), G of  is $-CH_2-$ to provide a cyclopropanated Ring B of formula:



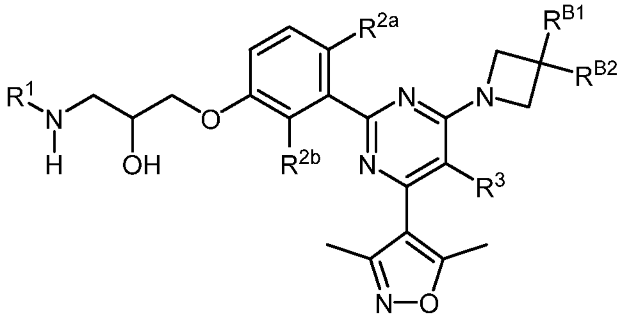
[00284] In certain embodiments of formula (xxix), Ring B is of formula:



(IX) Various Contemplated Combinations of Specific Embodiments

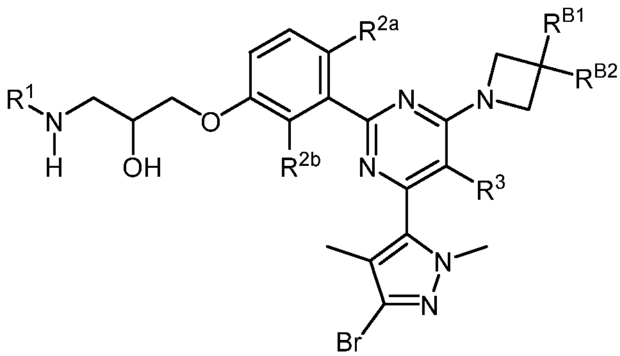
[00285] Various combinations of specific embodiments as described herein are specifically contemplated.

[00286] For example, in certain embodiments, wherein Ring B is of formula (i), and wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



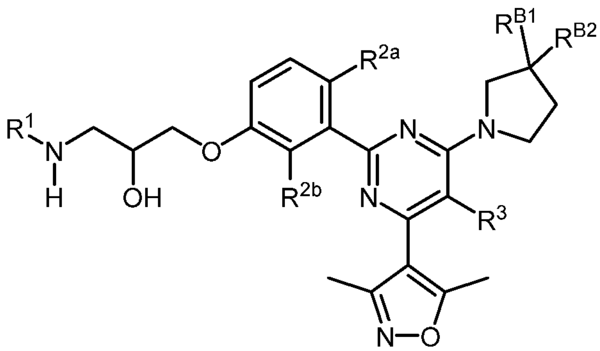
or a pharmaceutically acceptable salt thereof.

[00287] In certain embodiments, Ring B is of formula (i), wherein Ring A is of formula (A-ii), and wherein R^{A5} is $-CH_3$, R^{A4} is –Br, and R^{A3} is $-CH_3$, provided is a compound of formula:



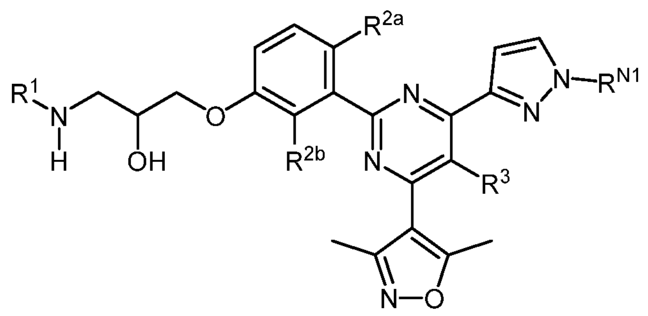
or a pharmaceutically acceptable salt thereof.

[00288] In certain embodiments, Ring B is of formula (ii), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



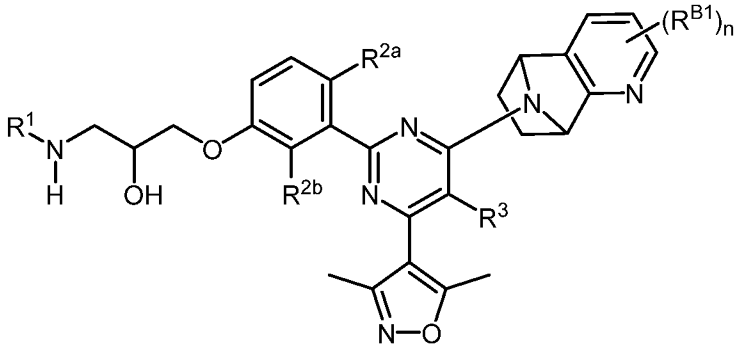
or a pharmaceutically acceptable salt thereof.

[00289] In certain embodiments, Ring B is of formula (iii), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



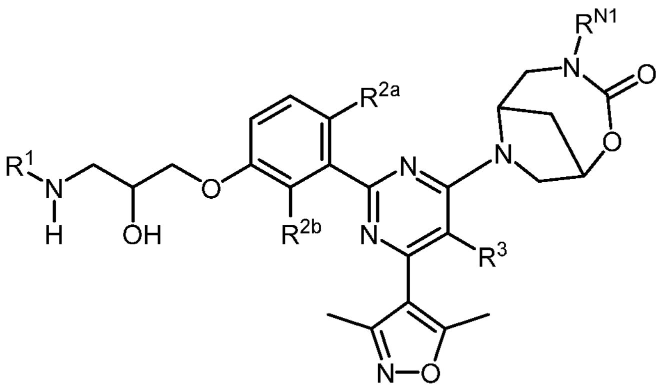
or a pharmaceutically acceptable salt thereof.

[00290] In certain embodiments, Ring B is of formula (iv), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



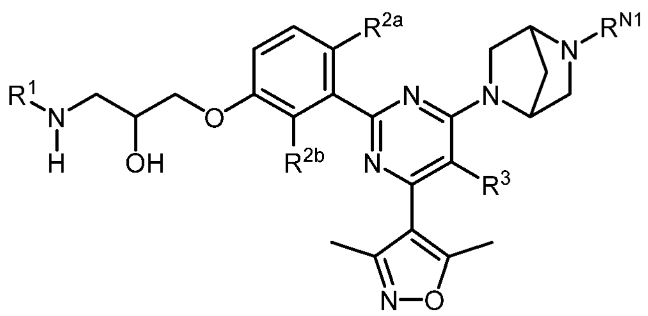
or a pharmaceutically acceptable salt thereof.

[00291] In certain embodiments, Ring B is of formula (v), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



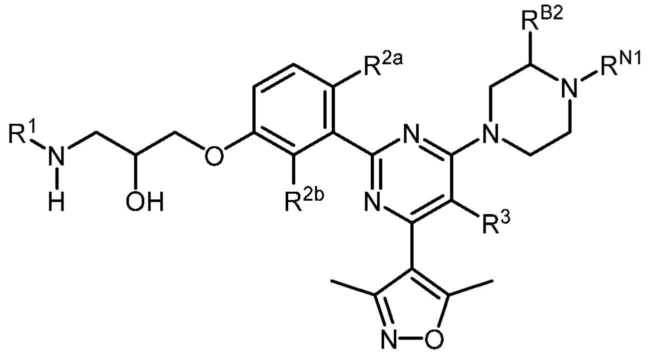
or a pharmaceutically acceptable salt thereof.

[00292] In certain embodiments, Ring B is of formula (vi), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



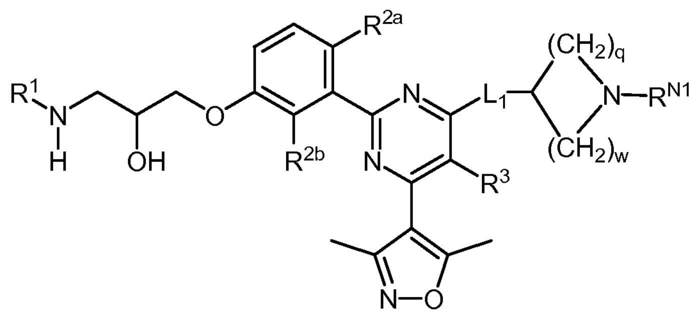
or a pharmaceutically acceptable salt thereof.

[00293] In certain embodiments, Ring B is of formula (vii), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



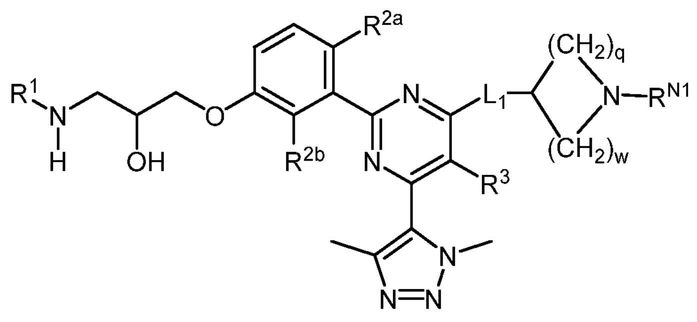
or a pharmaceutically acceptable salt thereof.

[00294] In certain embodiments, Ring B is of formula (viii), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



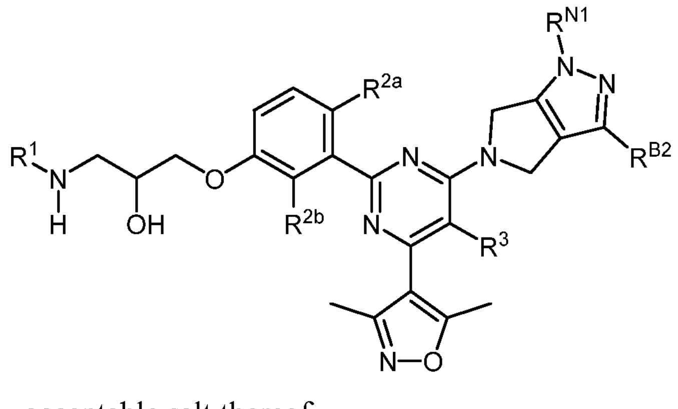
or a pharmaceutically acceptable salt thereof.

[00295] In certain embodiments, Ring B is of formula (viii), wherein Ring A is of formula (A-iii), and wherein each of R^{A3} and R^{A5} is $-CH_3$, provided is a compound of formula:



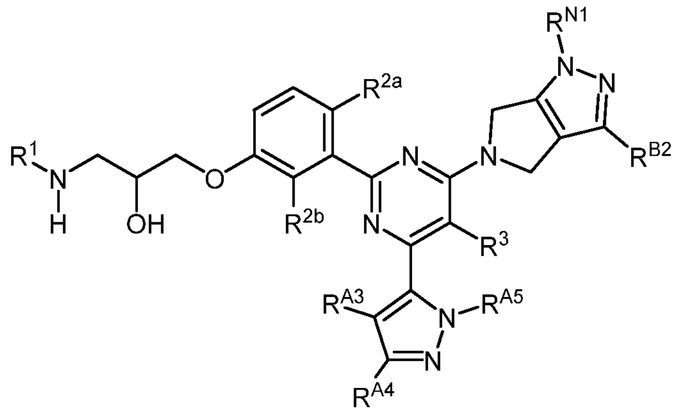
or a pharmaceutically acceptable salt thereof.

[00296] In certain embodiments, Ring B is of formula (ix), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



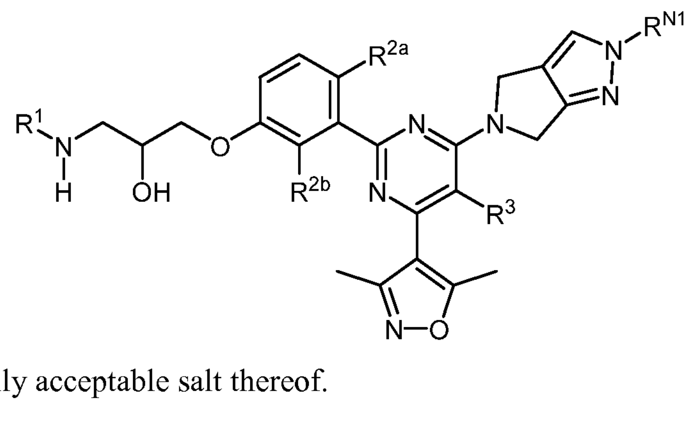
or a pharmaceutically acceptable salt thereof.

[00297] In certain embodiments, Ring B is of formula (ix), wherein Ring A is of formula (A-ii), and wherein R^{A3} is –Cl, R^{A4} is hydrogen, and R^{A5} is $-CH_3$, provided is a compound of formula:



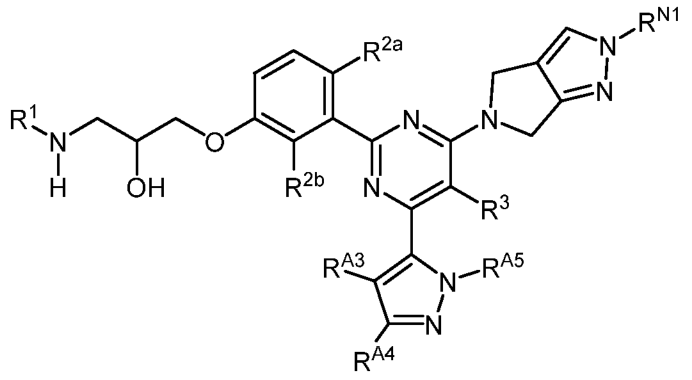
or a pharmaceutically acceptable salt thereof.

[00298] In certain embodiments, Ring B is of formula (x), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



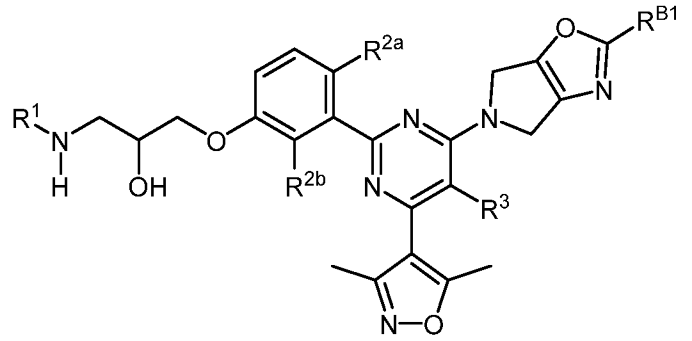
or a pharmaceutically acceptable salt thereof.

[00299] In certain embodiments, Ring B is of formula (x), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $-Cl$, R^{A4} is hydrogen, and R^{A5} is $-CH_3$, provided is a compound of formula:



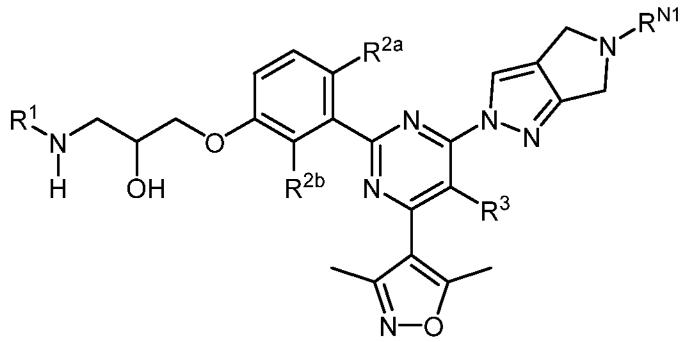
or a pharmaceutically acceptable salt thereof.

[00300] In certain embodiments, Ring B is of formula (xi), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



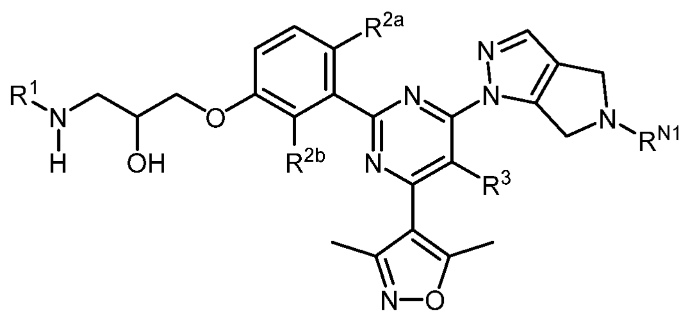
or a pharmaceutically acceptable salt thereof.

[00301] In certain embodiments, Ring B is of formula (xii), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



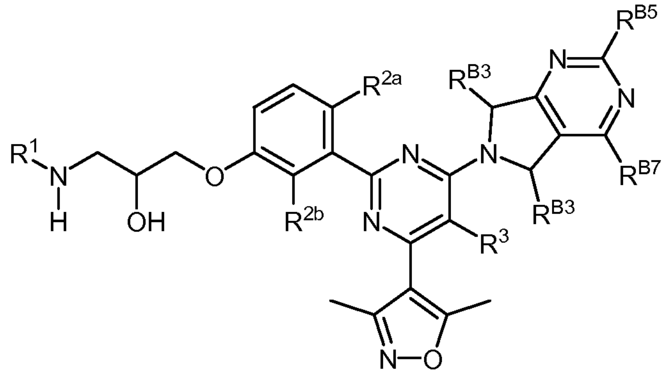
or a pharmaceutically acceptable salt thereof.

[00302] In certain embodiments, Ring B is of formula (xiii), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



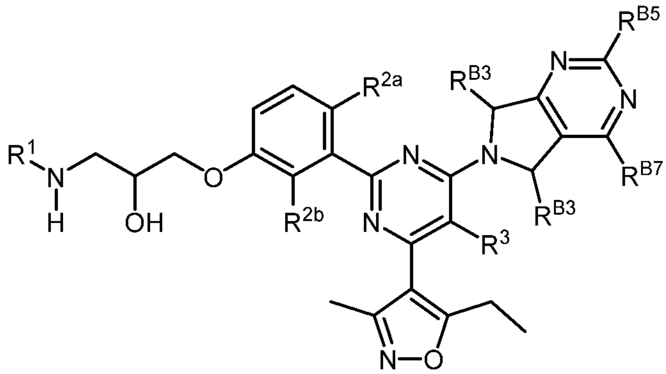
or a pharmaceutically acceptable salt thereof.

[00303] In certain embodiments, Ring B is of formula (xiv), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



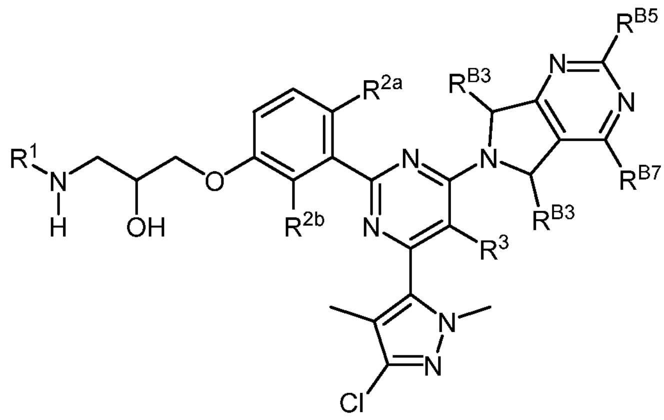
or a pharmaceutically acceptable salt thereof.

[00304] In certain embodiments, Ring B is of formula (xiv), wherein Ring A is of formula (A-i), and wherein R^{A1} is $-CH_3$ and R^{A2} is $-CH_2CH_3$, provided is a compound of formula:



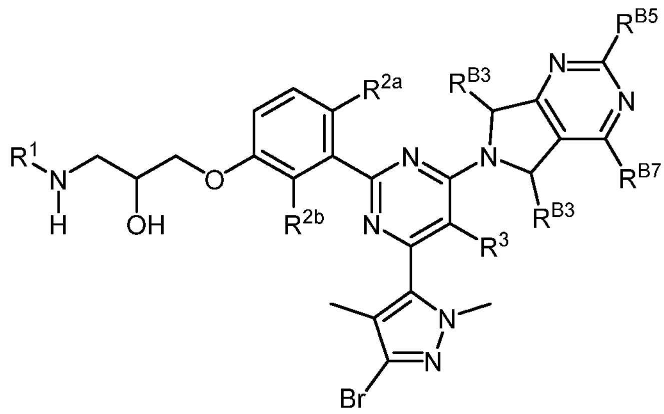
or a pharmaceutically acceptable salt thereof.

[00305] In certain embodiments, Ring B is of formula (xiv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $-CH_3$, R^{A4} is -Cl, and R^{A5} is $-CH_3$, provided is a compound of formula:



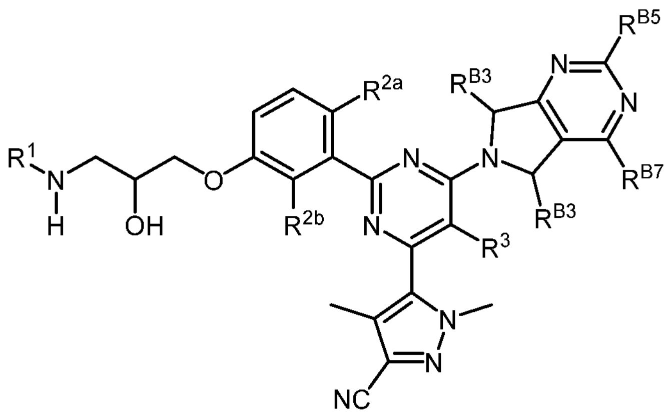
or a pharmaceutically acceptable salt thereof.

[00306] In certain embodiments, Ring B is of formula (xiv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $-CH_3$, R^{A4} is -Br, and R^{A5} is $-CH_3$, provided is a compound of formula:



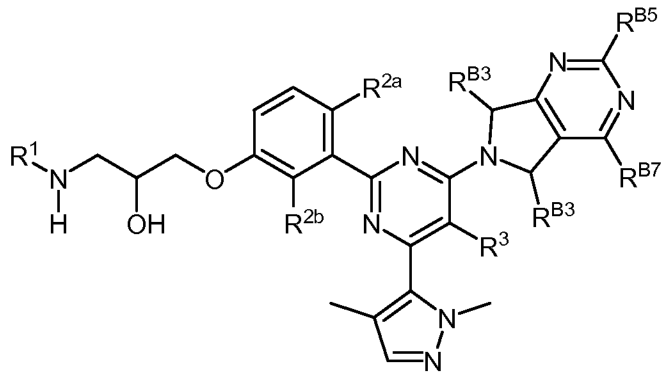
or a pharmaceutically acceptable salt thereof.

[00307] In certain embodiments, Ring B is of formula (xiv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $-CH_3$, R^{A4} is -CN, and R^{A5} is $-CH_3$, provided is a compound of formula:



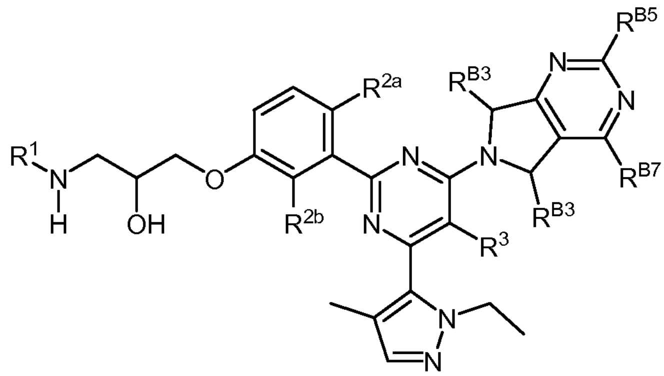
or a pharmaceutically acceptable salt thereof.

[00308] In certain embodiments, Ring B is of formula (xiv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $–CH_3$, R^{A4} is hydrogen, and R^{A5} is $–CH_3$, provided is a compound of formula:



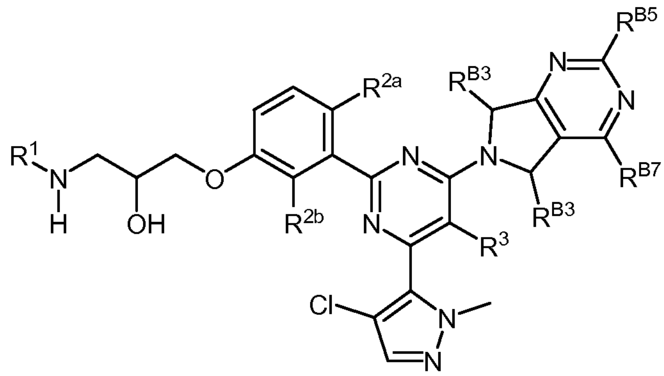
or a pharmaceutically acceptable salt thereof.

[00309] In certain embodiments, Ring B is of formula (xiv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $–CH_3$, R^{A4} is hydrogen, and R^{A5} is $–CH_2CH_3$, provided is a compound of formula:



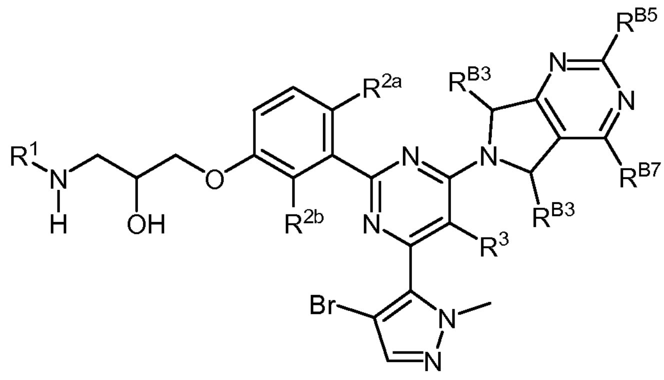
or a pharmaceutically acceptable salt thereof.

[00310] In certain embodiments, Ring B is of formula (xiv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is –Cl, R^{A4} is hydrogen, and R^{A5} is $–CH_3$, provided is a compound of formula:



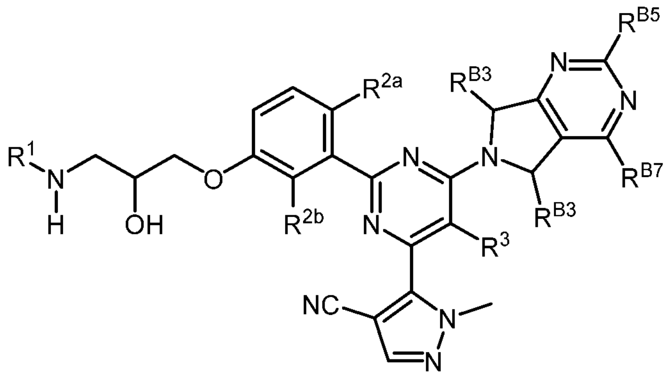
or a pharmaceutically acceptable salt thereof.

[00311] In certain embodiments, Ring B is of formula (xiv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is –Br, R^{A4} is hydrogen, and R^{A5} is $–CH_3$, provided is a compound of formula:



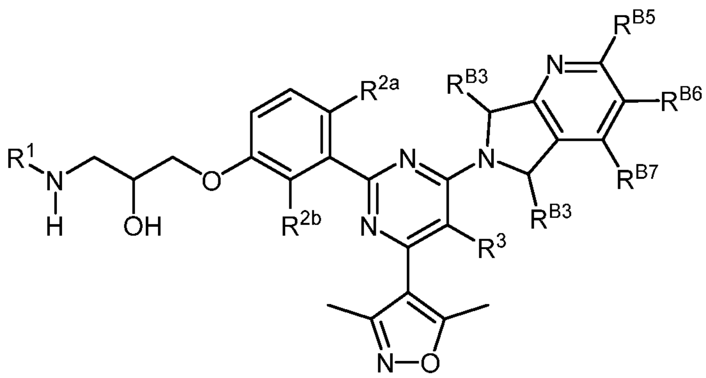
or a pharmaceutically acceptable salt thereof.

[00312] In certain embodiments, Ring B is of formula (xiv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is -CN, R^{A4} is hydrogen, and R^{A5} is $–CH_3$, provided is a compound of formula:



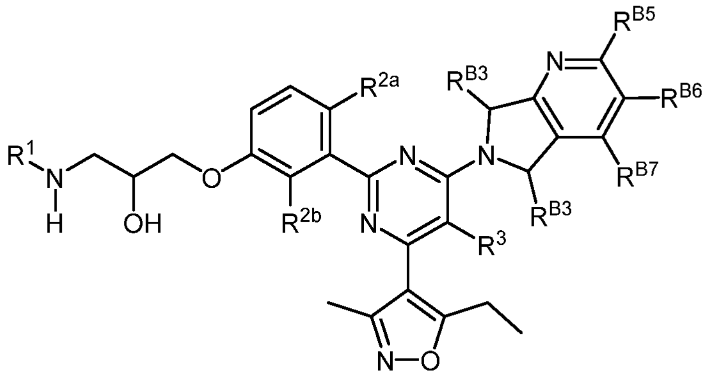
or a pharmaceutically acceptable salt thereof.

[00313] In certain embodiments, Ring B is of formula (xv), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $–CH_3$, provided is a compound of formula:



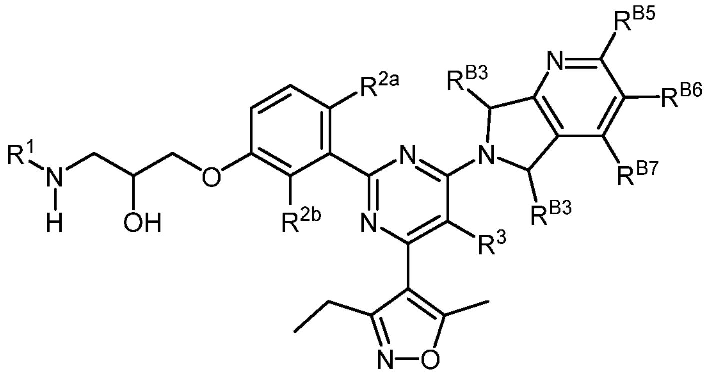
or a pharmaceutically acceptable salt thereof.

[00314] In certain embodiments, Ring B is of formula (xv), wherein Ring A is of formula (A-i), and wherein R^{A1} is $-CH_3$ and R^{A2} is $-CH_2CH_3$, provided is a compound of formula:



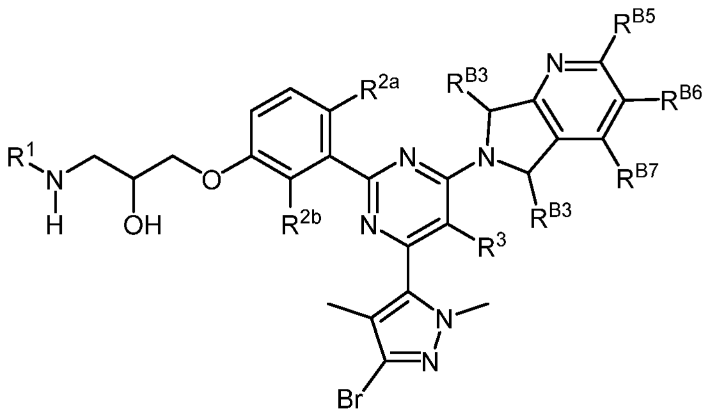
or a pharmaceutically acceptable salt thereof.

[00315] In certain embodiments, Ring B is of formula (xv), wherein Ring A is of formula (A-i), and wherein R^{A1} is $-CH_2CH_3$ and R^{A2} is $-CH_3$, provided is a compound of formula:



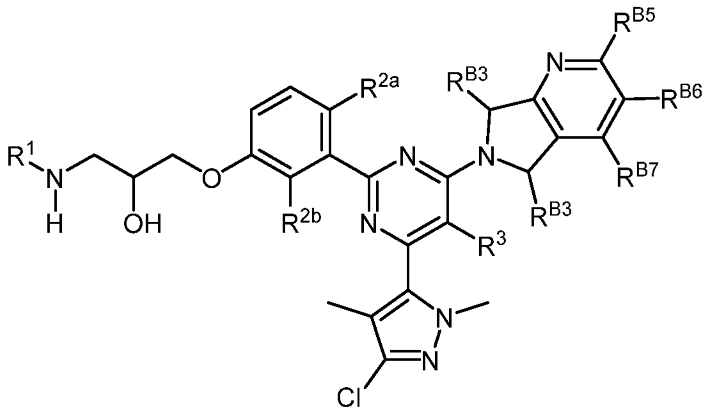
or a pharmaceutically acceptable salt thereof.

[00316] In certain embodiments, Ring B is of formula (xv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $-CH_3$, R^{A4} is -Br, and R^{A5} is $-CH_3$, provided is a compound of formula:



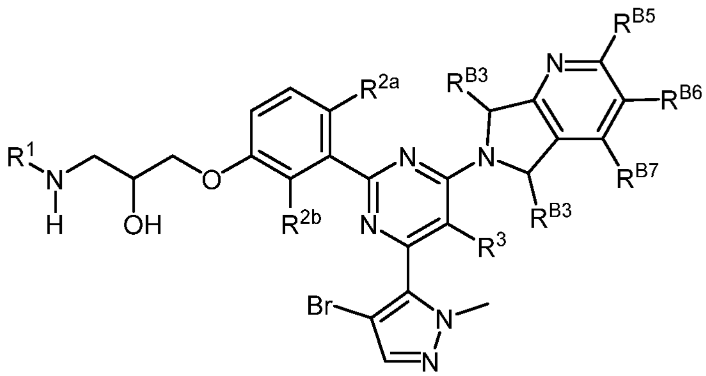
or a pharmaceutically acceptable salt thereof.

[00317] In certain embodiments, Ring B is of formula (xv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $-CH_3$, R^{A4} is -Cl, and R^{A5} is $-CH_3$, provided is a compound of formula:



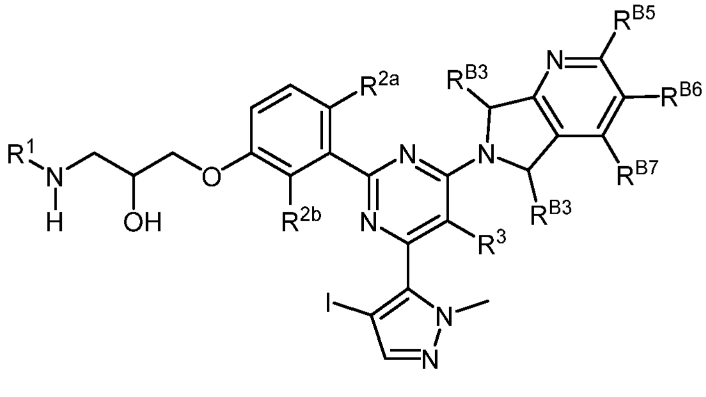
or a pharmaceutically acceptable salt thereof.

[00318] In certain embodiments, Ring B is of formula (xv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is –Br, R^{A4} is -hydrogen, and R^{A5} is $-CH_3$, provided is a compound of formula:



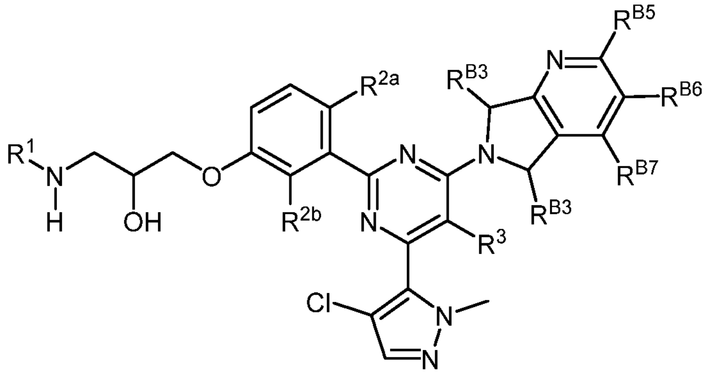
or a pharmaceutically acceptable salt thereof.

[00319] In certain embodiments, Ring B is of formula (xv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is –I, R^{A4} is -hydrogen, and R^{A5} is $-CH_3$, provided is a compound of formula:



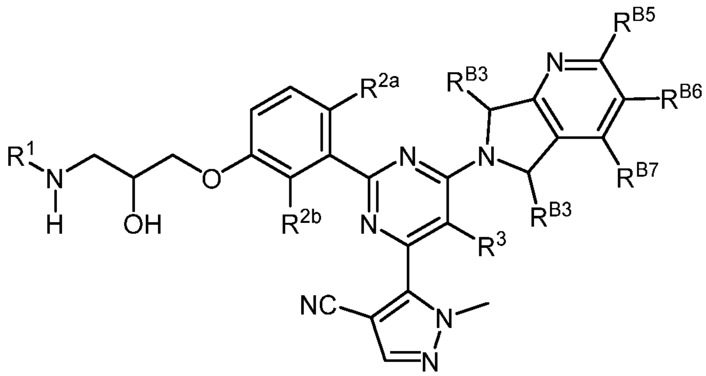
or a pharmaceutically acceptable salt thereof.

[00320] In certain embodiments, Ring B is of formula (xv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is –Cl, R^{A4} is -hydrogen, and R^{A5} is $–CH_3$, provided is a compound of formula:



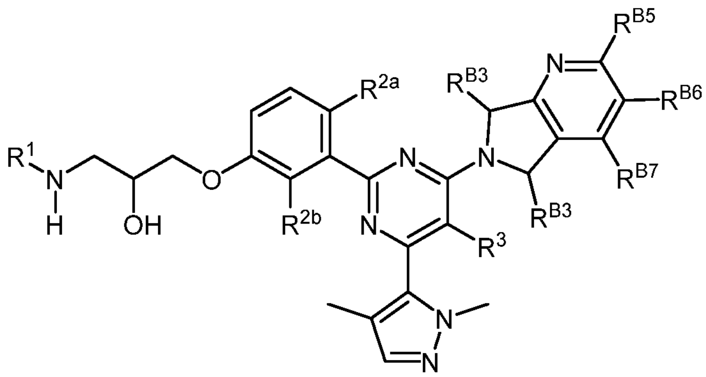
or a pharmaceutically acceptable salt thereof.

[00321] In certain embodiments, Ring B is of formula (xv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is –CN, R^{A4} is -hydrogen, and R^{A5} is $–CH_3$, provided is a compound of formula:



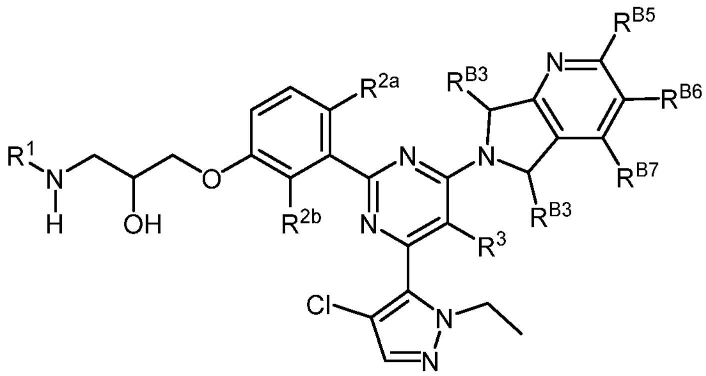
or a pharmaceutically acceptable salt thereof.

[00322] In certain embodiments, Ring B is of formula (xv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $–CH_3$, R^{A4} is -hydrogen, and R^{A5} is $–CH_3$, provided is a compound of formula:



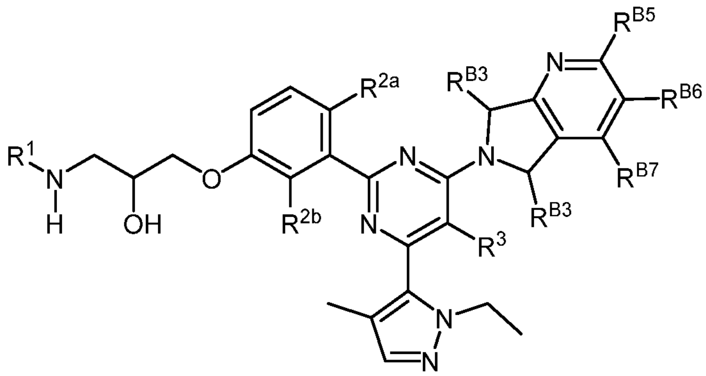
or a pharmaceutically acceptable salt thereof.

[00323] In certain embodiments, Ring B is of formula (xv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is –Cl, R^{A4} is -hydrogen, and R^{A5} is $–CH_2CH_3$, provided is a compound of formula:



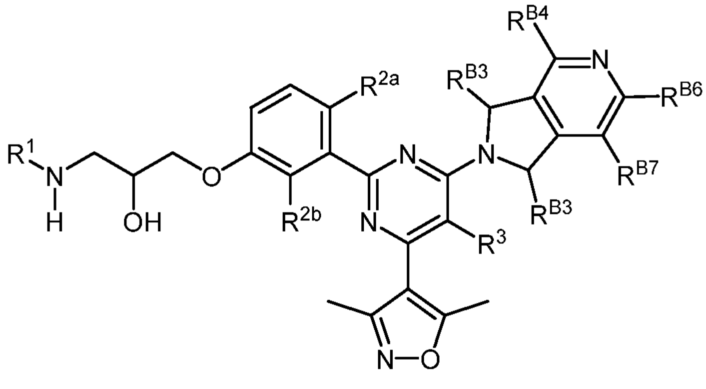
or a pharmaceutically acceptable salt thereof.

[00324] In certain embodiments, Ring B is of formula (xv), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $–CH_3$, R^{A4} is -hydrogen, and R^{A5} is $–CH_2CH_3$, provided is a compound of formula:



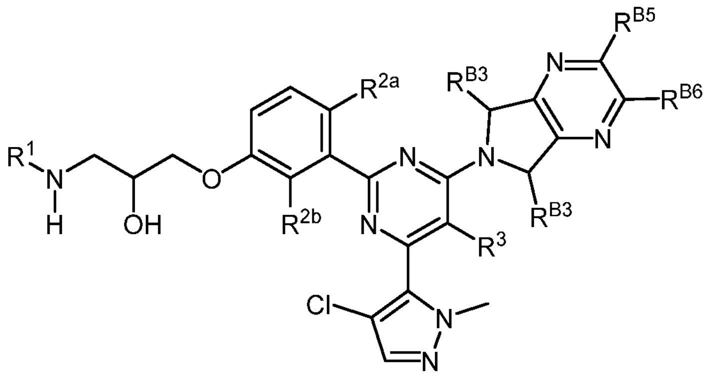
or a pharmaceutically acceptable salt thereof.

[00325] In certain embodiments, Ring B is of formula (xvi), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $–CH_3$, provided is a compound of formula:



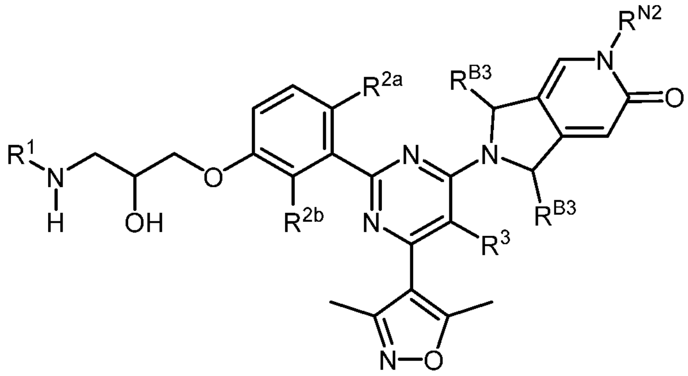
or a pharmaceutically acceptable salt thereof.

[00326] In certain embodiments, Ring B is of formula (xvii), wherein Ring A is of formula (A-ii), and wherein R^{A3} is –Cl, R^{A4} is -hydrogen, and R^{A5} is $–CH_3$, provided is a compound of formula:



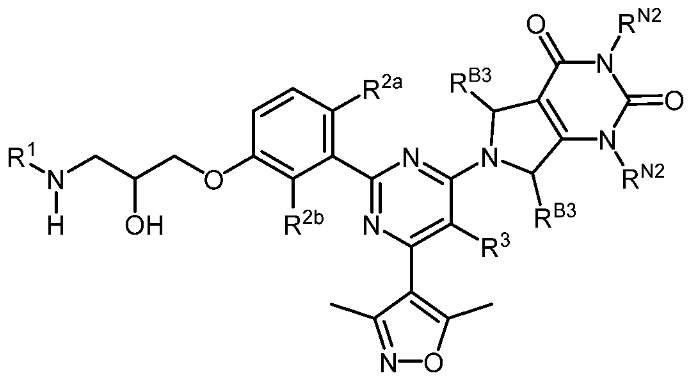
or a pharmaceutically acceptable salt thereof.

[00327] In certain embodiments, Ring B is of formula (xviii), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $–CH_3$, provided is a compound of formula:



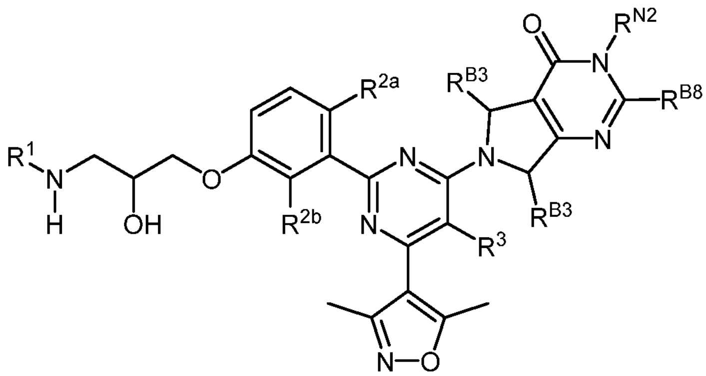
or a pharmaceutically acceptable salt thereof.

[00328] In certain embodiments, Ring B is of formula (xix), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $–CH_3$, provided is a compound of formula:



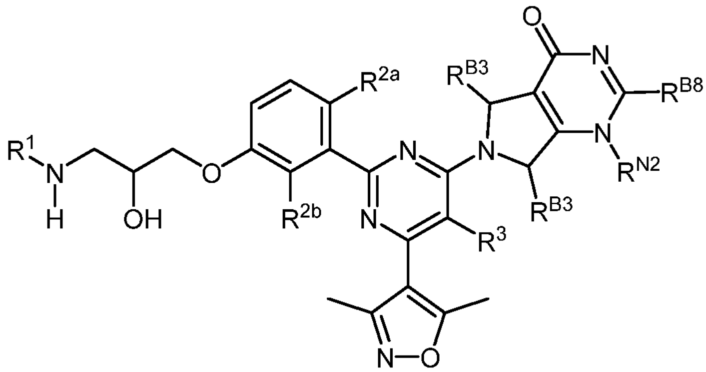
or a pharmaceutically acceptable salt thereof.

[00329] In certain embodiments, Ring B is of formula (xx), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $–CH_3$, provided is a compound of formula:



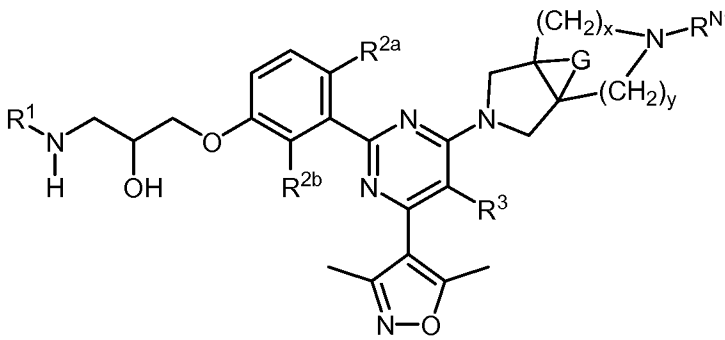
or a pharmaceutically acceptable salt thereof.

[00330] In certain embodiments, Ring B is of formula (xxi), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



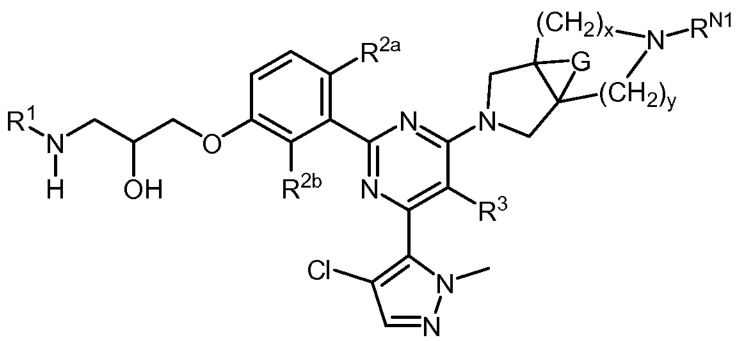
or a pharmaceutically acceptable salt thereof.

[00331] In certain embodiments, Ring B is of formula (xxii), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



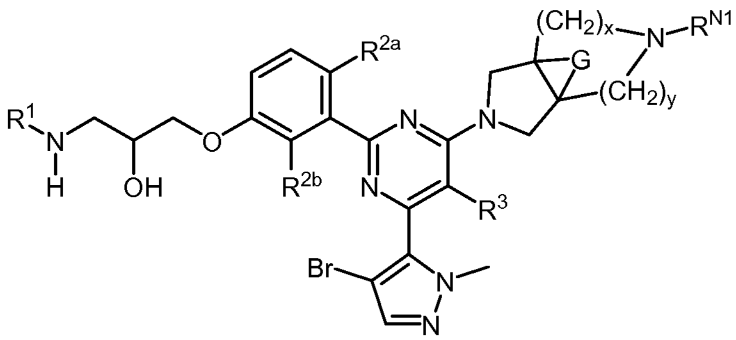
or a pharmaceutically acceptable salt thereof.

[00332] In certain embodiments, Ring B is of formula (xxii), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $-Cl$, R^{A4} is -hydrogen, and R^{A5} is $-CH_3$, provided is a compound of formula:



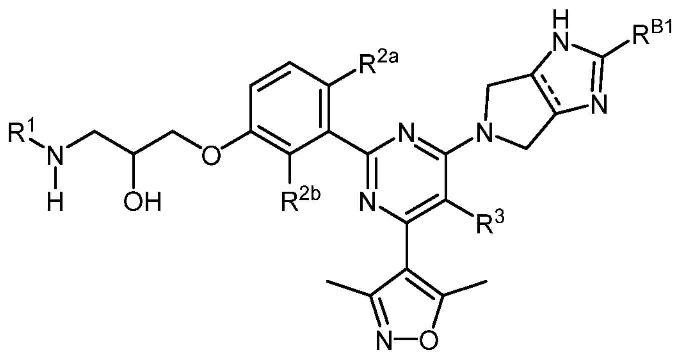
or a pharmaceutically acceptable salt thereof.

[00333] In certain embodiments, Ring B is of formula (xxii), wherein Ring A is of formula (A-ii), and wherein R^{A3} is –Br, R^{A4} is -hydrogen, and R^{A5} is $–CH_3$, provided is a compound of formula:



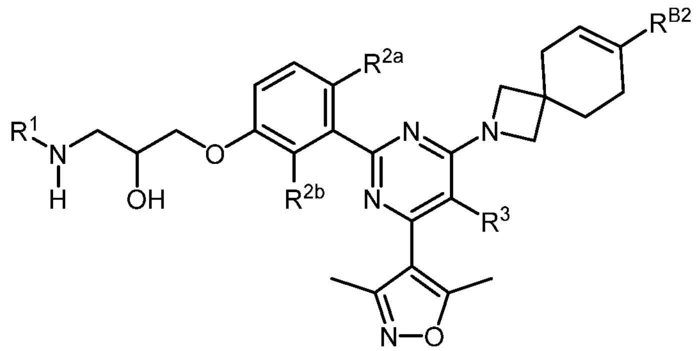
or a pharmaceutically acceptable salt thereof.

[00334] In certain embodiments, Ring B is of formula (xxiii), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $–CH_3$, provided is a compound of formula:



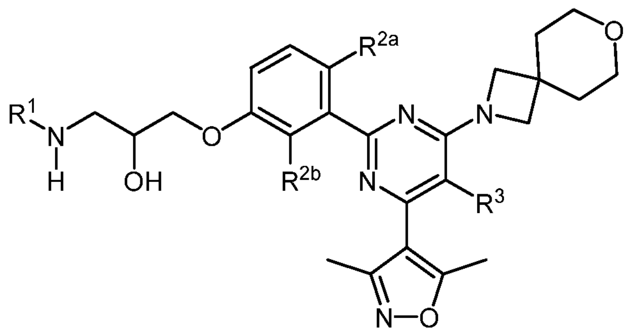
or a pharmaceutically acceptable salt thereof.

[00335] In certain embodiments, Ring B is of formula (xxiv), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $–CH_3$, provided is a compound of formula:



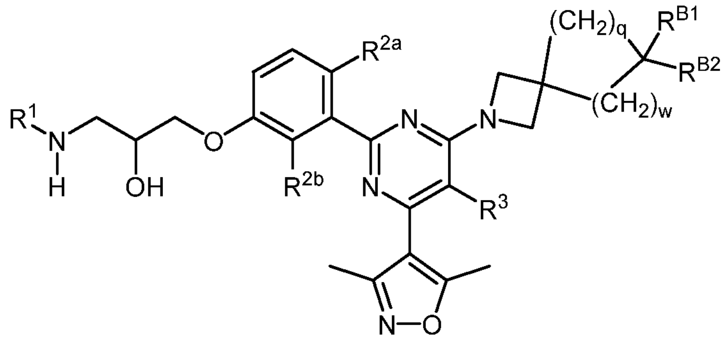
or a pharmaceutically acceptable salt thereof.

[00336] In certain embodiments, Ring B is of formula (xxv), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



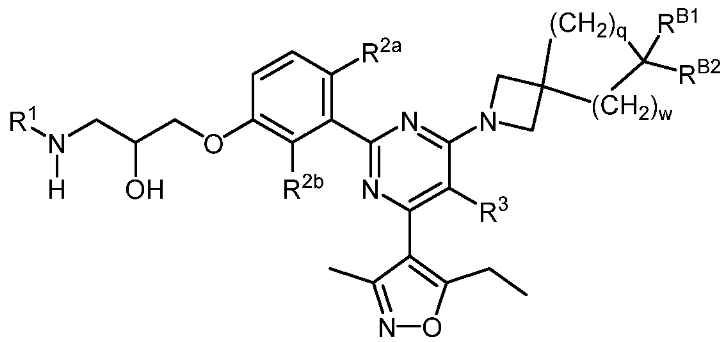
or a pharmaceutically acceptable salt thereof.

[00337] In certain embodiments, Ring B is of formula (xxvi), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



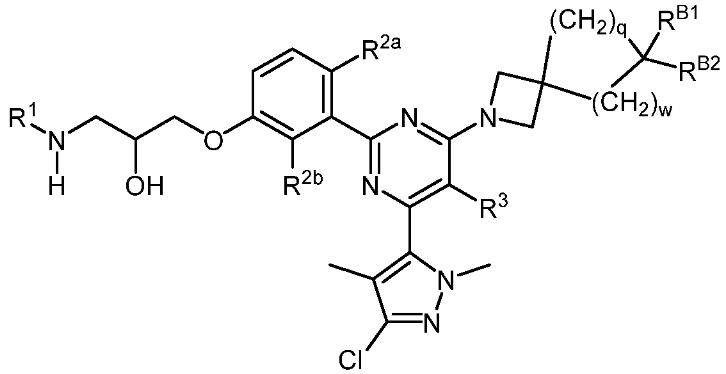
or a pharmaceutically acceptable salt thereof.

[00338] In certain embodiments, Ring B is of formula (xxvi), wherein Ring A is of formula (A-i), and wherein R^{A1} is $-CH_3$ and nd R^{A2} is $-CH_3$, provided is a compound of formula:



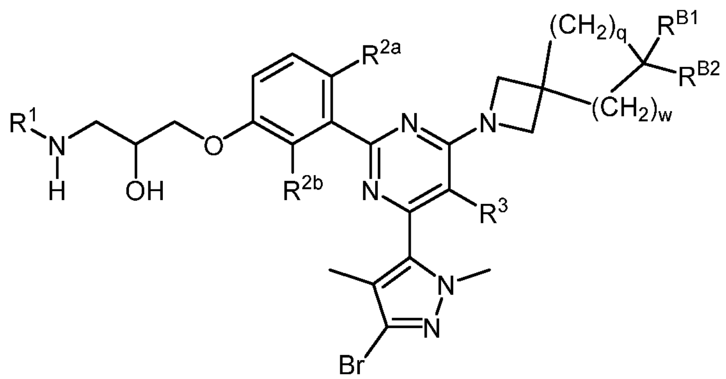
or a pharmaceutically acceptable salt thereof.

[00339] In certain embodiments, Ring B is of formula (xxvi), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $-CH_3$, R^{A4} is -Cl, and R^{A5} is $-CH_3$, provided is a compound of formula:



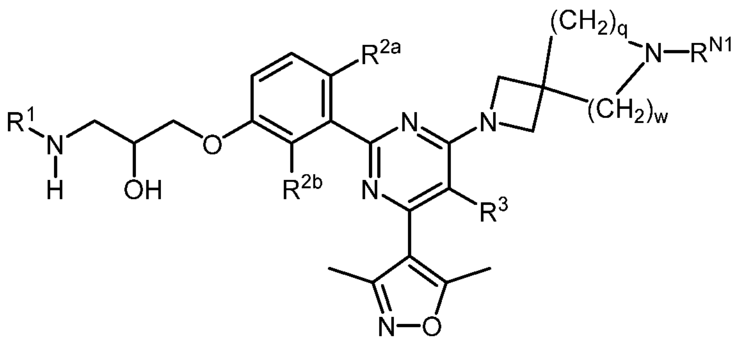
or a pharmaceutically acceptable salt thereof.

[00340] In certain embodiments, Ring B is of formula (xxvi), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $-CH_3$, R^{A4} is -Br, and R^{A5} is $-CH_3$, provided is a compound of formula:



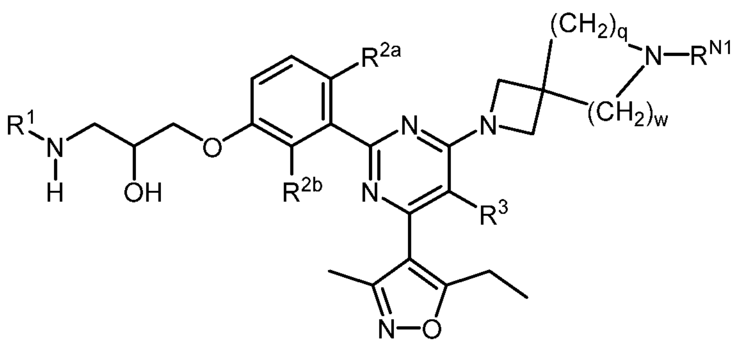
or a pharmaceutically acceptable salt thereof.

[00341] In certain embodiments, Ring B is of formula (xxvii), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



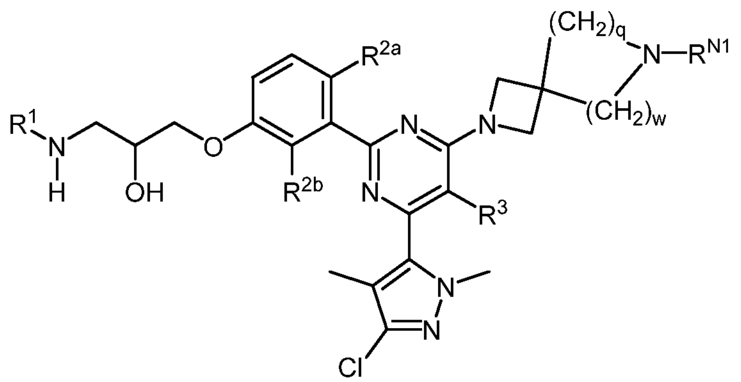
or a pharmaceutically acceptable salt thereof.

[00342] In certain embodiments, Ring B is of formula (xxvii), wherein Ring A is of formula (A-i), and wherein R^{A1} is $–CH_3$ and R^{A2} is $–CH_2CH_3$, provided is a compound of formula:



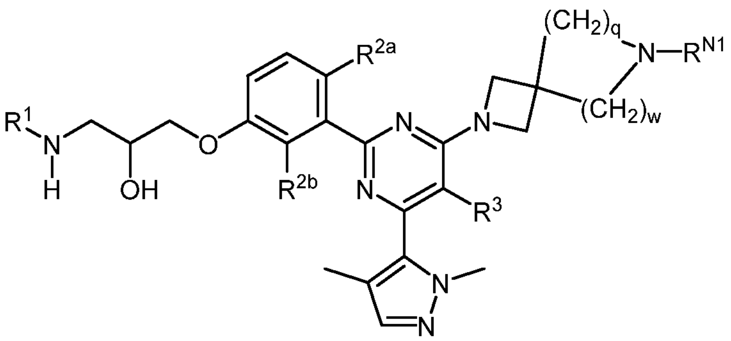
or a pharmaceutically acceptable salt thereof.

[00343] In certain embodiments, Ring B is of formula (xxvii), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $–CH_3$, R^{A4} is -Cl, and R^{A5} is $–CH_3$, provided is a compound of formula:



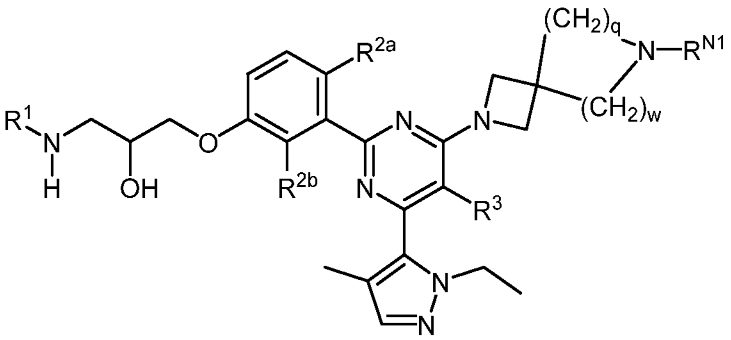
or a pharmaceutically acceptable salt thereof.

[00344] In certain embodiments, Ring B is of formula (xxvii), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $–CH_3$, R^{A4} is hydrogen, and R^{A5} is $–CH_3$, provided is a compound of formula:



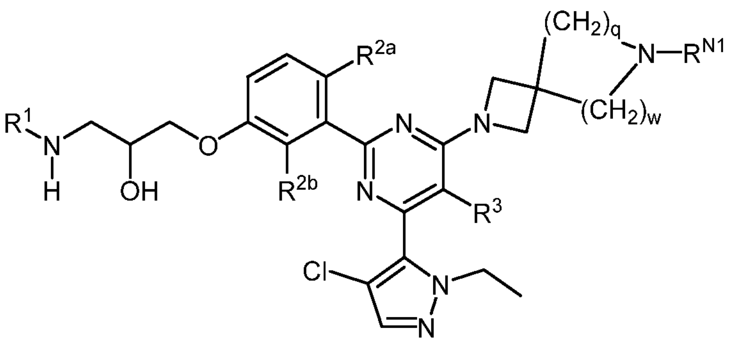
or a pharmaceutically acceptable salt thereof.

[00345] In certain embodiments, Ring B is of formula (xxvii), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $-CH_3$, R^{A4} is hydrogen, and R^{A5} is $-CH_2CH_3$, provided is a compound of formula:



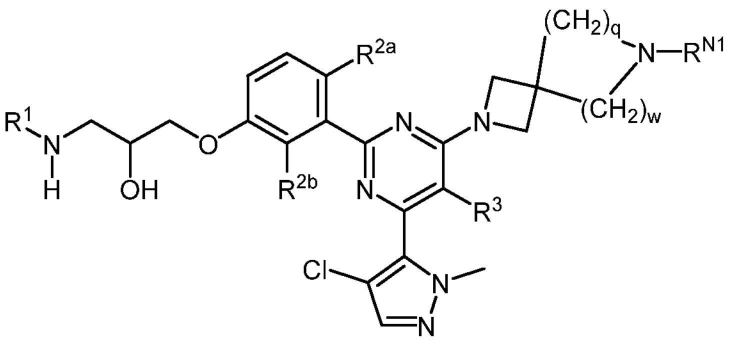
or a pharmaceutically acceptable salt thereof.

[00346] In certain embodiments, Ring B is of formula (xxvii), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $-Cl$, R^{A4} is hydrogen, and R^{A5} is $-CH_2CH_3$, provided is a compound of formula:



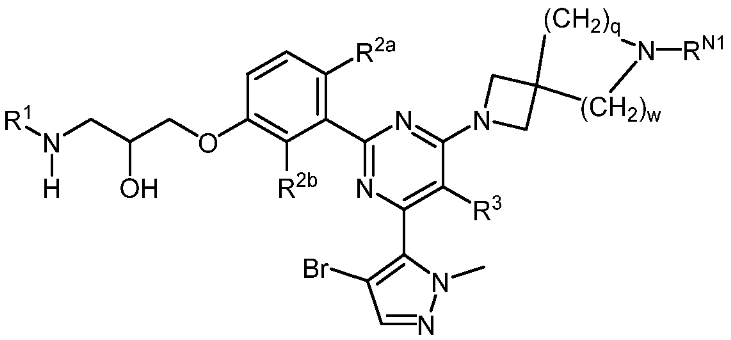
or a pharmaceutically acceptable salt thereof.

[00347] In certain embodiments, Ring B is of formula (xxvii), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $-Cl$, R^{A4} is hydrogen, and R^{A5} is $-CH_3$, provided is a compound of formula:



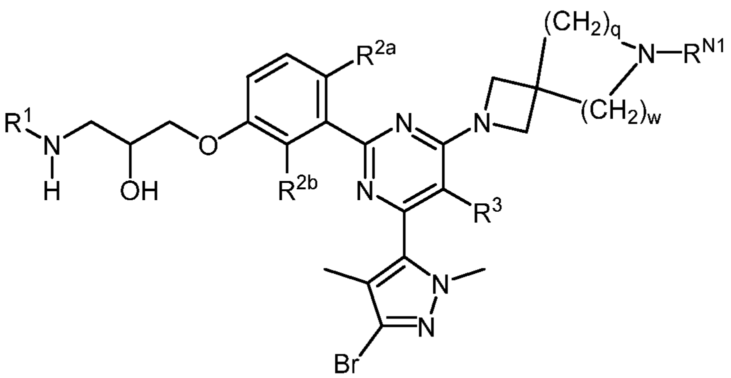
or a pharmaceutically acceptable salt thereof.

[00348] In certain embodiments, Ring B is of formula (xxvii), wherein Ring A is of formula (A-ii), and wherein R^{A3} is –Br, R^{A4} is hydrogen, and R^{A5} is $–CH_3$, provided is a compound of formula:



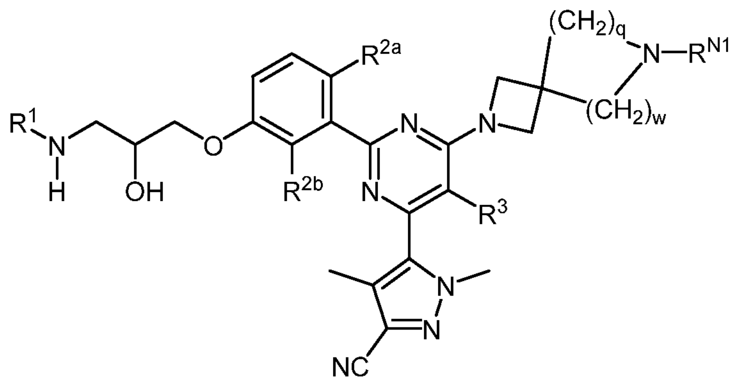
or a pharmaceutically acceptable salt thereof.

[00349] In certain embodiments, Ring B is of formula (xxvii), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $–CH_3$, R^{A4} is -Br, and R^{A5} is $–CH_3$, provided is a compound of formula:



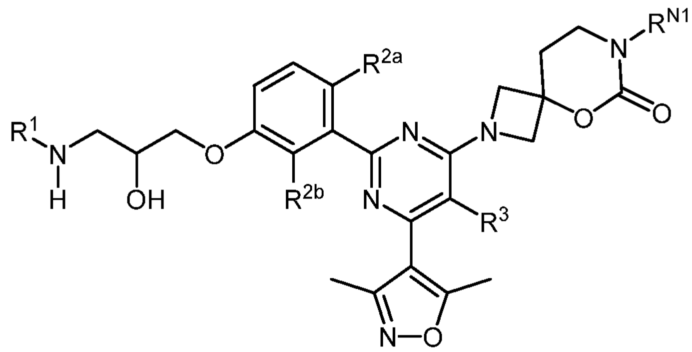
or a pharmaceutically acceptable salt thereof.

[00350] In certain embodiments, Ring B is of formula (xxvii), wherein Ring A is of formula (A-ii), and wherein R^{A3} is $–CH_3$, R^{A4} is -CN, and R^{A5} is $–CH_3$, provided is a compound of formula:



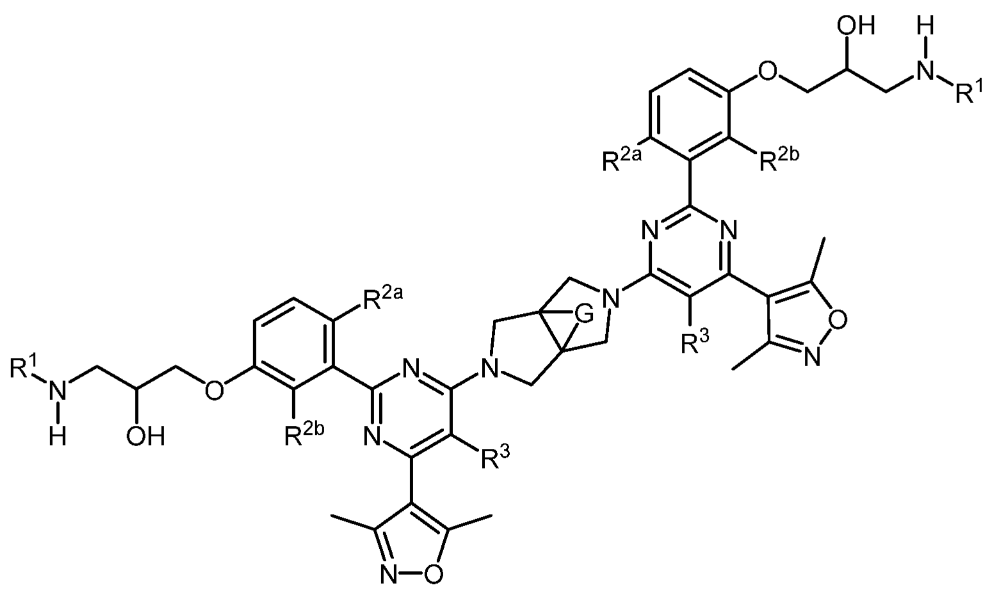
or a pharmaceutically acceptable salt thereof.

[00351] In certain embodiments, Ring B is of formula (xxviii), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



or a pharmaceutically acceptable salt thereof.

[00352] In certain embodiments, Ring B is of formula (xxix), wherein Ring A is of formula (A-i), and wherein each of R^{A1} and R^{A2} is $-CH_3$, provided is a compound of formula:



or a pharmaceutically acceptable salt thereof.

(X) Exemplary Compounds

[00353] In certain embodiments, a compound of Formula (**I**) is selected from any one of the compounds provided in Table 1, and pharmaceutically acceptable salts thereof.

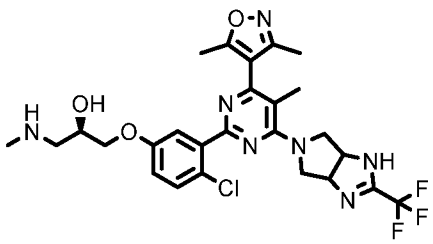
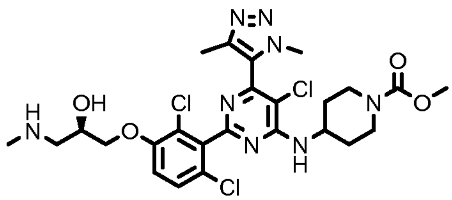
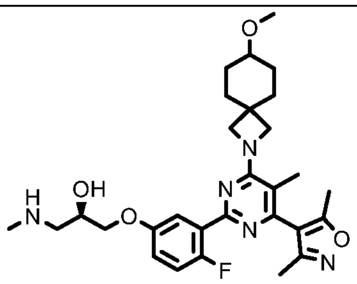
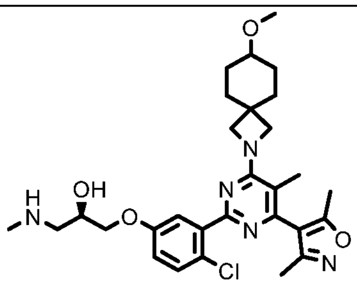
Table 1. Exemplary Compounds				
#	**Structure**	***Biochem IC_{50} (uM)**	***Cellular IC_{50} (uM)**	**LC-MS m/z (M+H)**
1		0.0061	>20	580.2
2		0.0401	>20	615.2
3		0.0067	0.105	539.8
4		0.0078	0.051	555.8

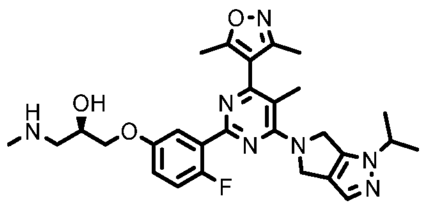
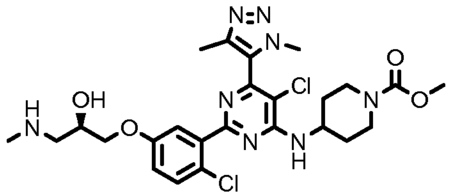
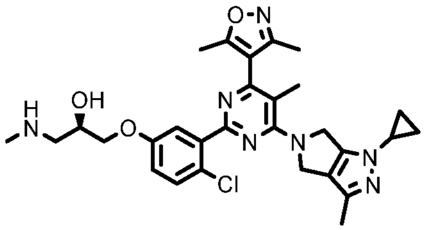
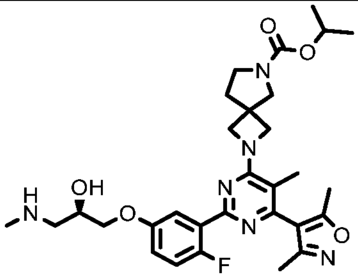
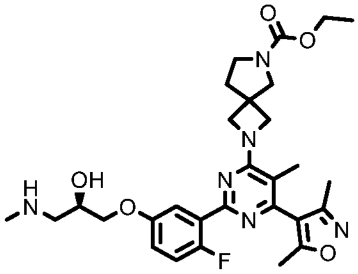
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC$_{50}$ (uM)	*Cellular IC$_{50}$ (uM)	LC-MS m/z (M+H)
5		0.0021	0.049	536.2
6		0.0047	0.455	579.2
7		0.0031	0.105	564.2
8		0.0033	0.103	583.3
9		0.0040	0.150	569.3

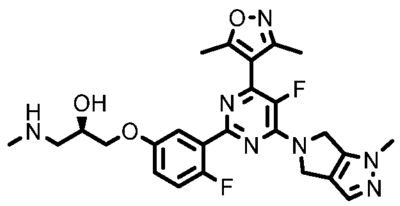
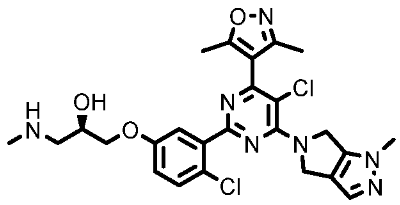
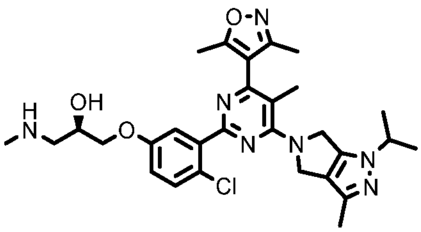
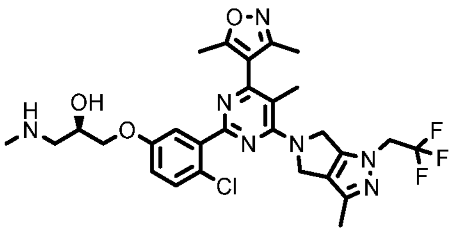
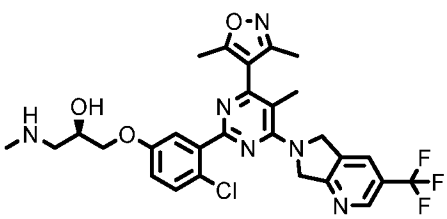
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
10		0.0023	0.126	512.3
11		0.0607	>20	544.3
12		0.0041	0.081	566.2
13		0.0036	0.074	606.2
14		0.0022	0.044	589.2

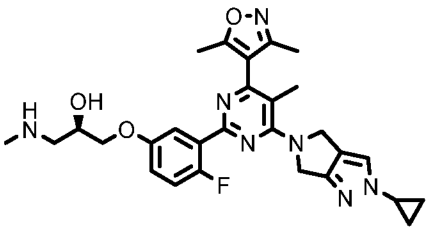
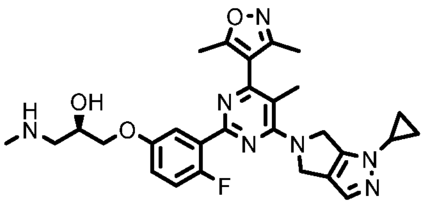
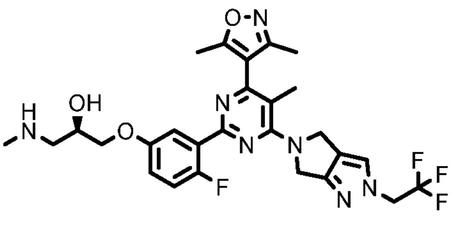
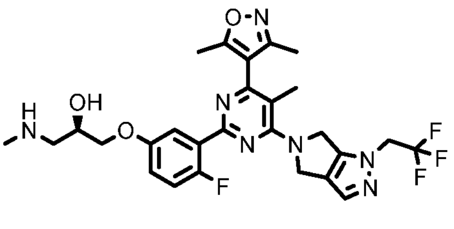
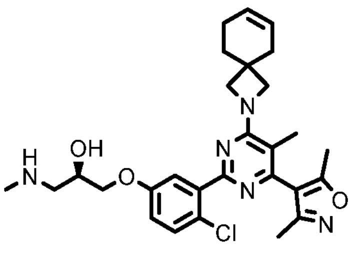
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
15		0.0019	0.140	533.8
16		0.0021	0.056	533.8
17		0.0024	0.162	575.7
18		0.0031	0.069	575.8
19		0.0041	0.195	524.2

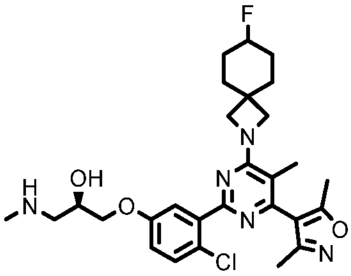
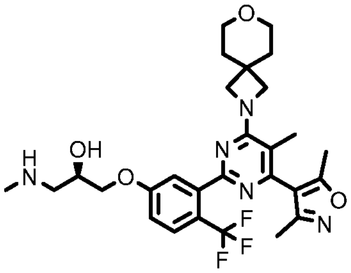
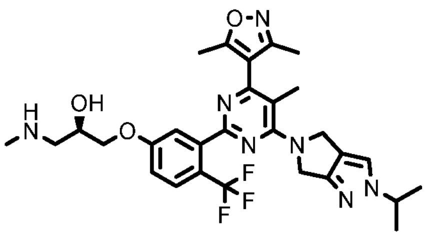
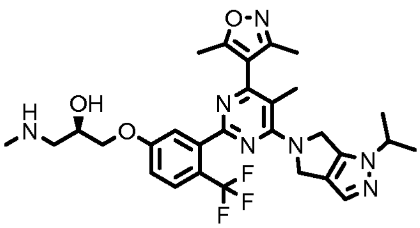
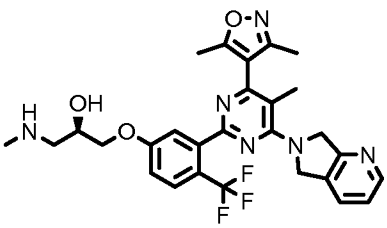
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
20		0.0074	0.125	544.3
21		0.0166	0.179	562.1
22		0.0063	0.181	585.7
23		0.0047	0.111	585.7
24		0.0054	0.188	555.1

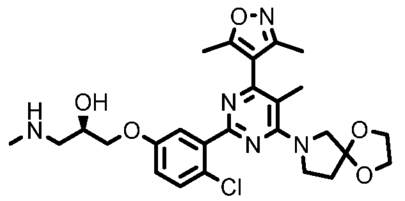
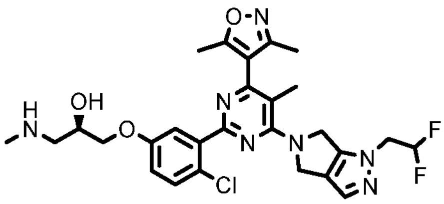
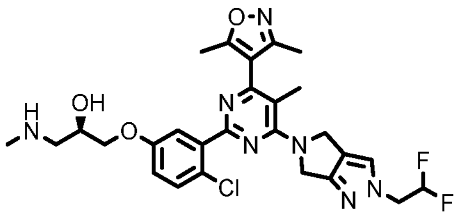
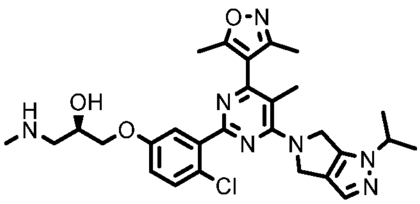
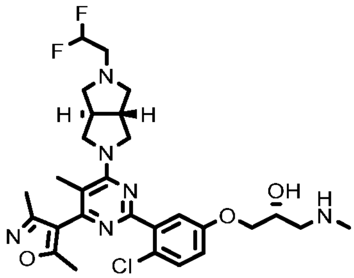
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
25		0.0056	0.452	530
26		0.0034	0.066	574.2
27		0.0037	0.115	574.2
28		0.0032	0.041	551.8
29		0.0102	0.263	577.3

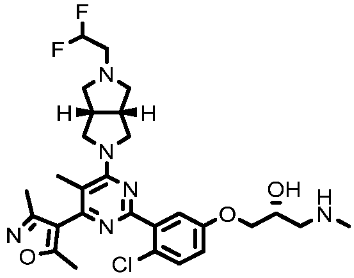
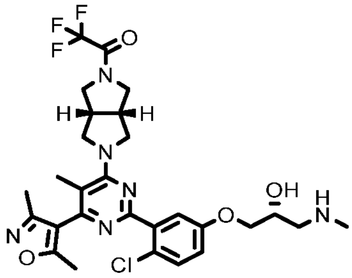
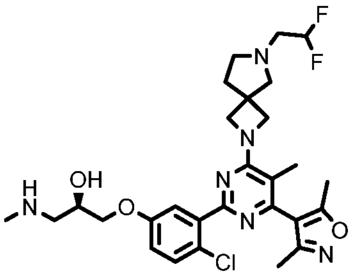
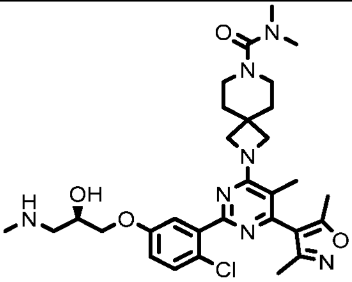
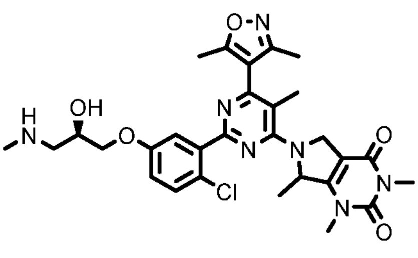
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
30		0.0070	0.166	577.3
31		0.0014	2.154	609.2
32		0.0070	0.053	577
33		0.0072	0.083	598.3
34		0.0051	0.120	596.2

Table 1. Exemplary Compounds

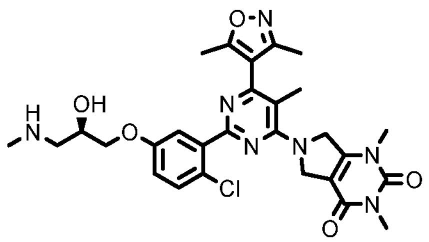
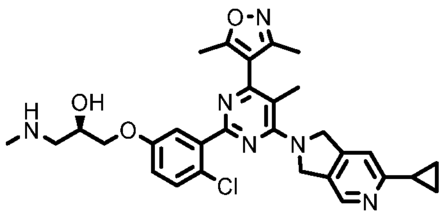
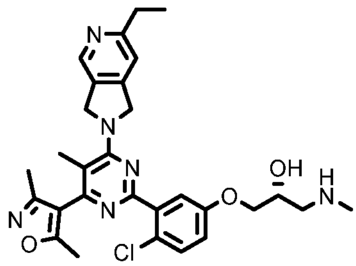
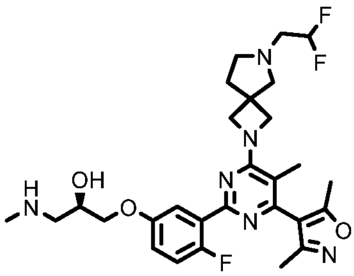
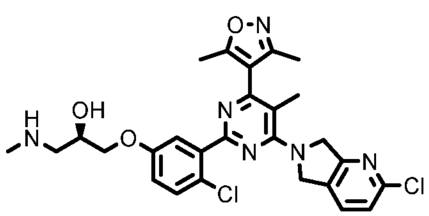
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
35		0.0037	0.412	582.2
36		0.0024	0.049	560.8
37		0.0026	0.037	548.8
38		0.0057	0.076	561.1
39		0.0020	0.032	555.2

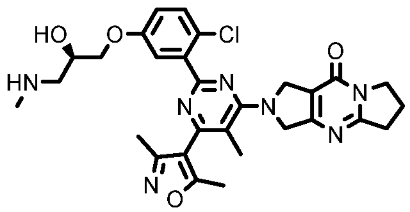
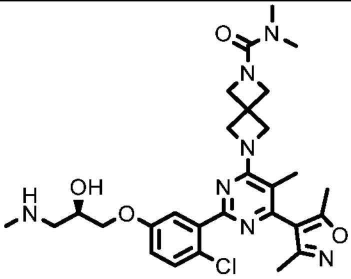
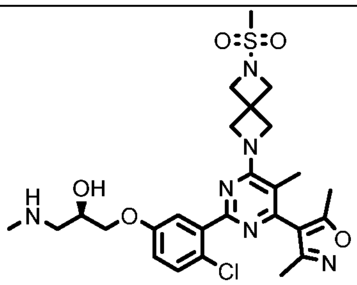
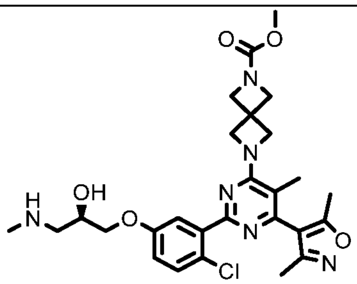
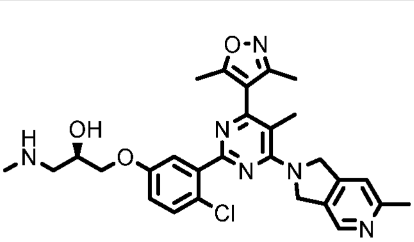
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
40		0.0028	0.391	578.2
41		0.0087	0.546	570.2
42		0.0104	0.406	577.2
43		0.0100	0.084	557.2
44		0.0029	0.027	534.8

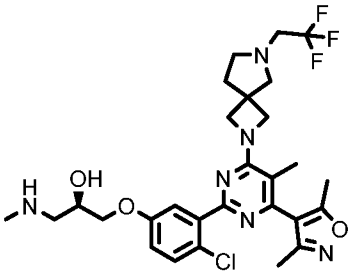
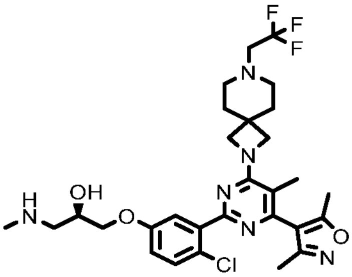
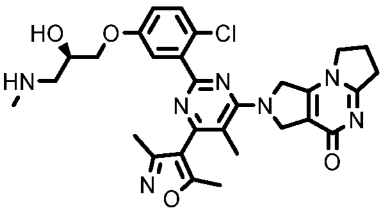
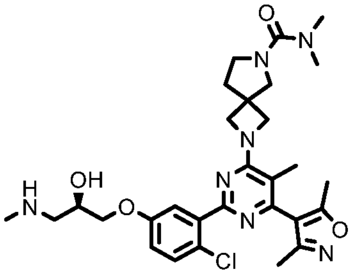
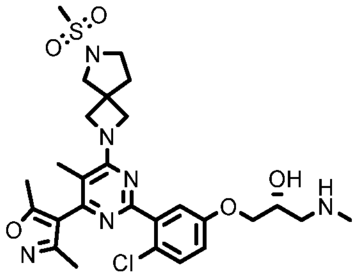
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
45		0.0119	0.040	595.1
46		0.0174	0.035	609.1
47		0.0063	>20	578.2
48		0.0127	0.238	584.2
49		0.0077	0.399	591.1

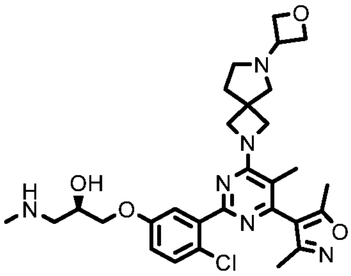
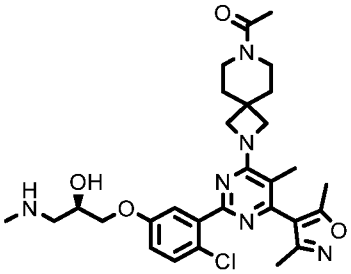
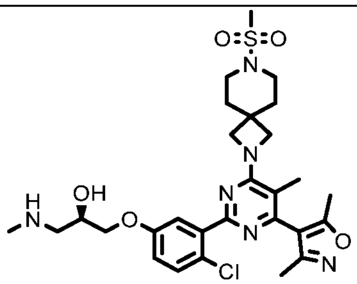
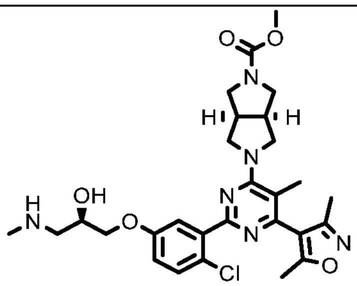
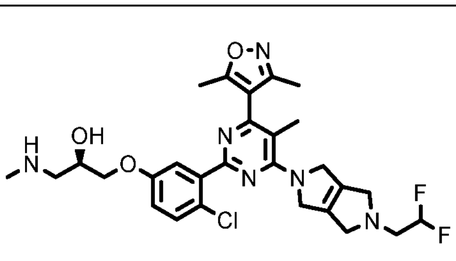
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
50		0.0088	0.155	569.2
51		0.0108	0.356	569.3
52		0.0073	0.230	605.2
53		0.0053	0.198	571.1
54		0.0044	0.045	575

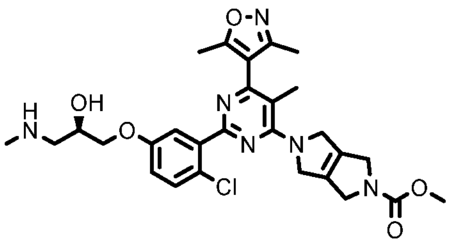
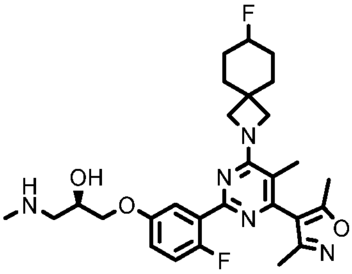
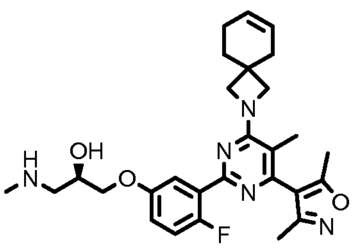
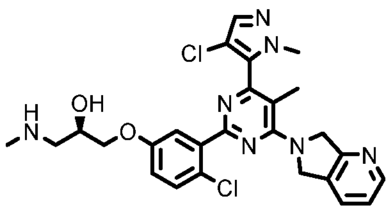
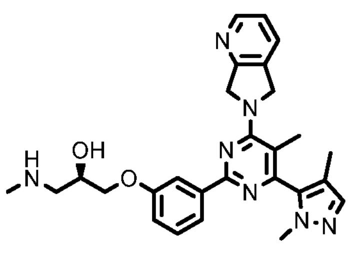
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
55		0.0036	0.013	569.1
56		0.0038	0.113	528.1
57		0.0034	0.276	508.1
58		0.0014	0.073	540.2
59		0.0018	0.292	486.1

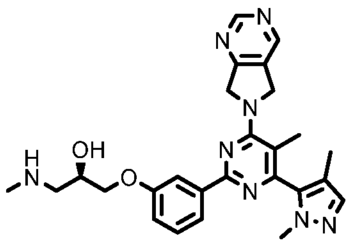
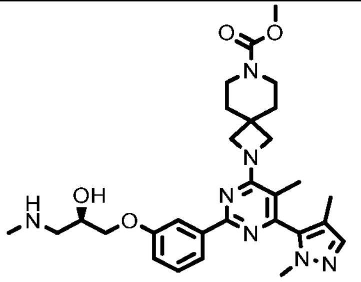
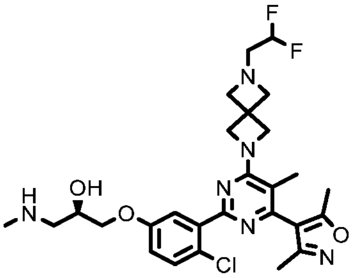
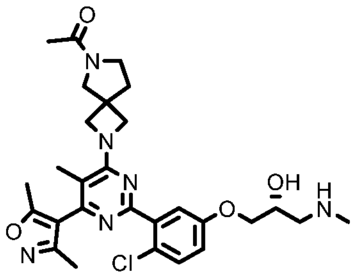
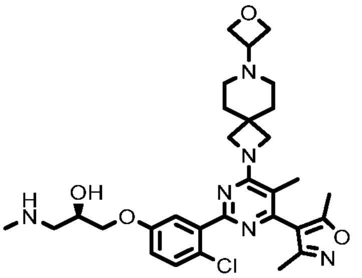
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
60		0.0039	0.389	487.1
61		0.0137	0.874	550.2
62		0.0647	0.526	563.2
63		0.0110	2.064	555.1
64		0.0110	0.111	583.1

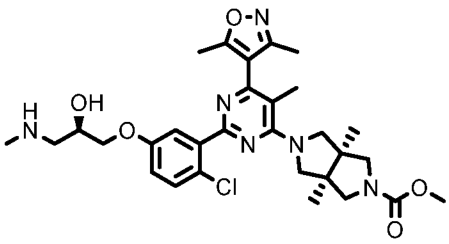
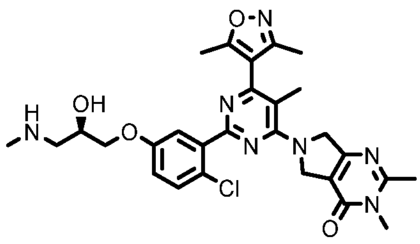
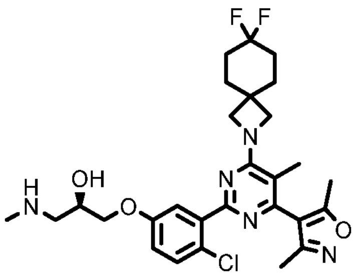
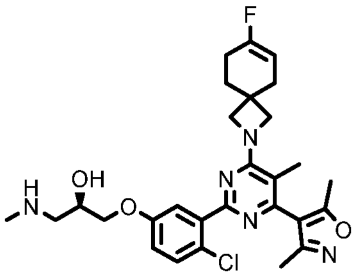
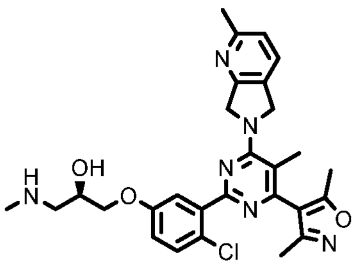
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
65		0.0078	0.234	599.1
66		0.0037	0.261	566.2
67		0.0050	0.071	562.1
68		0.0039	0.144	542.1
69		0.0012	0.022	535.1

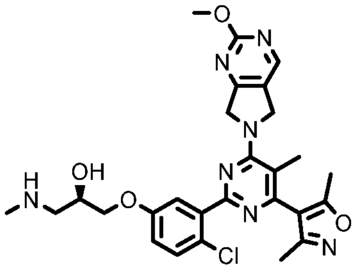
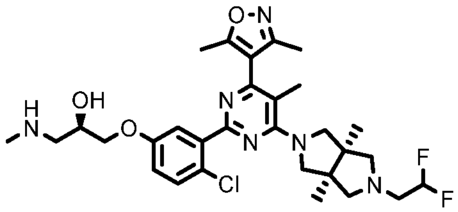
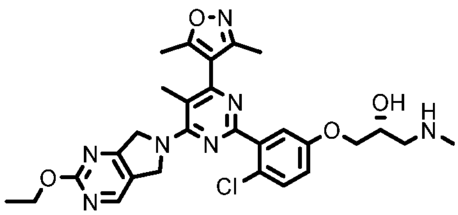
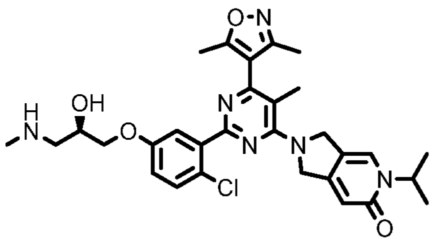
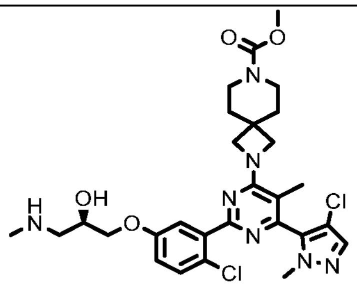
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
70		0.0032	0.019	552.2
71		0.0056	0.221	605.2
72		0.0029	0.012	566.2
73		0.0061	0.422	578.8
74		0.0097	0.207	604.2

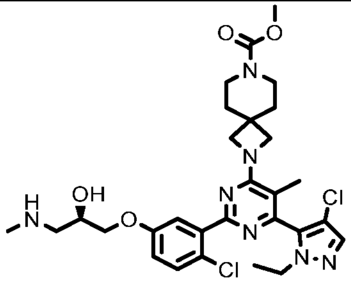
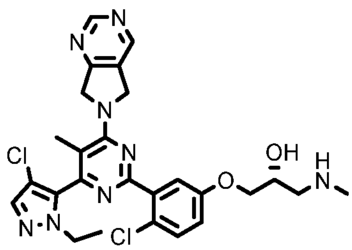
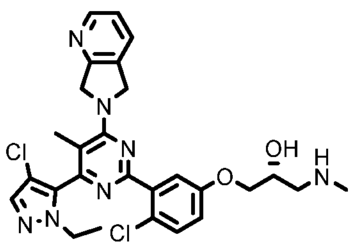
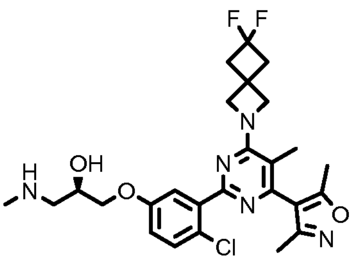
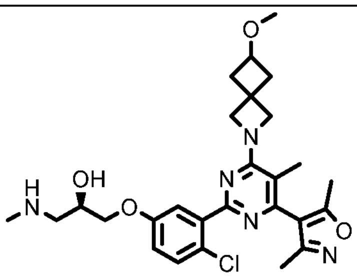
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
75		0.0125	0.396	618
76		0.0048	0.268	555
77		0.0037	0.293	554
78		0.0056	0.112	534
79		0.0093	0.060	528

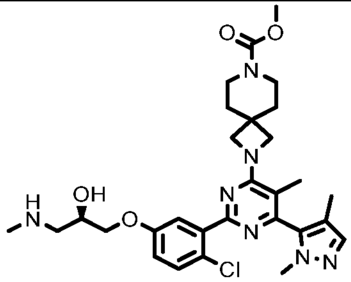
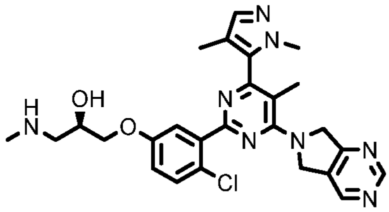
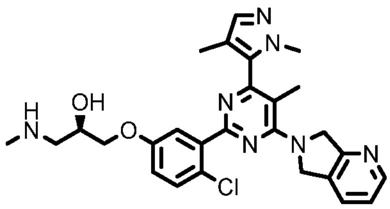
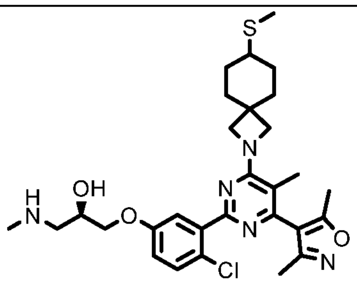
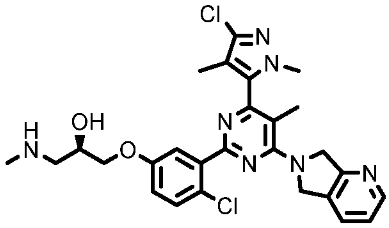
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC$_{50}$ (uM)	*Cellular IC$_{50}$ (uM)	LC-MS m/z (M+H)
80		0.0088	0.182	584.2
81		0.0038	0.112	521.3
82		0.0021	0.056	520.2
83		0.0033	0.074	572.2
84		0.0016	0.028	554.2

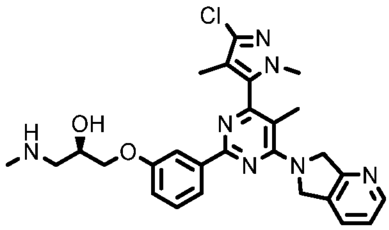
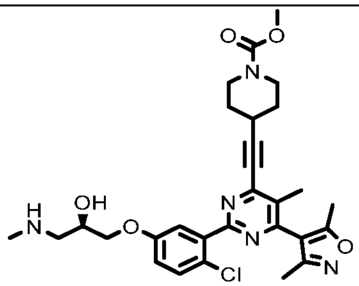
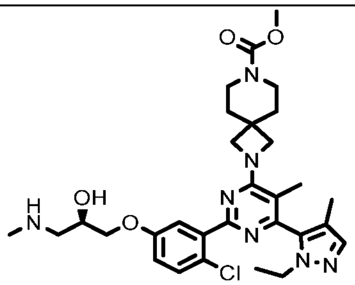
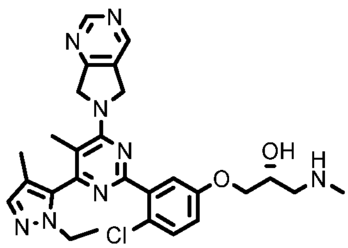
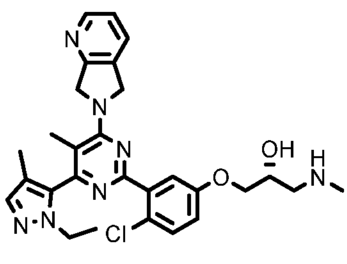
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC$_{50}$ (uM)	*Cellular IC$_{50}$ (uM)	LC-MS m/z (M+H)
85		0.0011	0.083	520.2
86		0.0970	0.283	568.2
87		0.0090	0.205	598.2
88		0.0046	0.222	535.2
89		0.0037	0.165	534.2

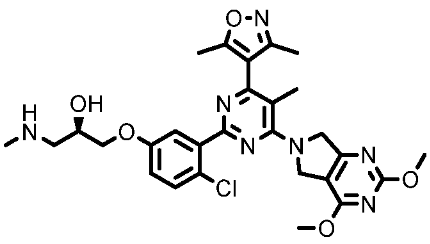
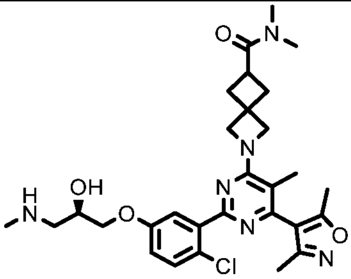
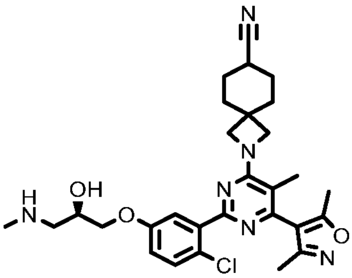
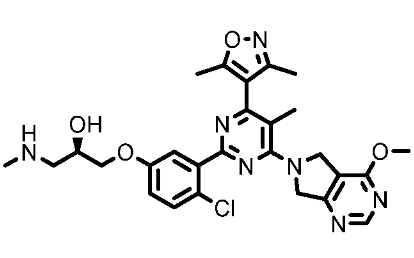
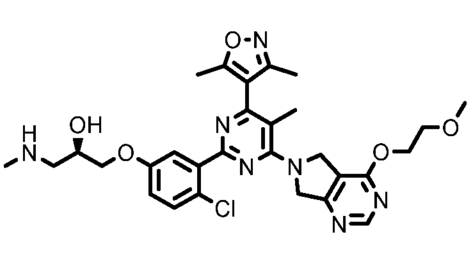
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC50 (uM)	*Cellular IC50 (uM)	LC-MS m/z (M+H)
90		0.0022	0.032	582.1
91		0.0055	0.092	569.1
92		0.0052	0.064	551.2
93		0.0023	0.033	552.1
94		0.0023	0.044	596.3

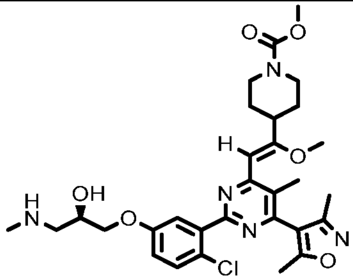
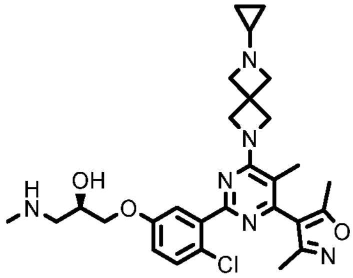
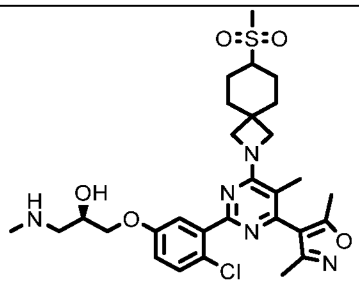
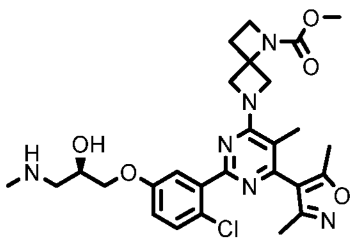
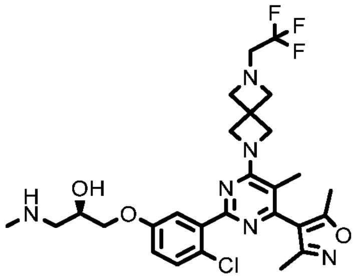
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
95		0.0112	0.995	600.1
96		0.0021	0.054	539.1
97		0.0109	0.394	604.1
98		0.0084	0.099	557.2
99		0.0110	0.039	581.1

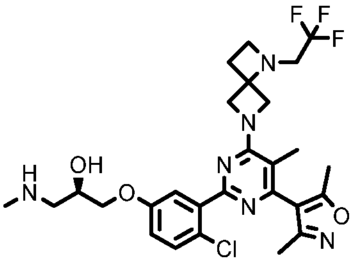
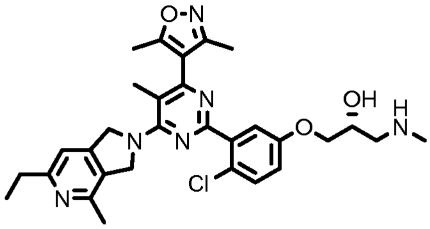
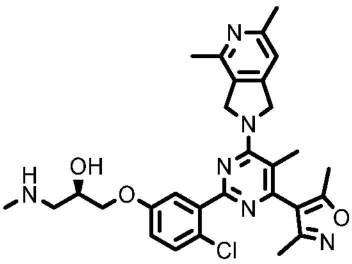
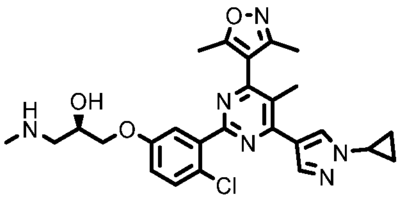
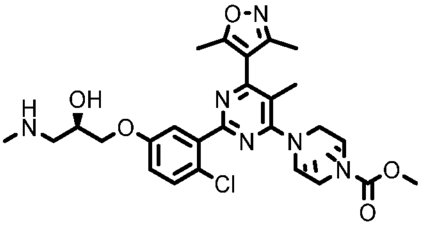
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
100		0.0113	0.068	581.1
101		0.0044	0.038	563.1
102		0.0045	0.027	549.1
103		0.0081	0.130	509.2
104		0.0108	0.368	557.1

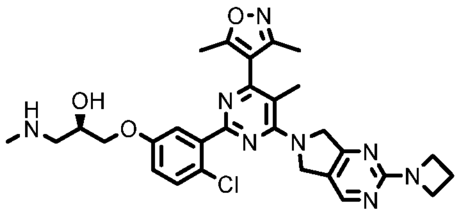
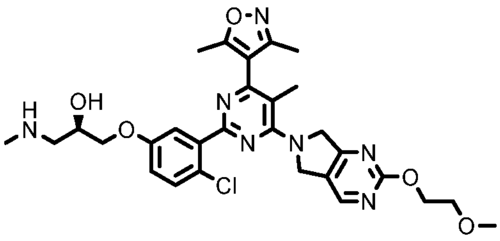
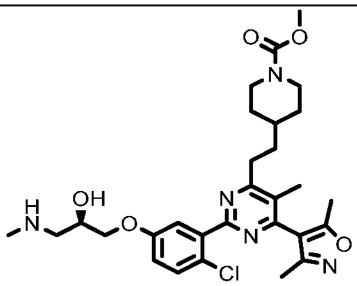
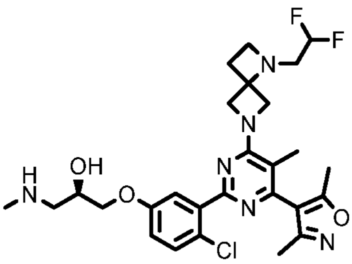
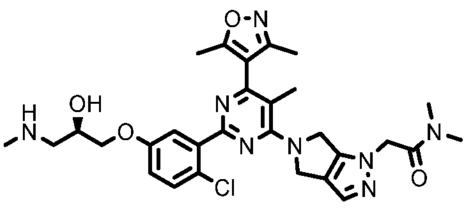
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
105		0.0032	0.011	577
106		0.0055	0.025	596
107		0.0112	0.176	572.2
108		0.0183	0.164	563.2
109		0.0064	2.841	595.2

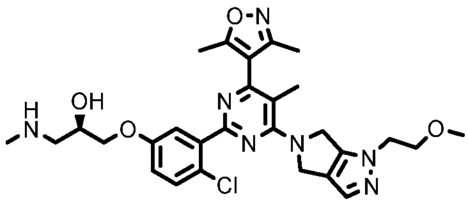
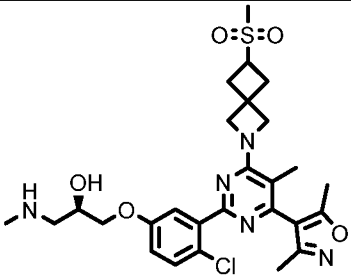
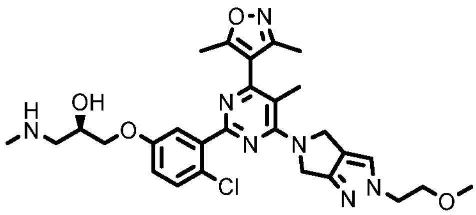
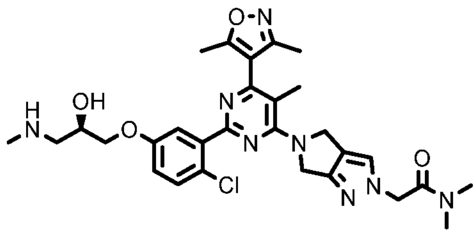
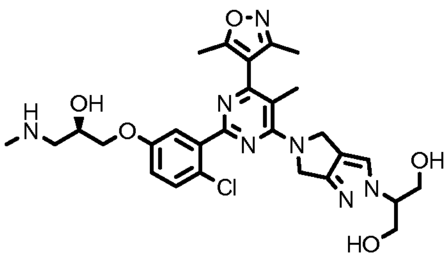
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC$_{50}$ (uM)	*Cellular IC$_{50}$ (uM)	LC-MS m/z (M+H)
110		0.0048	0.052	568.2
111		0.0112	0.822	576.2
112		0.0072	0.066	568.2
113		0.0088	1.149	595.2
114		0.0078	5.847	584.2

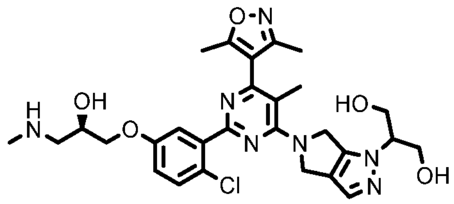
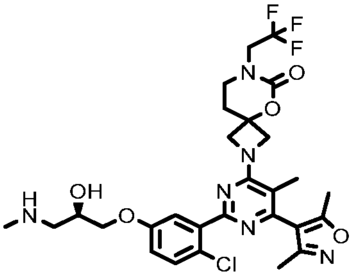
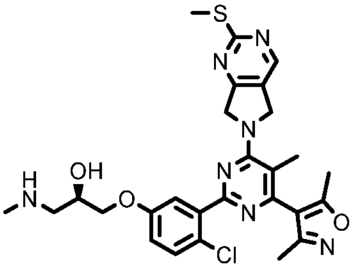
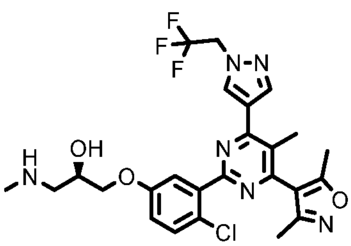
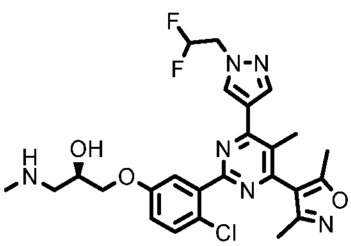
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
115		0.0099	9.129	584.2
116		0.0138	0.339	625
117		0.0039	0.031	568.2
118		0.0090	0.428	551.2
119		0.0076	0.340	533.2

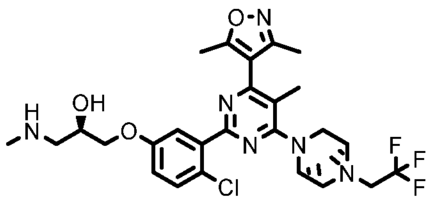
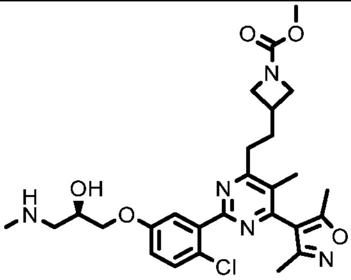
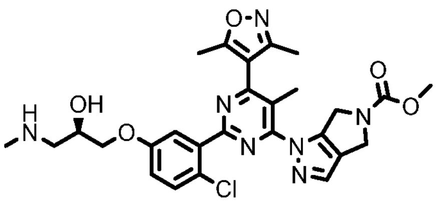
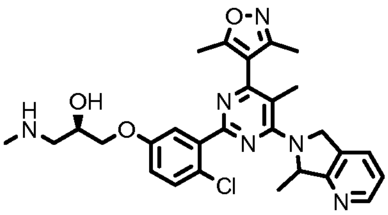
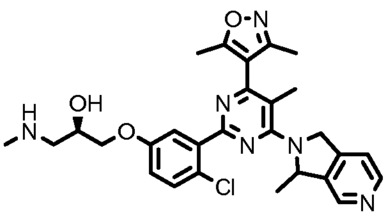
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC$_{50}$ (uM)	*Cellular IC$_{50}$ (uM)	LC-MS m/z (M+H)
120		0.0088	0.389	581.1
121		0.0134	0.257	544
122		0.0137	1.810	568.1
123		0.0034	0.163	535
124		0.0052	0.175	535

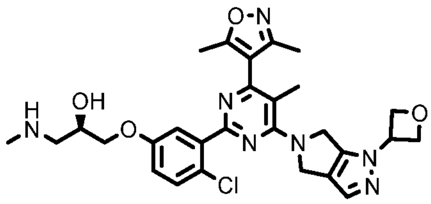
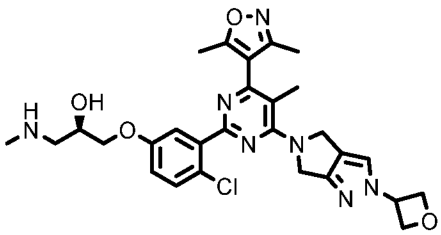
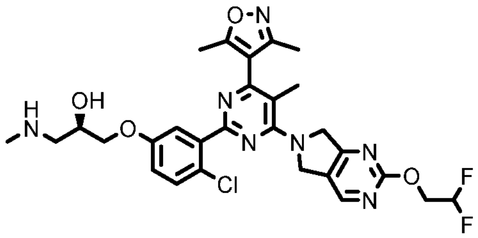
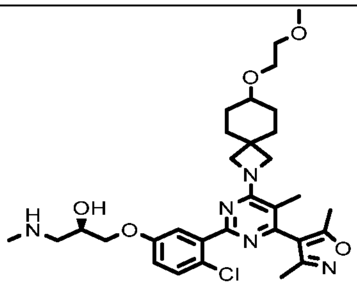
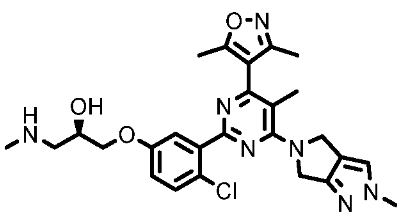
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC$_{50}$ (uM)	*Cellular IC$_{50}$ (uM)	LC-MS m/z (M+H)
125		0.0065	0.150	566.2
126		0.0062	0.157	566.2
127		0.0078	0.032	602
128		0.0163	0.099	600
129		0.0077	0.046	524.2

Table 1. Exemplary Compounds

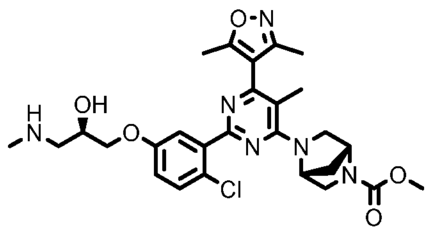
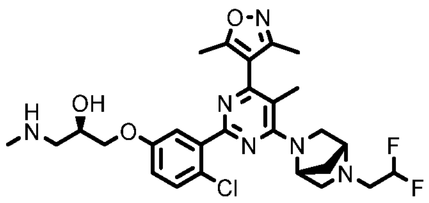
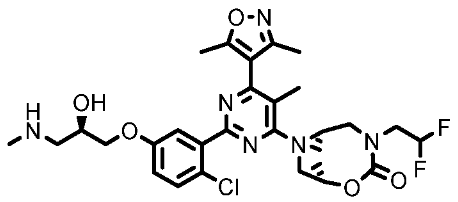
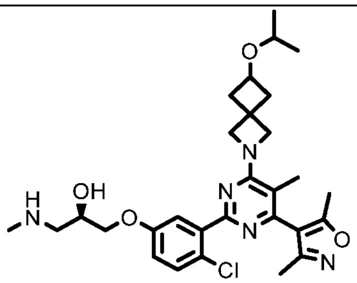
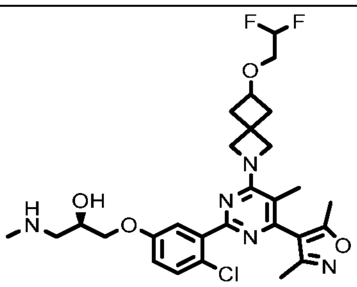
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
130		0.0059	0.960	557.1
131		0.0090	0.612	563
132		0.0066	0.637	607
133		0.0099	0.042	556
134		0.0085	0.045	578

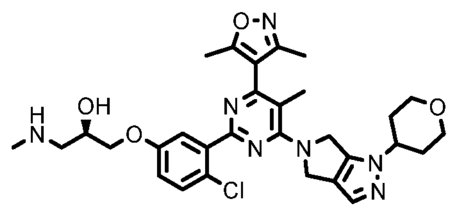
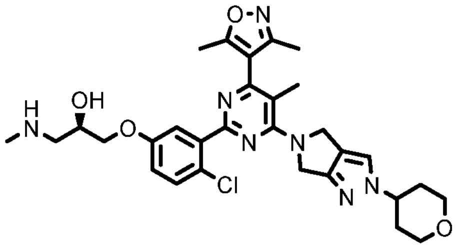
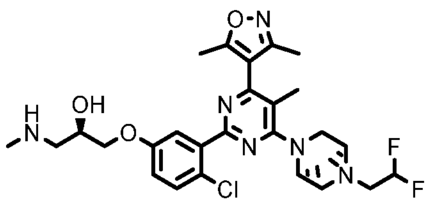
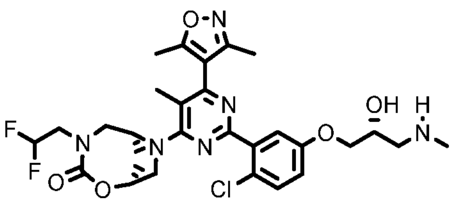
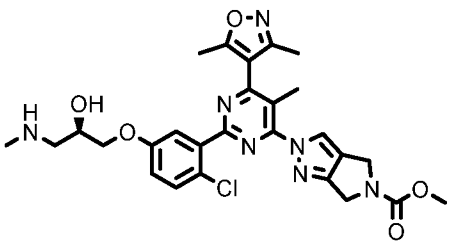
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC$_{50}$ (uM)	*Cellular IC$_{50}$ (uM)	LC-MS m/z (M+H)
135		0.0046	0.093	594.2
136		0.0051	0.172	594.2
137		0.0080	0.311	563.1
138		0.0046	0.581	607
139		0.0052	0.131	568

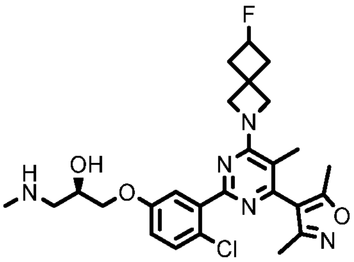
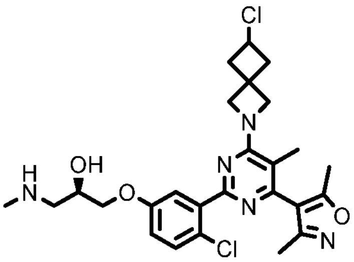
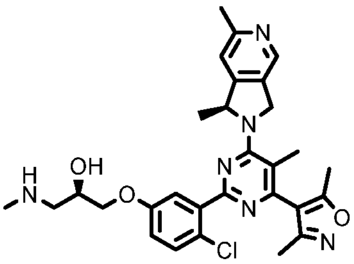
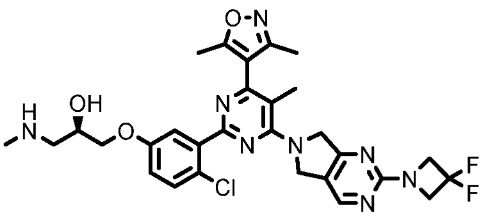
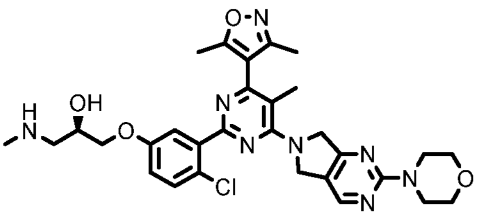
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
140		0.0042	0.241	516
141		0.0037	0.173	532
142		0.0036	0.065	549.2
143		0.0028	0.015	613
144		0.0033	0.022	607.2

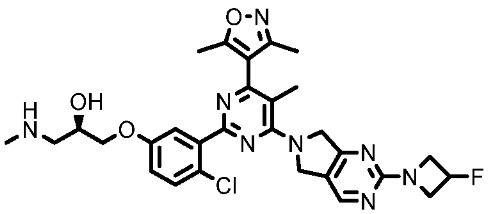
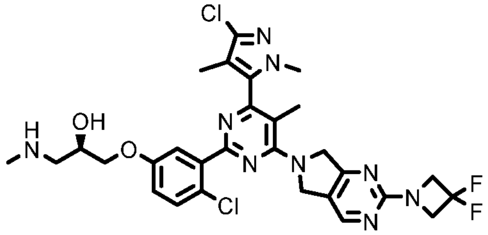
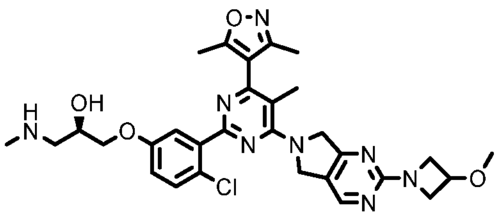
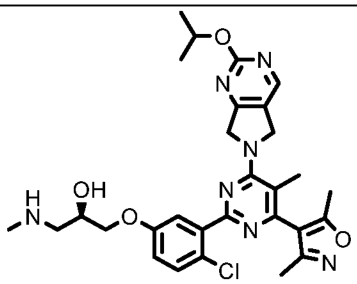
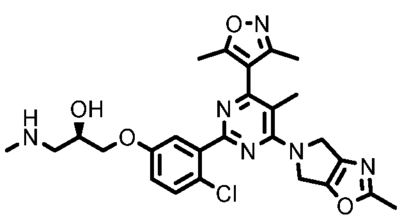
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC$_{50}$ (uM)	*Cellular IC$_{50}$ (uM)	LC-MS m/z (M+H)
145		0.0020	0.015	595
146		0.0027	0.026	646.2
147		0.0028	0.016	607.1
148		0.0037	0.039	580
149		0.0031	0.052	525.2

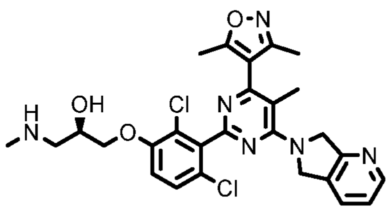
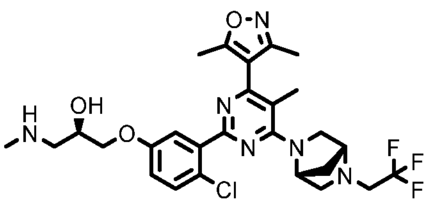
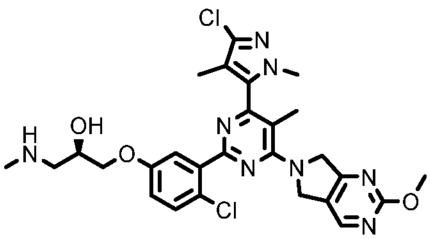
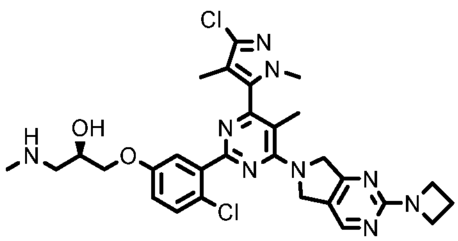
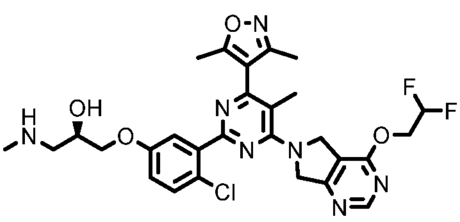
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
150		0.0162	2.020	555.2
151		0.0121	0.668	581.1
152		0.0019	0.018	585
153		0.0019	0.015	610.1
154		0.0031	0.057	602.1

Table 1. Exemplary Compounds

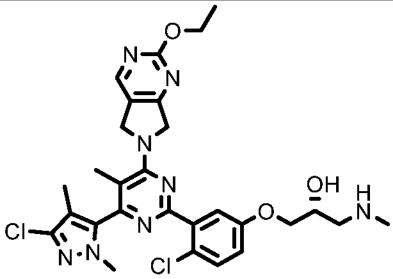
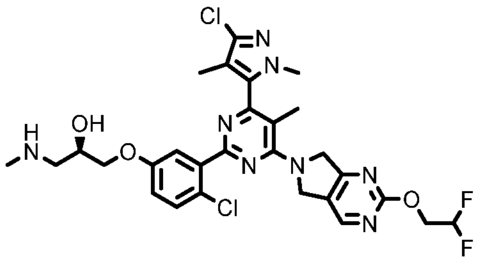
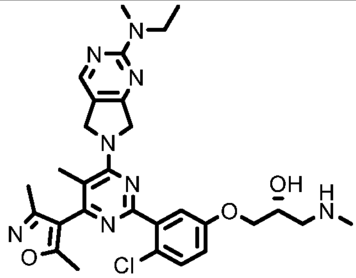
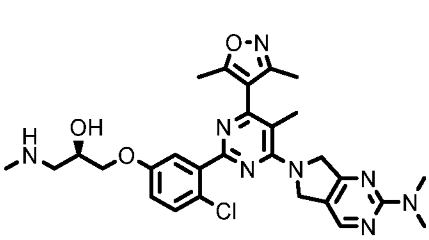
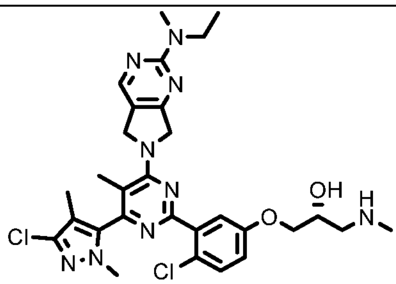
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
155		0.0024	0.018	599
156		0.0035	0.031	635
157		0.0024	0.026	579.1
158		0.0029	0.018	565.1
159		0.0020	0.039	612

Table 1. Exemplary Compounds

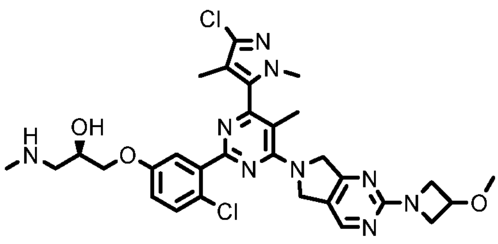
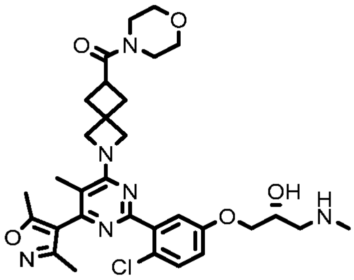
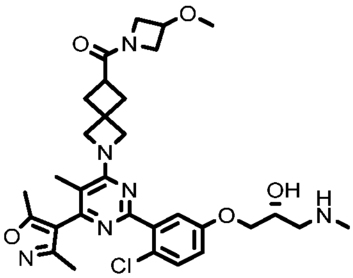
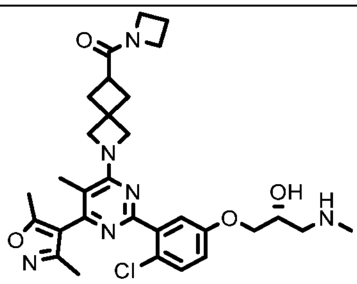
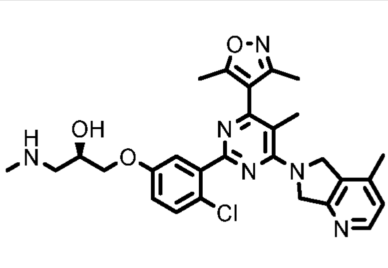
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
160		0.0030	0.026	641.2
161		0.0074	0.239	611.2
162		0.0069	0.550	611.2
163		0.0062	0.292	581.2
164		0.0022	0.055	535

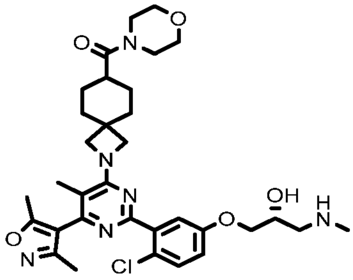
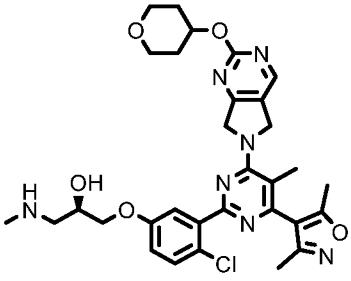
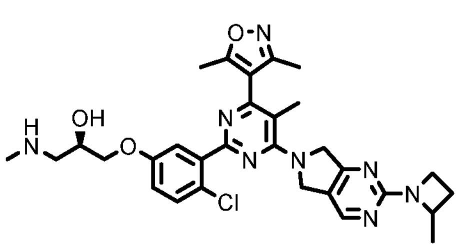
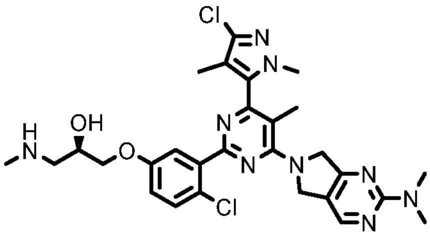
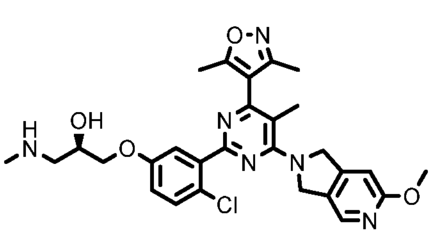
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
165		0.0058	0.322	639
166		0.0051	0.049	622.2
167		0.0019	0.019	591.1
168		0.0025	0.026	598
169		0.0021	0.034	551.1

Table 1. Exemplary Compounds

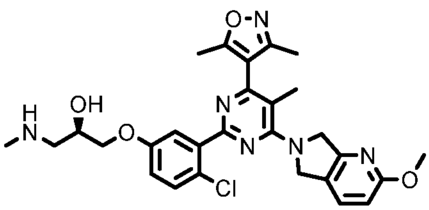
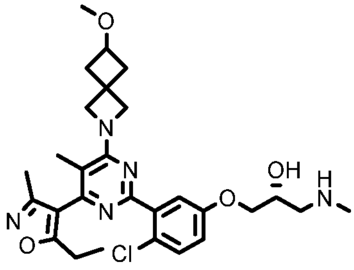
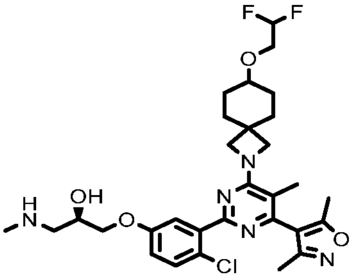
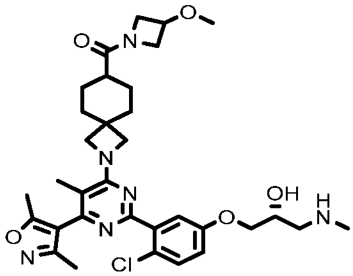
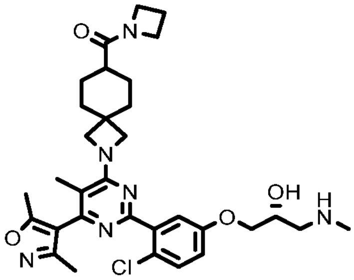
#	Structure	*Biochem IC$_{50}$ (uM)	*Cellular IC$_{50}$ (uM)	LC-MS m/z (M+H)
170		0.0019	0.038	551
171		0.0058	0.174	542.1
172		0.0047	0.057	606
173		0.0050	0.408	639
174		0.0039	0.271	609

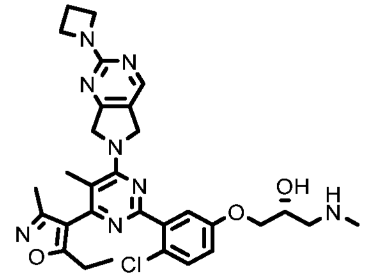
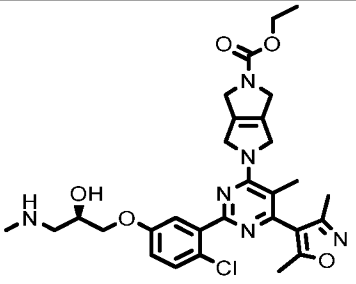
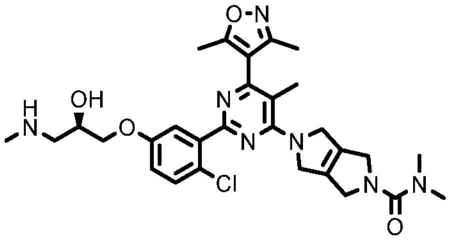
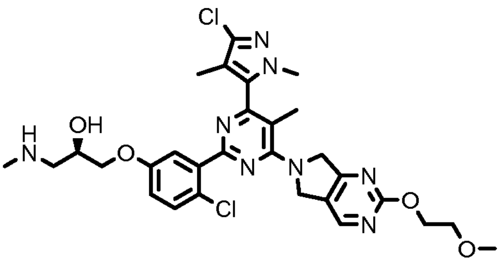
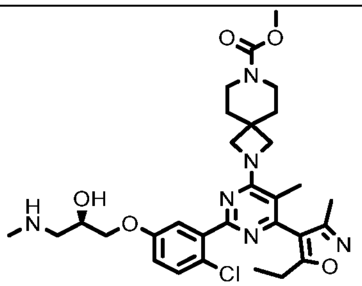
Table 1. Exemplary Compounds				
#	**Structure**	***Biochem IC_{50} (uM)**	***Cellular IC_{50} (uM)**	**LC-MS m/z (M+H)**
175		0.0017	0.013	591.2
176		0.0027	0.026	583
177		0.0036	0.087	582
178		0.0014	0.024	629.2
179		0.0051	0.119	599.1

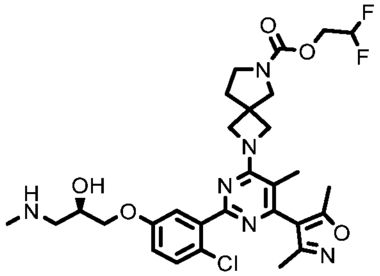
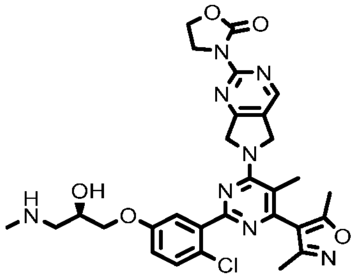
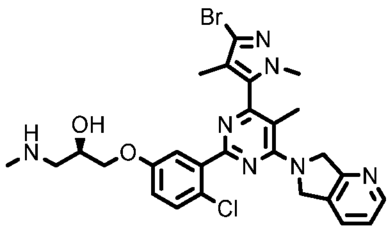
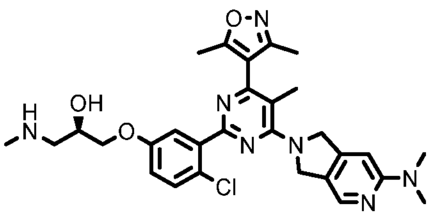
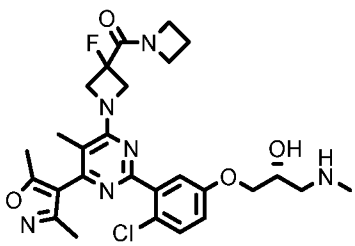
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC$_{50}$ (uM)	*Cellular IC$_{50}$ (uM)	LC-MS m/z (M+H)
180		0.0041	0.121	621.2
181		0.0018	0.459	607.2
182		0.0008	0.021	600.1
183		0.0018	0.031	564.2
184		0.0061	0.488	559.2

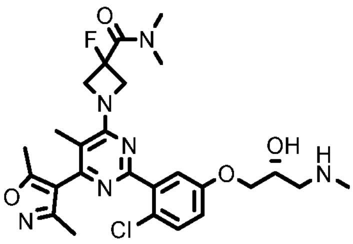
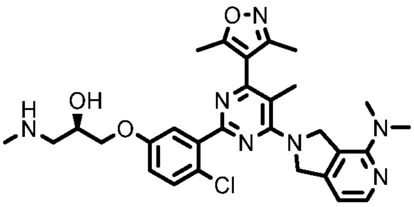
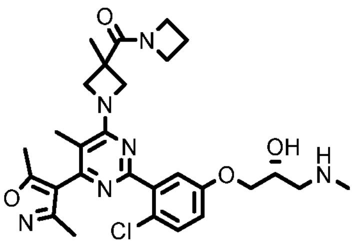
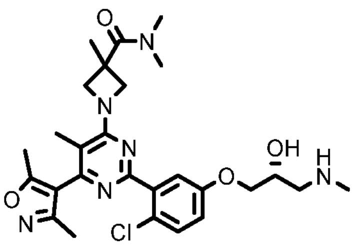
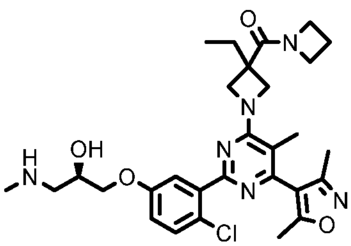
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
185		0.0051	0.346	547
186		0.0018	0.049	564.2
187		0.0058	0.337	555
188		0.0052	0.150	543
189		0.0057	0.246	569.3

Table 1. Exemplary Compounds

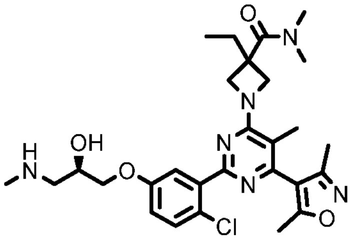
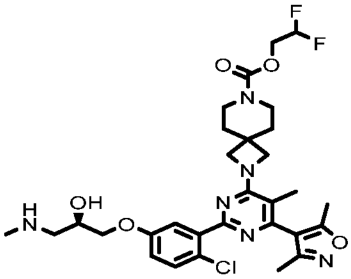
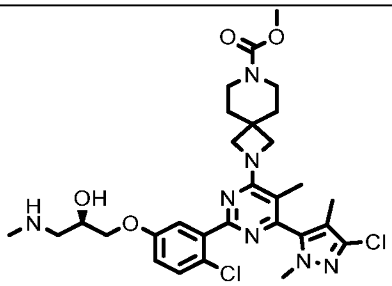
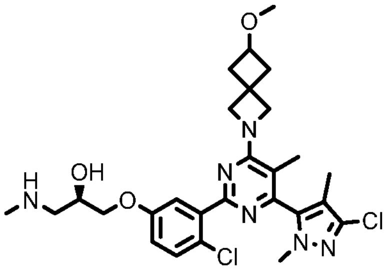
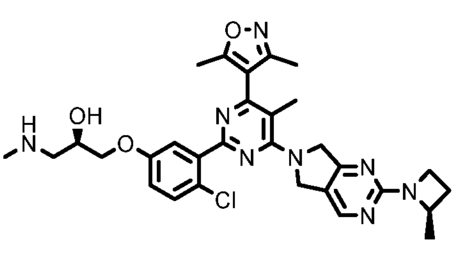
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
190		0.0062	0.138	557.3
191		0.0105	0.174	635.2
192		0.0047	0.058	617.2
193		0.0041	0.052	561.2
194		0.0018	0.013	591

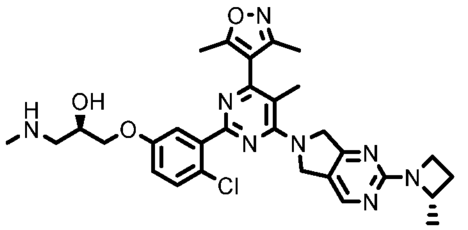
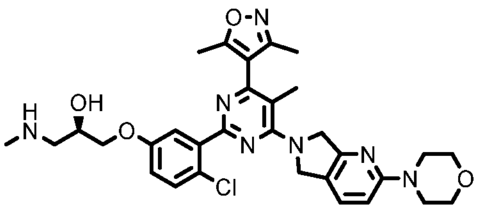
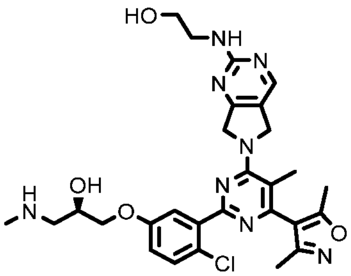
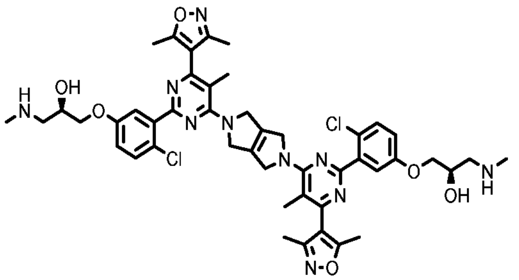
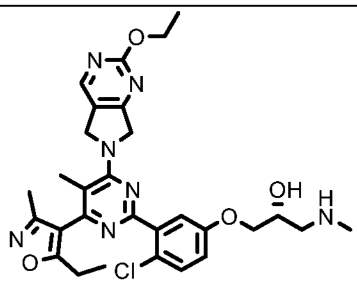
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
195		0.0018	0.013	591
196		0.0020	0.020	606.2
197		0.0026	0.381	581.3
198		0.0004	0.171	911.3
199		0.0057	0.084	580.2

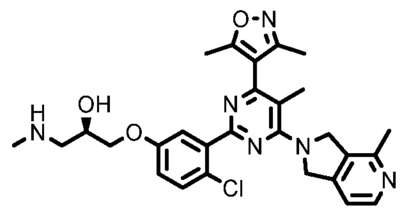
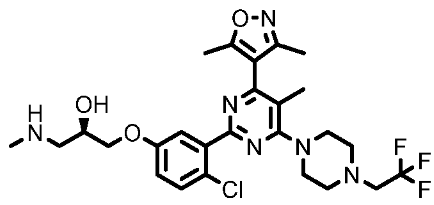
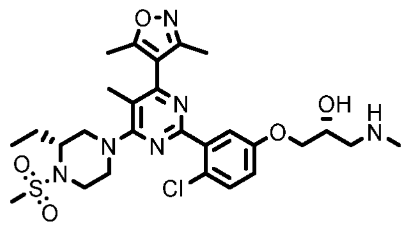
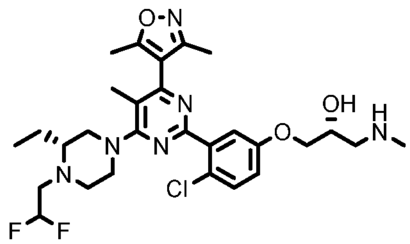
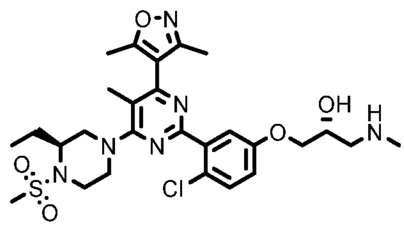
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
200		0.0021	0.047	536.1
201		0.0048	0.295	569
202		0.0033	0.233	593
203		0.0046	0.200	579
204		0.0043	0.486	593

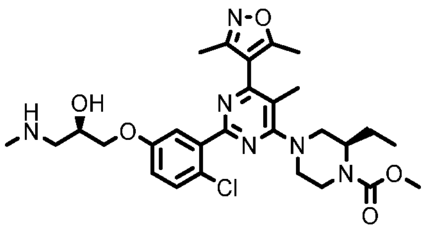
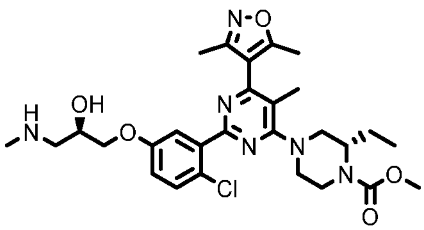
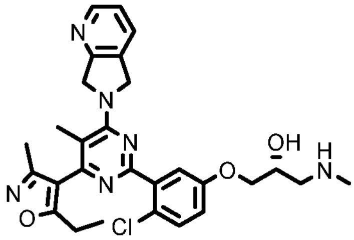
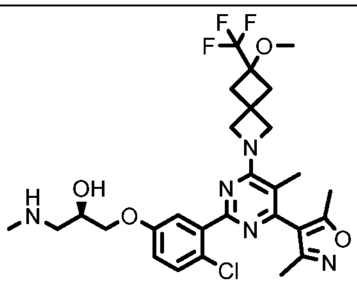
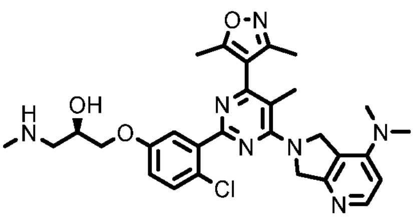
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
205		0.0037	0.202	573.1
206		0.0054	0.696	573
207		0.0015	0.074	535.2
208		0.0052	0.142	596.3
209		0.0006	0.129	564.2

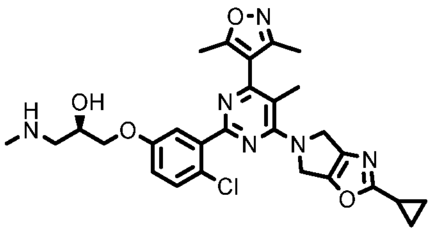
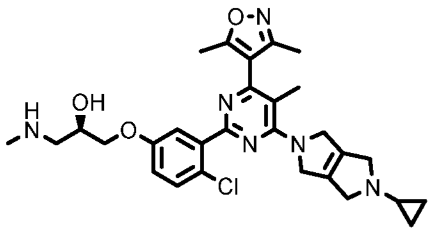
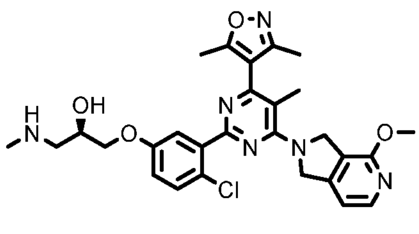
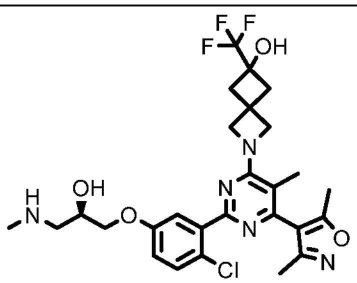
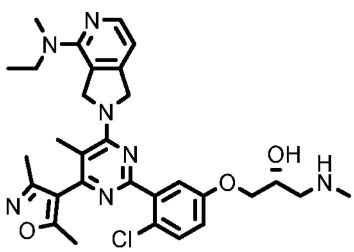
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC$_{50}$ (uM)	*Cellular IC$_{50}$ (uM)	LC-MS m/z (M+H)
210		0.0021	0.120	551
211		0.0017	0.075	551.2
212		0.0021	0.040	551.1
213		0.0054	0.330	582.2
214		0.0011	0.046	578.2

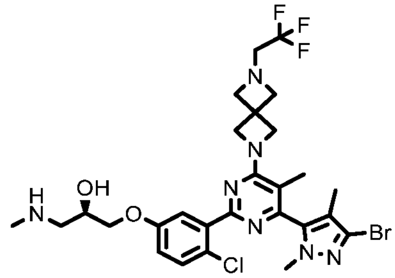
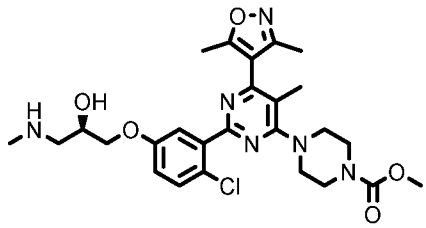
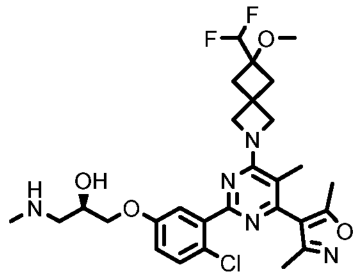
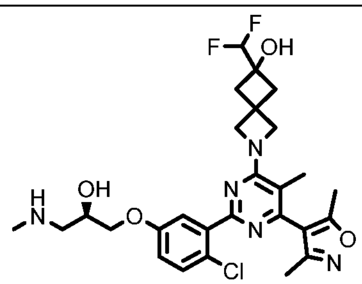
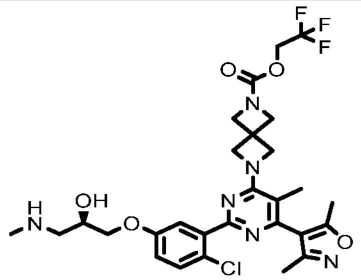
Table 1. Exemplary Compounds				
#	**Structure**	***Biochem IC_{50} (uM)**	***Cellular IC_{50} (uM)**	**LC-MS m/z (M+H)**
215		0.0044	0.023	660.1
216		0.0054	0.415	545
217		0.0047	0.101	578.3
218		0.0060	0.419	564.02
219		0.0055	0.129	625

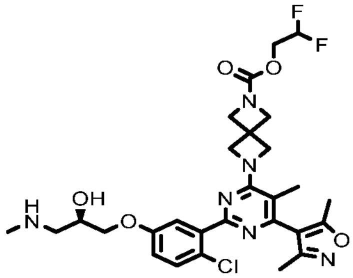
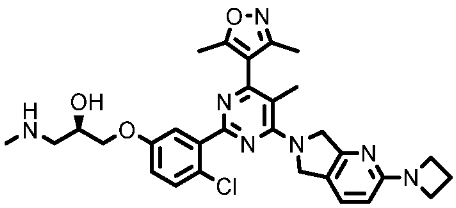
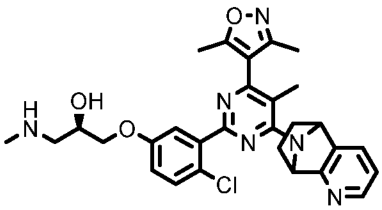
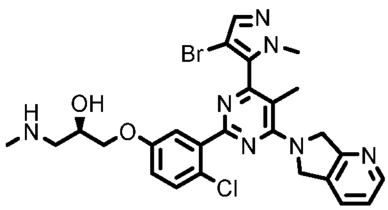
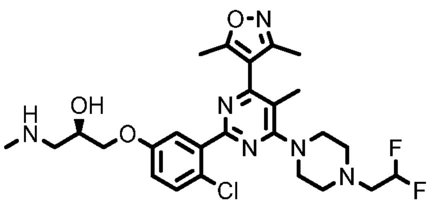
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC50 (uM)	*Cellular IC50 (uM)	LC-MS m/z (M+H)
220		0.0042	0.221	607.1
221		0.0015	0.017	576
222		0.0060	1.396	547.2
223		0.0012	0.071	586
224		0.0068	0.330	551.2

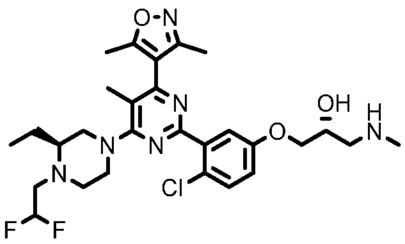
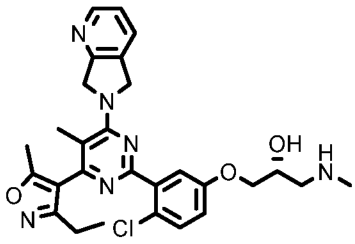
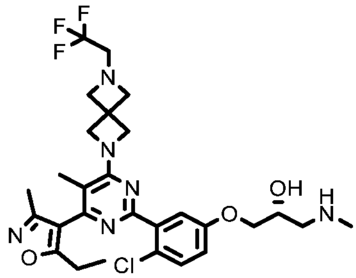
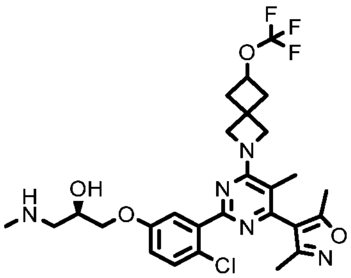
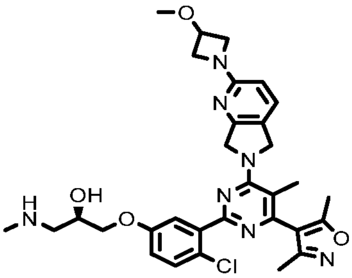
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
225		0.0093	0.445	579.1
226		0.0046	0.134	535.2
227		0.0080	0.059	595.2
228		0.0047	0.073	582.1
229		0.0019	0.014	606.2

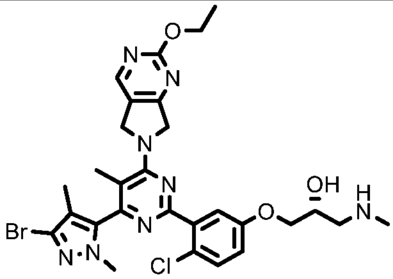
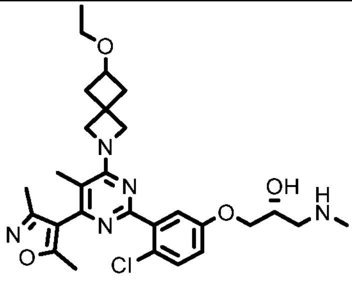
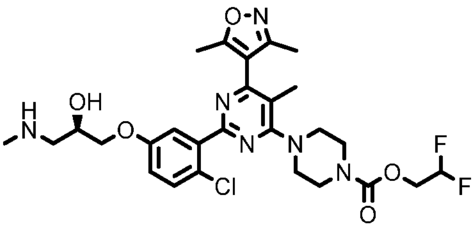
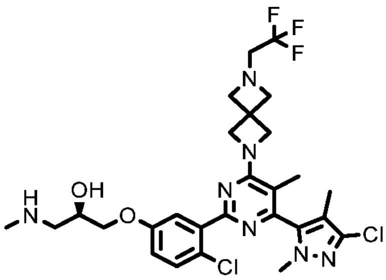
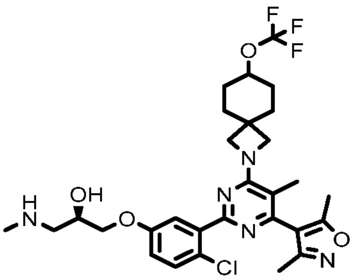
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC$_{50}$ (uM)	*Cellular IC$_{50}$ (uM)	LC-MS m/z (M+H)
230		0.0018	0.017	469.1
231		0.0046	0.041	542.1
232		0.0049	0.348	595
233		0.0043	0.029	614
234		0.0061	0.105	610

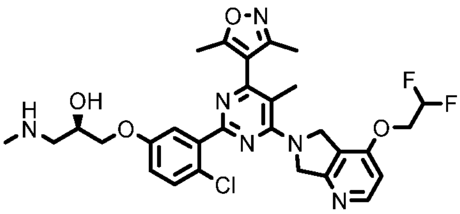
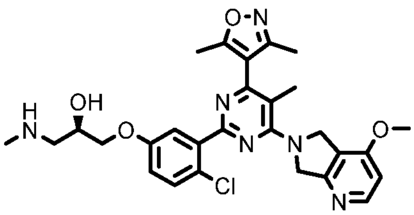
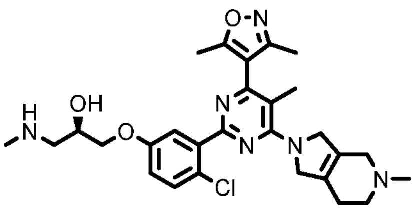
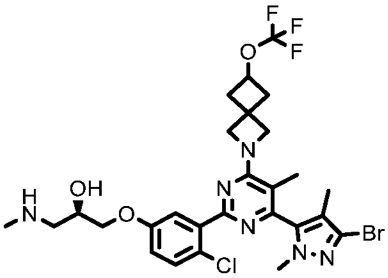
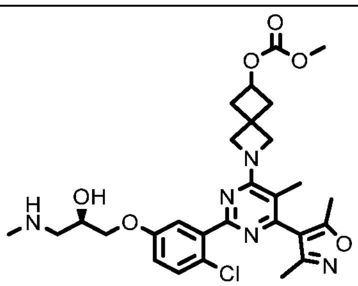
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
235		0.0007	0.054	601.2
236		0.0018	0.063	551
237		0.0006	0.157	539.2
238		0.0050	0.116	660.8
239		0.0047	0.052	572.3

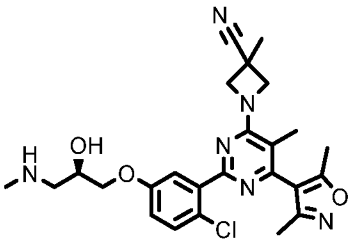
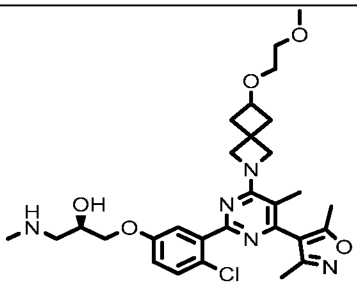
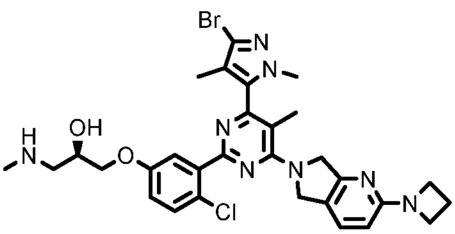
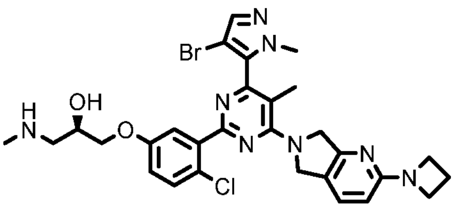
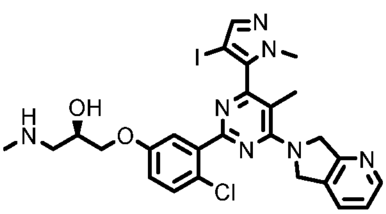
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
240		0.0041	0.398	497
241		0.0062	0.084	572
242		0.0012	0.030	655
243		0.0008	0.037	638.9
244		0.0012	0.141	632.1

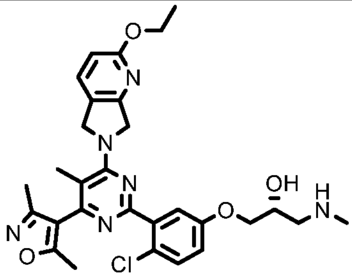
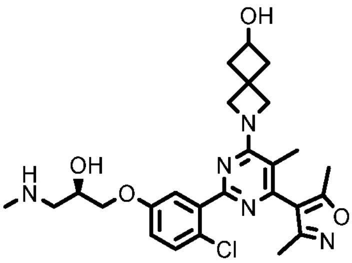
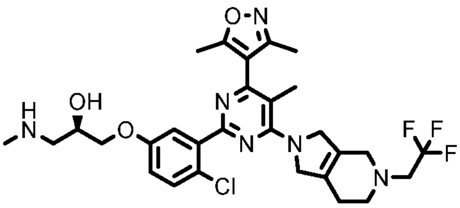
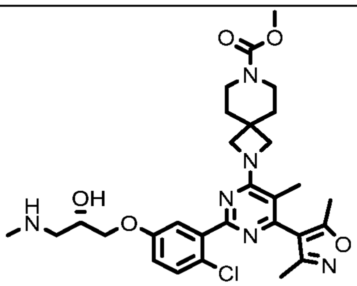
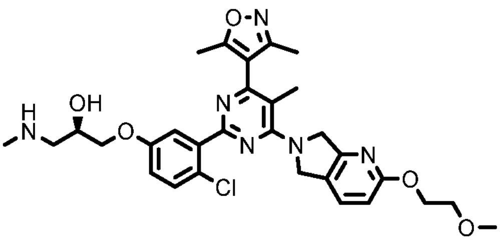
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
245		0.0020	0.038	565.2
246		0.0067	0.352	514
247		0.0040	0.062	607.2
248		0.0058	0.294	585.3
249		0.0020	0.027	595.2

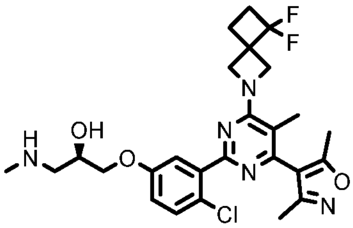
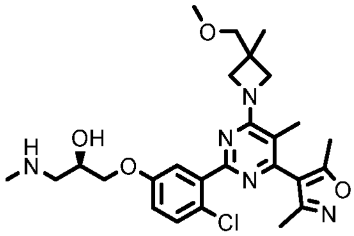
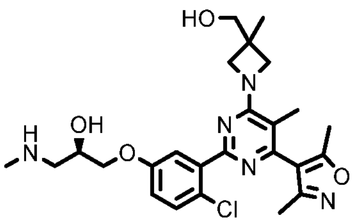
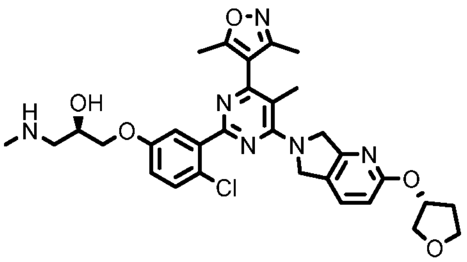
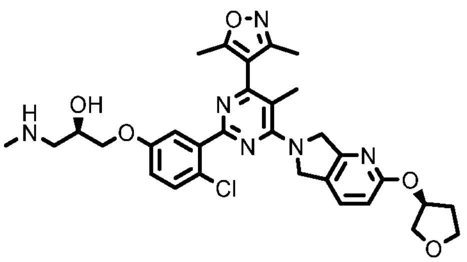
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
250		0.00394	0.21705	534
251		0.00651	0.19256	516.2
252		0.00801	0.56093	502
253		0.00236	0.02919	607.2
254		0.00239	0.03713	607.1

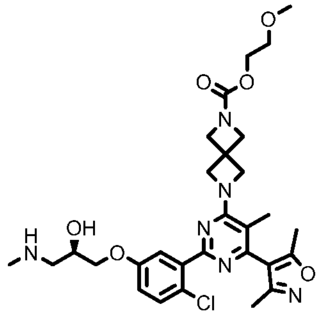
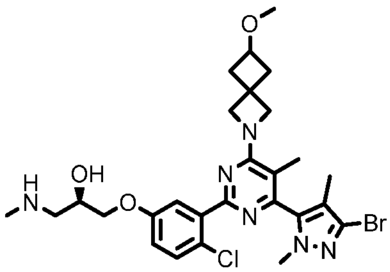
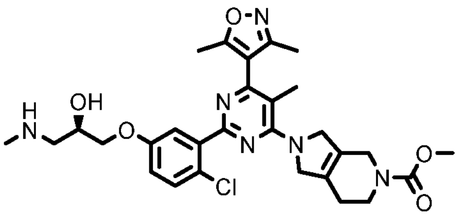
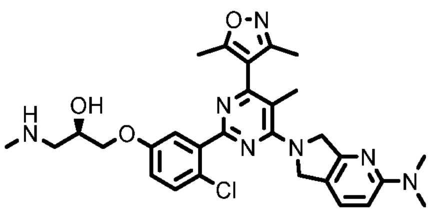
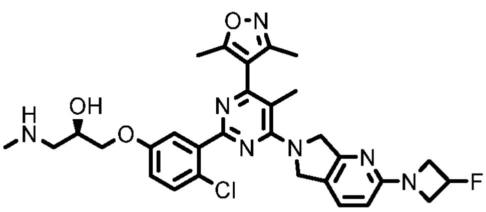
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC$_{50}$ (uM)	*Cellular IC$_{50}$ (uM)	LC-MS m/z (M+H)
255		0.00722	0.37722	601
256		0.00396	0.04322	605.2
257		0.0024	0.02268	583.2
258		0.00183	0.02985	564
259		0.00217	0.0229	594.1

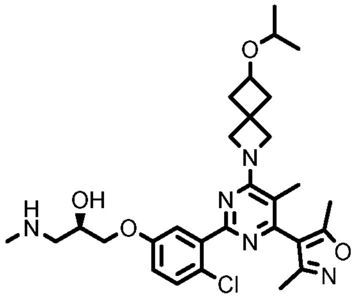
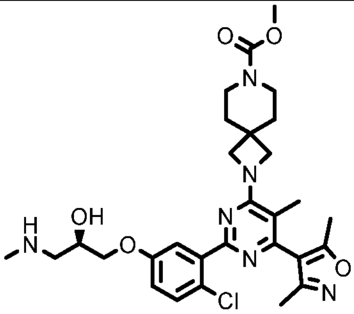
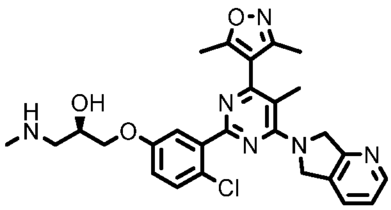
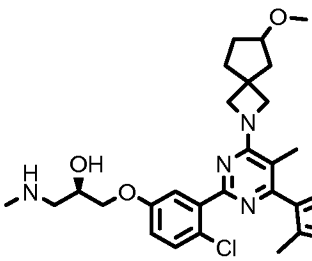
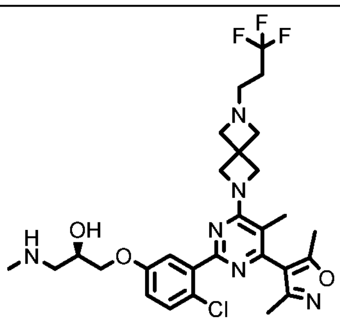
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC50 (uM)	*Cellular IC50 (uM)	LC-MS m/z (M+H)
260		0.00595	0.04546	556.2
261		0.00401	0.05391	585.2
262		0.00234	0.03257	521
263		0.00536	0.09086	542
264		0.00411	0.05187	595

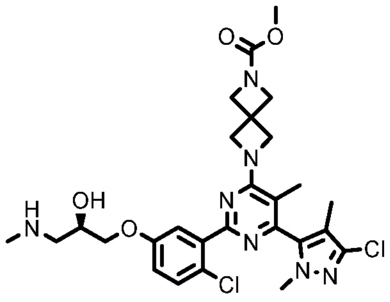
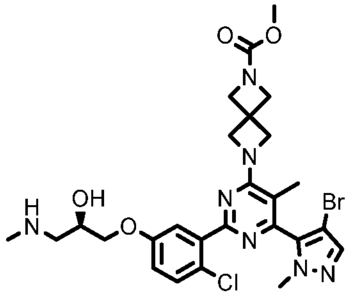
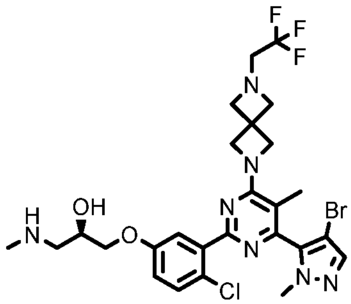
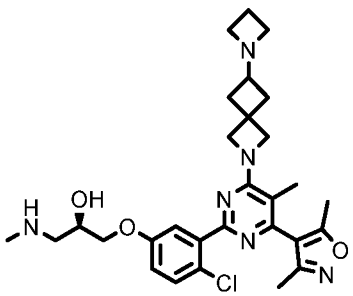
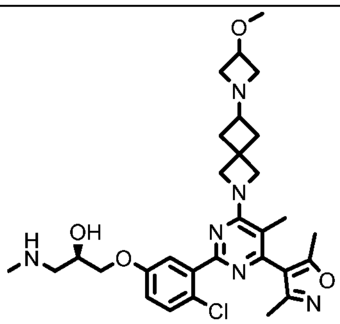
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC$_{50}$ (uM)	*Cellular IC$_{50}$ (uM)	LC-MS m/z (M+H)
265		0.0042	0.08773	590
266		0.00683	0.30986	622
267		0.00897	0.1208	645.9
268		0.00126	1.35264	553
269		0.0008	0.35455	583

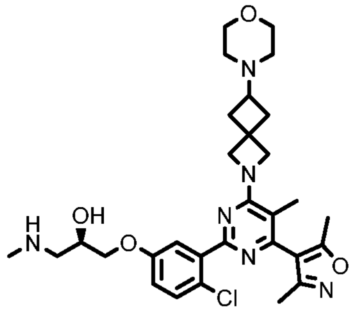
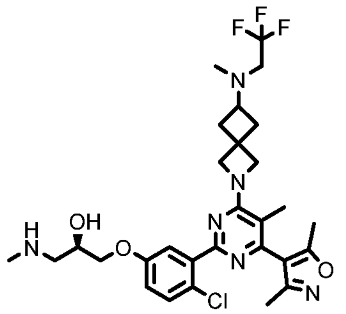
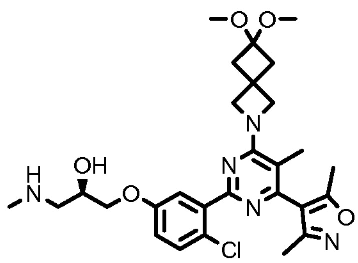
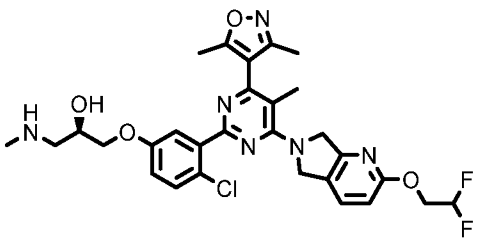
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
270		0.00495	0.26902	583
271		0.00742	0.08906	609.2
272		0.00543	0.07897	558.2
273		0.00226	0.06192	601

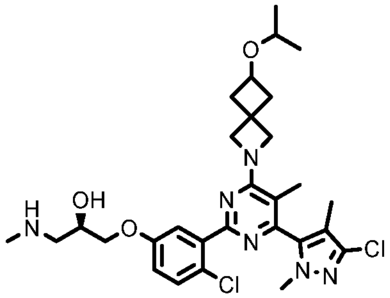
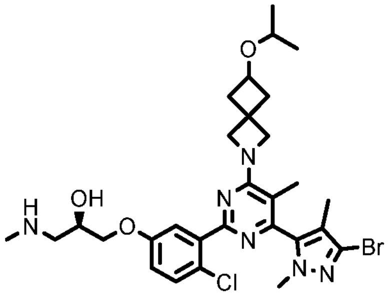
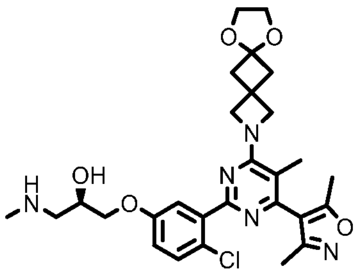
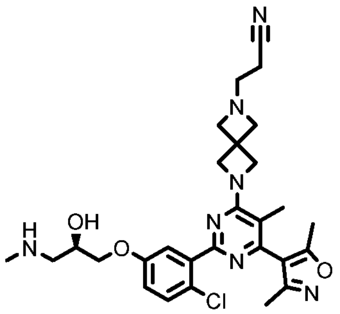
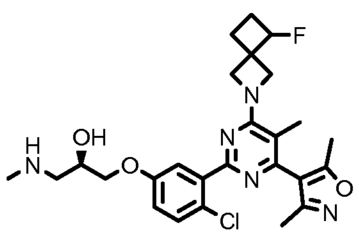
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
274		0.00503	0.04876	589
275		0.00353	0.04499	634.9
276		0.00492	0.07573	556
277		0.00824	1.46961	552
278		0.00411	0.5443	516.3

Table 1. Exemplary Compounds

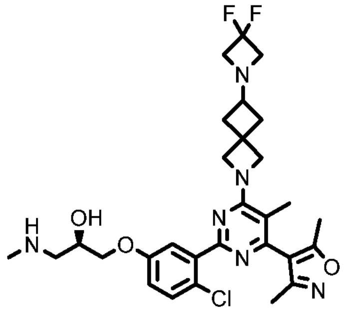
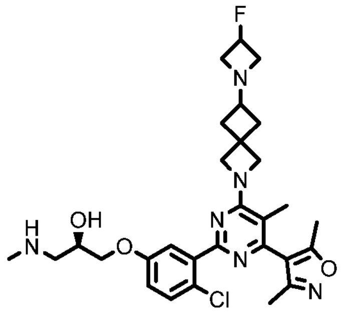
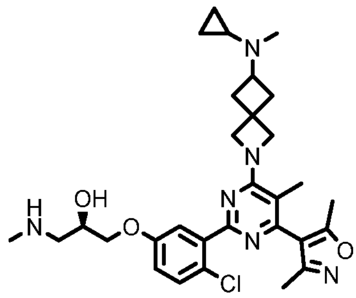
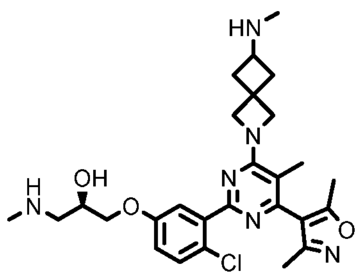
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
279		0.00575	0.05421	589.2
280		0.00209	0.10456	571.2
281		0.00104	0.0792	567.1
282		0.0009	2.21372	527

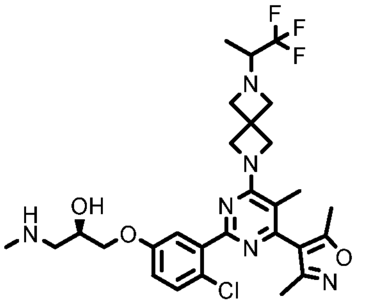
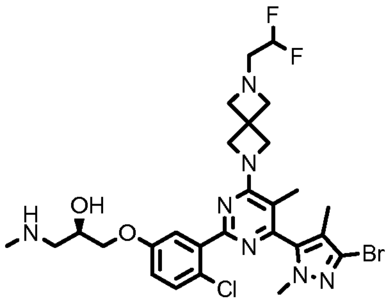
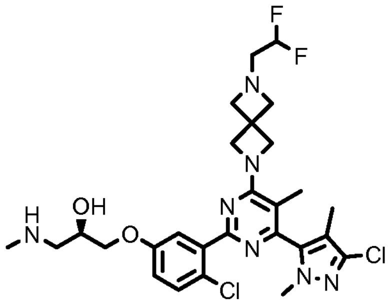
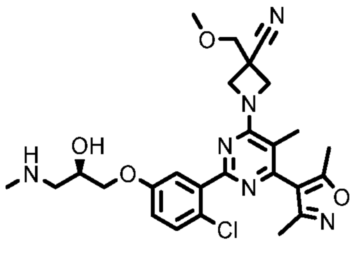
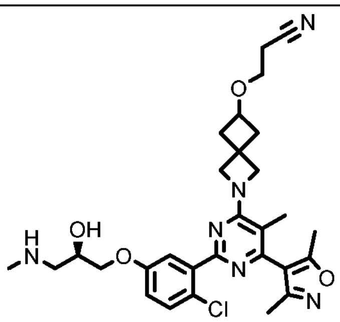
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
283		0.00567	0.04841	595.2
284		0.00236	0.03916	642
285		0.0024	0.04607	596
286		0.00417	0.28207	527.3
287		0.00446	0.06909	567.2

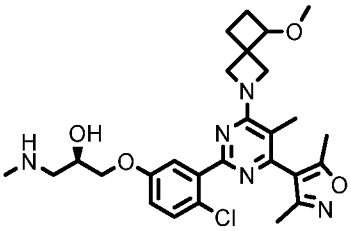
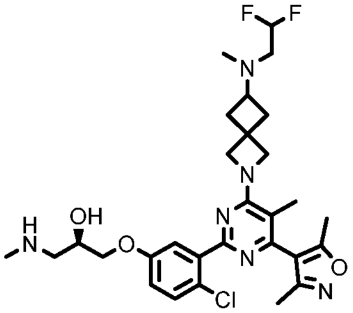
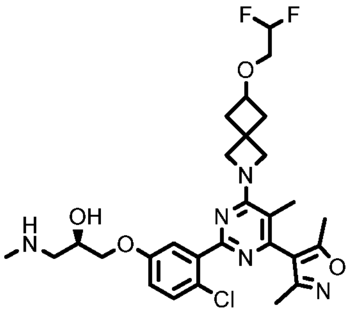
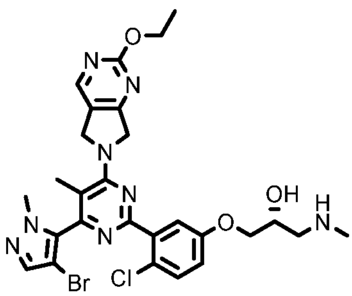
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
288		0.00386	0.23408	528.2
289		0.00408	0.07595	591
290		0.00339	0.03824	578.2
291		0.002	0.0368	630.8

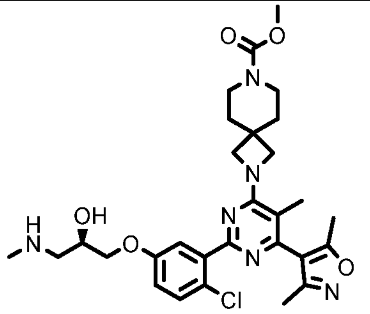
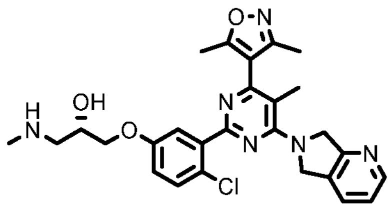
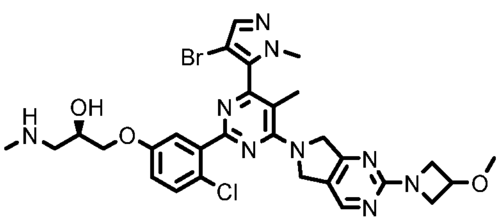
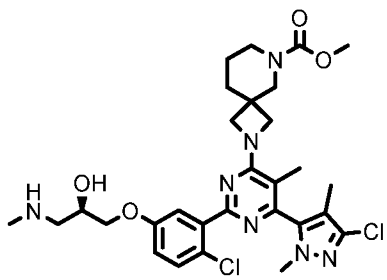
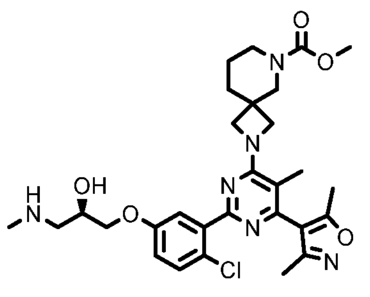
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC$_{50}$ (uM)	*Cellular IC$_{50}$ (uM)	LC-MS m/z (M+H)
292		0.00349	0.06671	585.3
293		0.00142	0.1549	521
294		0.00117	0.01624	671.9
295		0.00378	0.08272	618
296		0.0064	0.137	585

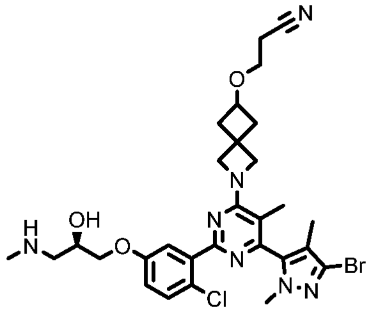
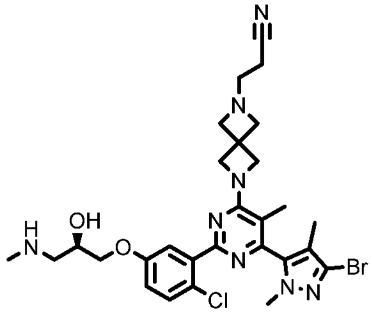
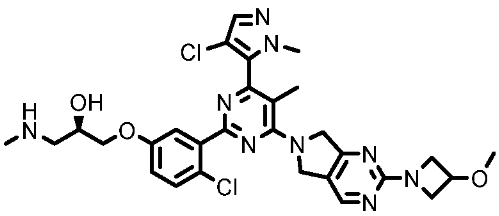
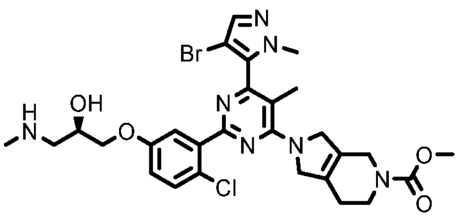
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC50 (uM)	*Cellular IC50 (uM)	LC-MS m/z (M+H)
297		0.00283	0.03938	646
298		0.00311	0.24435	630.9
299		0.00294	0.01758	626
300		0.00476	0.0423	648.1

Table 1. Exemplary Compounds

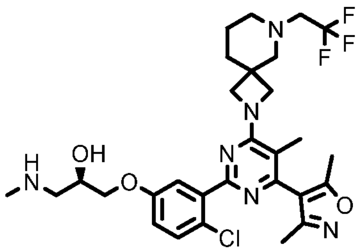
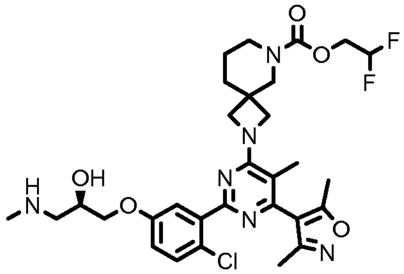
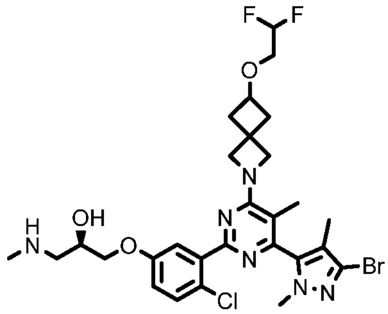
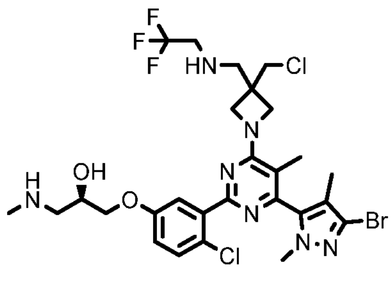
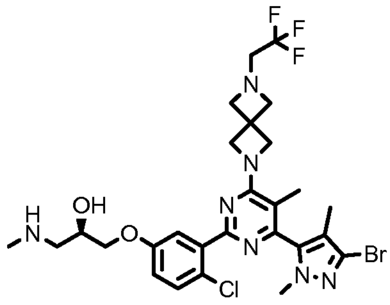
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
301		0.00799	0.12512	609.2
302		0.00518	0.07024	635
303		0.00591	0.03759	657
304		0.00681	0.14155	695.8
305		0.00835	0.02769	657.9

Table 1. Exemplary Compounds

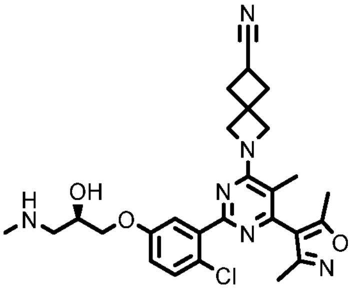
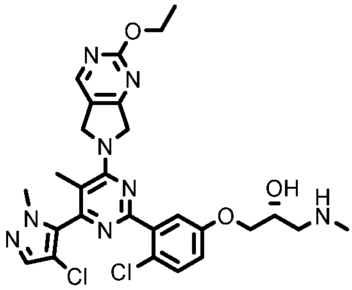
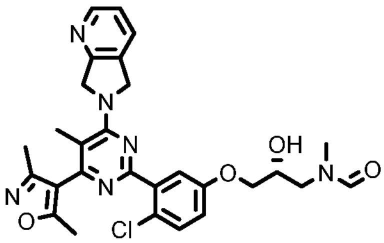
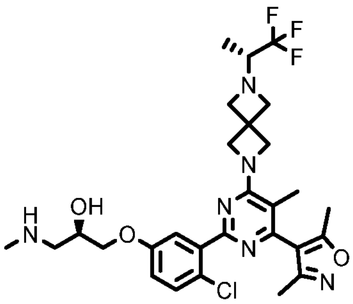
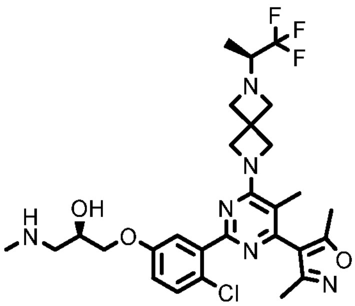
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
306		0.00652	0.17326	523
307		0.00386	0.04542	585
308		0.12031	1.81987	549.3
309		--	--	595
310		--	--	595

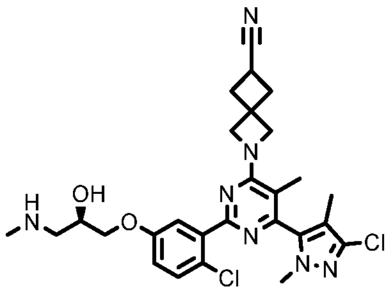
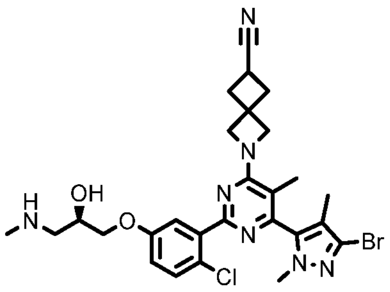
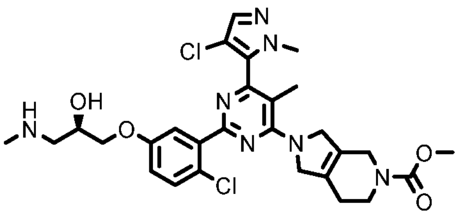
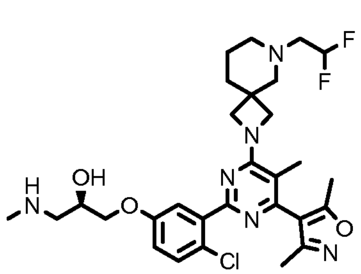
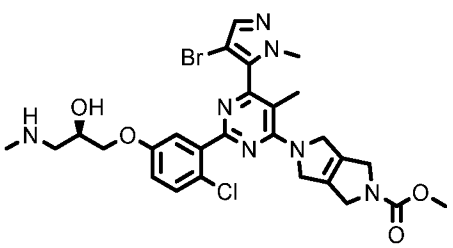
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC$_{50}$ (uM)	*Cellular IC$_{50}$ (uM)	LC-MS m/z (M+H)
311		--	--	556
312		--	--	601.9
313		--	--	602
314		--	--	--
315		--	--	--

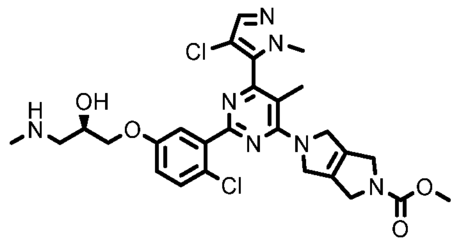
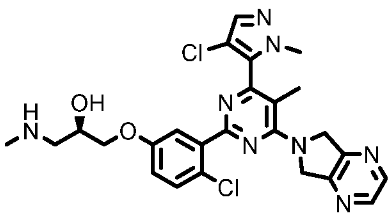
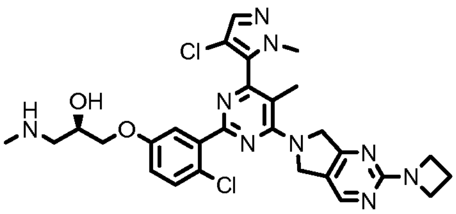
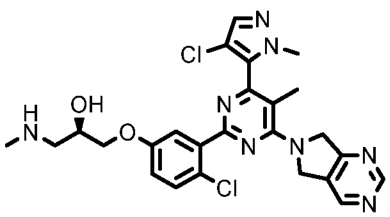
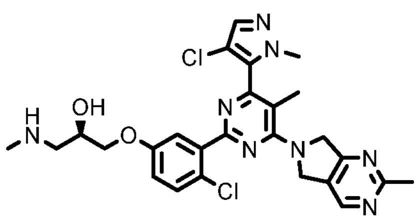
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
316		--	--	--
317		--	--	--
318		--	--	--
319		--	--	--
320		--	--	--

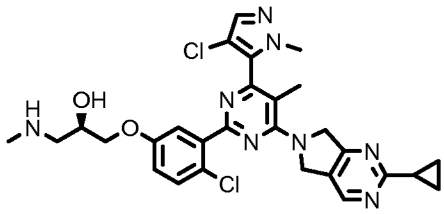
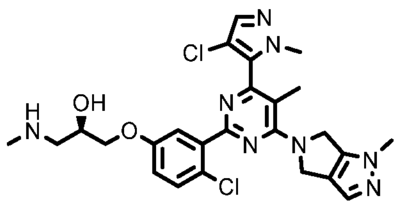
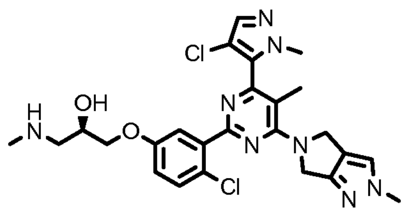
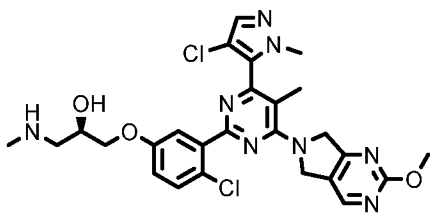
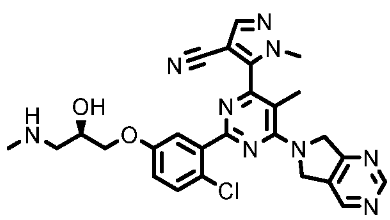
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
321		--	--	--
322		--	--	--
323		--	--	--
324		--	--	--
325		--	--	--

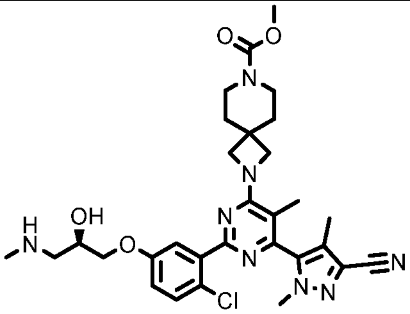
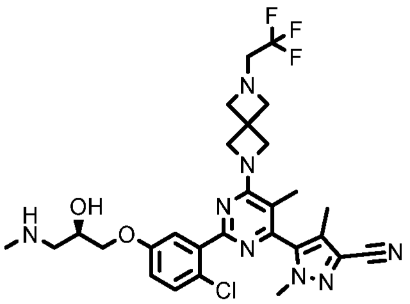
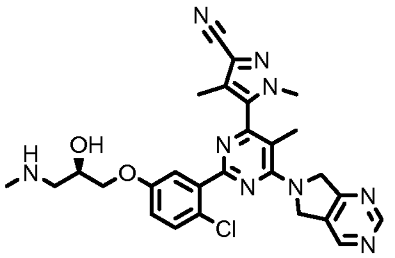
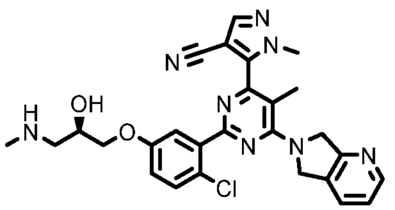
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
326		--	--	--
327		--	--	--
328		--	--	--
329		--	--	--

Table 1. Exemplary Compounds

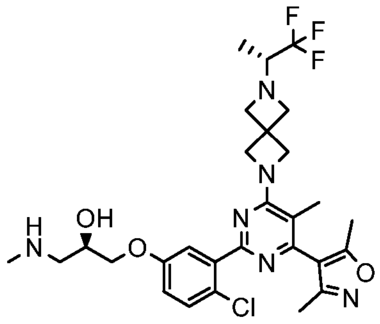
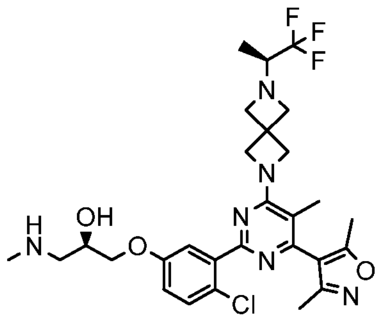
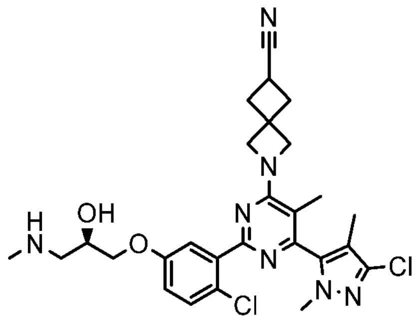
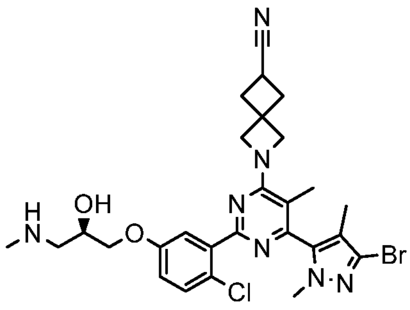
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
330		0.00483	0.04089	595
331		0.00631	0.03291	595
332		0.0041	0.0809	556
333		0.00246	0.06444	601.9

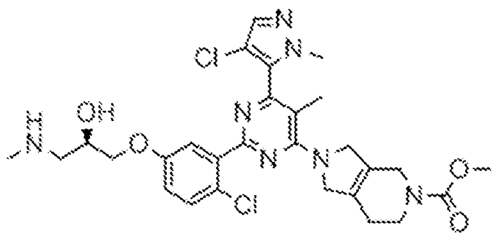
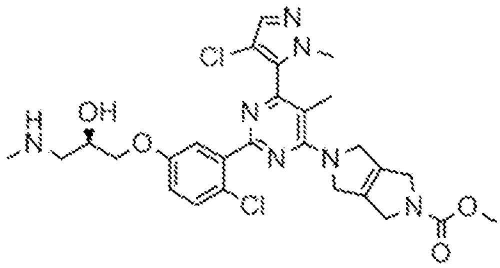
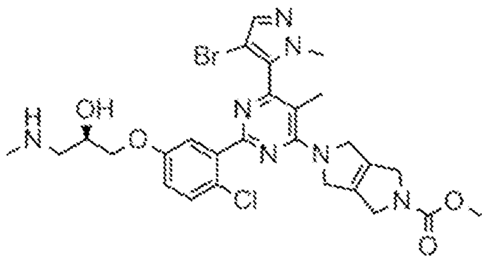
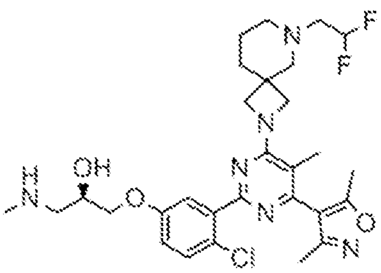
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
334		0.00253	0.0434	602
335		0.00228	0.03046	588
336		0.00303	0.03212	633.9
337		0.00498	0.05999	591

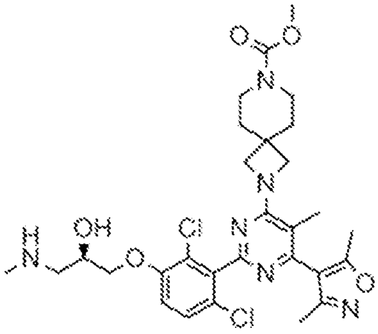
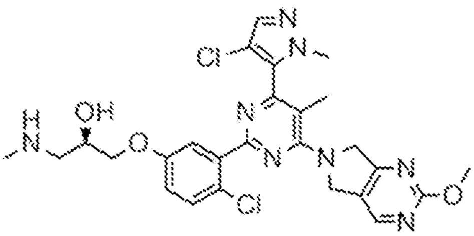
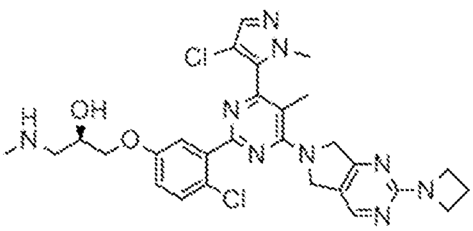
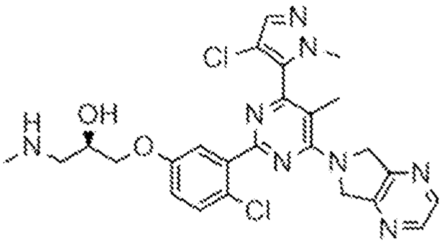
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
338		0.03113	1.82143	619
339		0.00254	0.06536	571.1
340		0.002	0.01749	596
341		0.0027	0.18444	541

Table 1. Exemplary Compounds

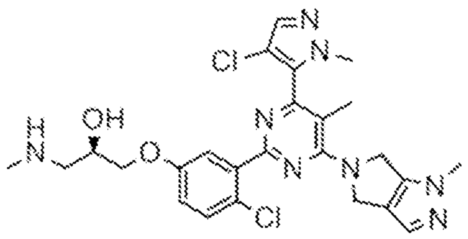
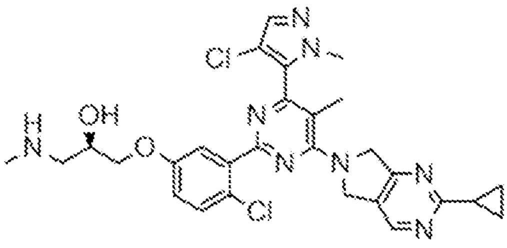
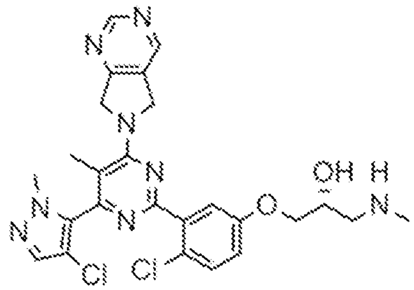
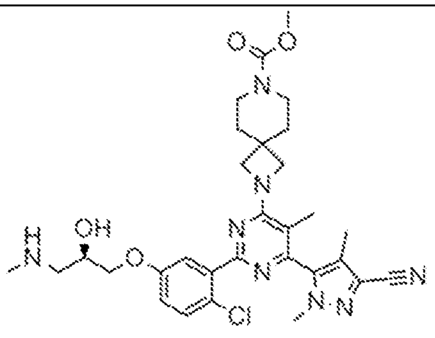
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
342		0.00274	0.12292	543.1
343		0.00176	0.05417	582.09
344		0.01285	0.71347	541.1
345		0.00566	0.26177	609.3

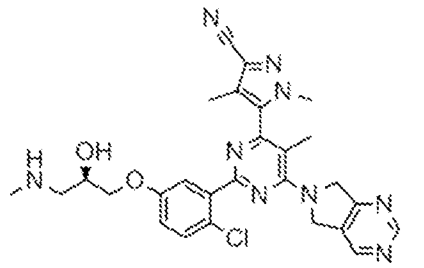
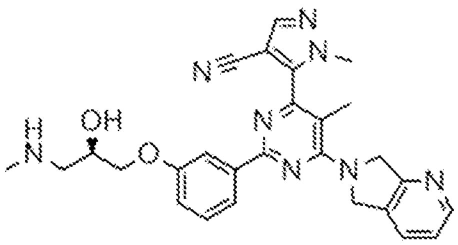
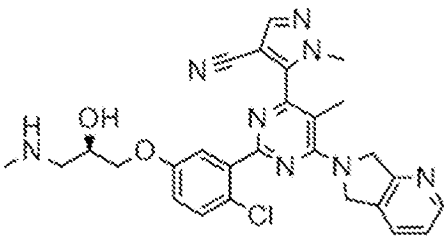
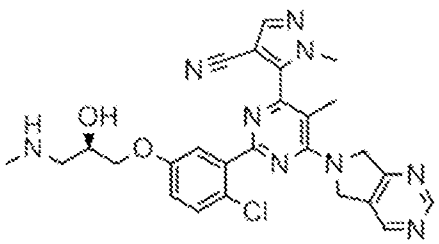
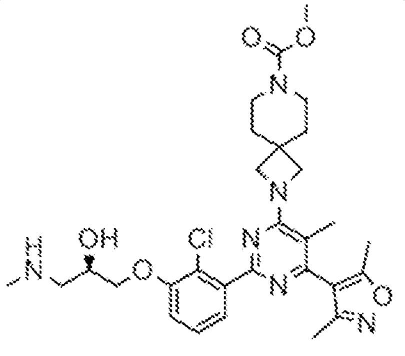
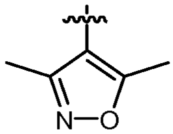
Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
346		0.00231	0.14038	546.2
347		0.02822	> 2.0	497
348		0.00567	1.67001	531
349		0.00781	3.11349	532

Table 1. Exemplary Compounds				
#	Structure	*Biochem IC_{50} (uM)	*Cellular IC_{50} (uM)	LC-MS m/z (M+H)
350		0.03715	7.19989	585.2

**Biochemical and Cellular-based (PABP1me2a) ICW (In Cell Western) assay results*

[00354] In certain embodiments, the compound of Formula (**I**) is not a compound or pharmaceutically acceptable salt thereof as disclosed in PCT/US2014/028463, the disclosure of which is incorporated herein by reference.

[00355] In certain embodiments, compounds of Formula (**I**), wherein R^{A1} and R^{A2} are each $-CH_3$, *i.e.,* to provide a Ring A of formula:



are specifically excluded.

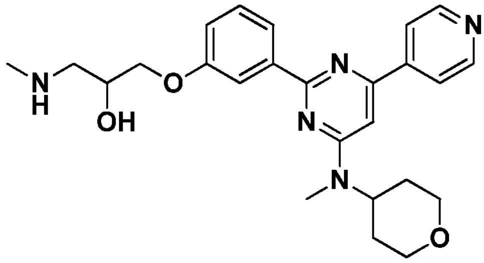
[00356] In certain embodiments, compounds of Formula (**I**), wherein R^{2a}, R^{2b}, and R^3 are any of the following specific combinations:

a. R^{2a} is hydrogen, R^{2b} is hydrogen, and R^3 is $-CH_3$; and/or
b. R^{2a} is hydrogen, R^{2b} is hydrogen, and R^3 is –F; and/or
c. R^{2a} is hydrogen, R^{2b} is hydrogen, and R^3 is –Cl; and/or
d. R^{2a} is -Cl, R^{2b} is hydrogen, and R^3 is –Cl; and/or
e. R^{2a} is -Cl, R^{2b} is hydrogen, and R^3 is –F; and/or
f. R^{2a} is -F, R^{2b} is hydrogen, and R^3 is –Cl; and/or
g. R^{2a} is -Cl, R^{2b} is hydrogen, and R^3 is $-CH_3$; and/or
h. R^{2a} is -F, R^{2b} is hydrogen, and R^3 is $-CH_3$; and/or
i. R^{2a} is $-CF_3$, R^{2b} is hydrogen, and R^3 is $-CH_3$; and/or
j. R^{2a} is $-CH_3$, R^{2b} is hydrogen, and R^3 is $-CH_3$; and/or

k. R^{2a} is hydrogen, R^{2b} is -Cl, and R^3 is $-CH_3$;

are specifically excluded.

[00357] In certain embodiments, any one or all of the below compounds, and pharmaceutically acceptable salts thereof, are specifically excluded:



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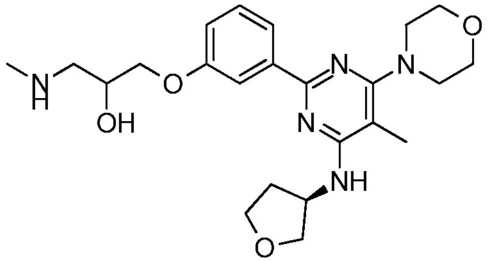

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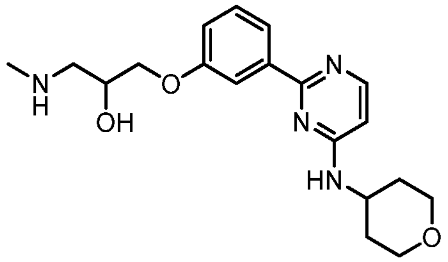

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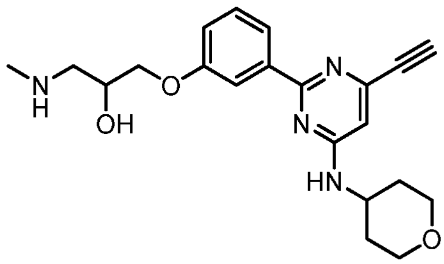

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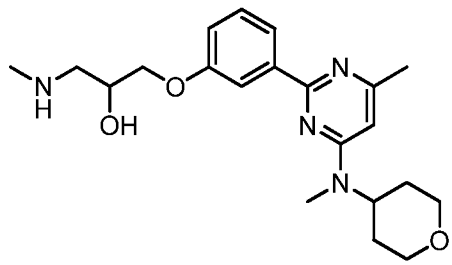

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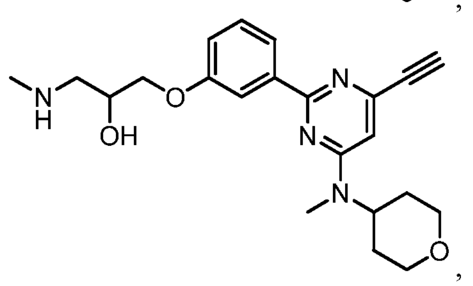

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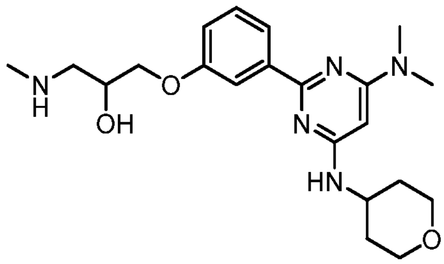
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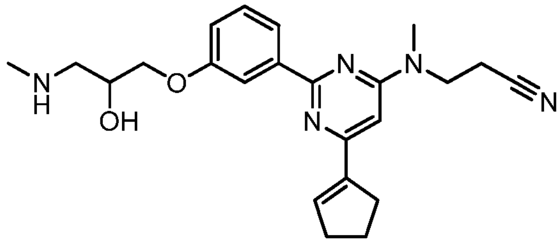
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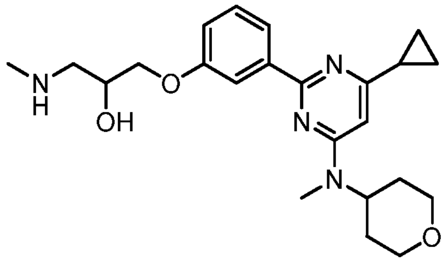
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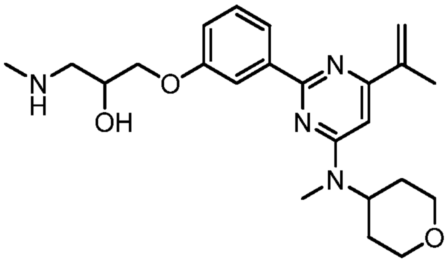
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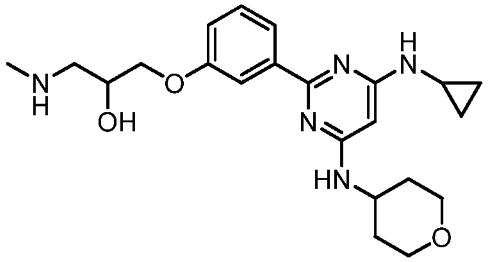
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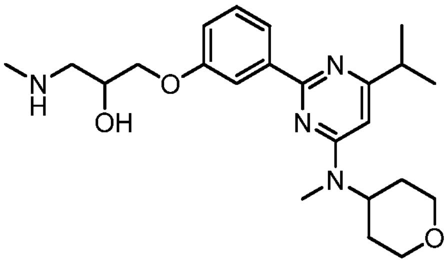
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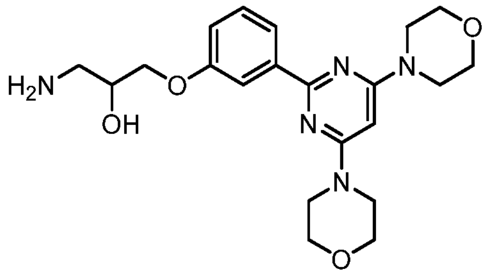

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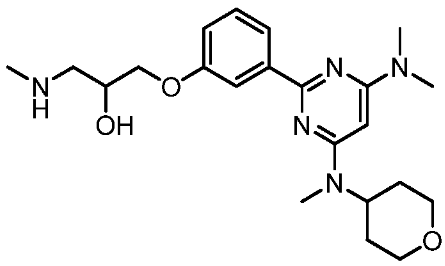

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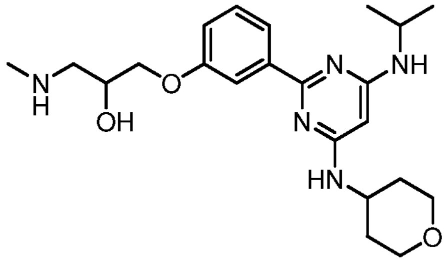

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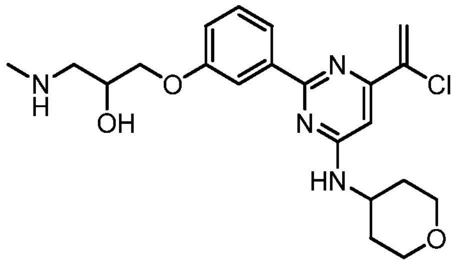

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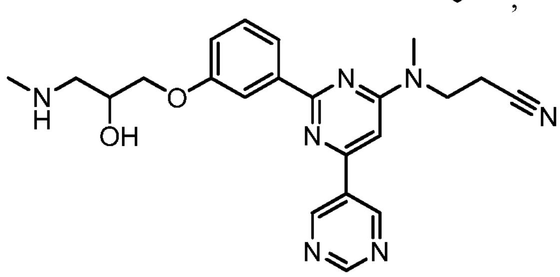

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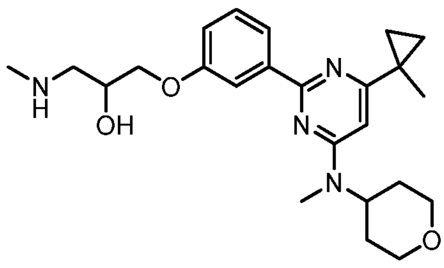

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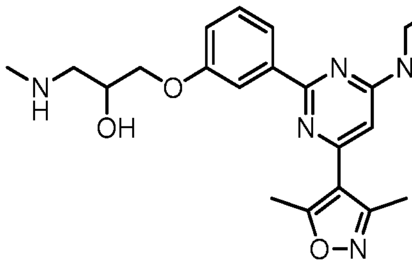
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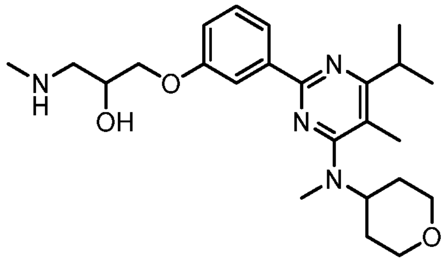
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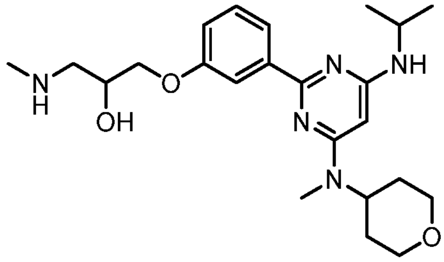
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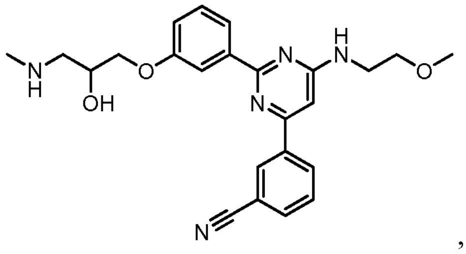
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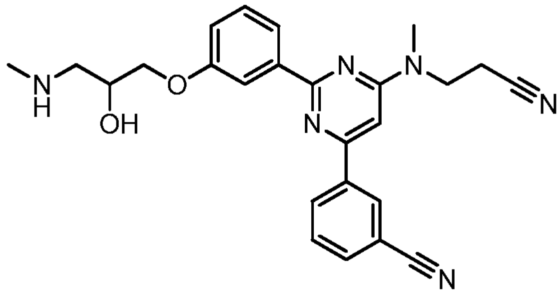
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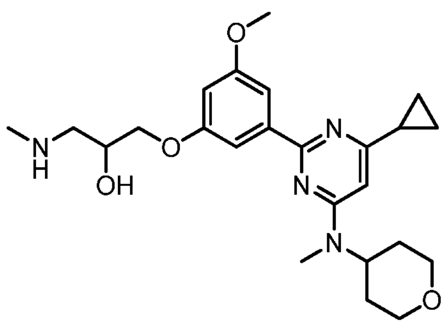
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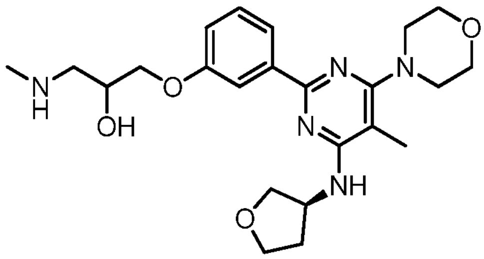
N
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OH
O
N
N
N
O
NH
O

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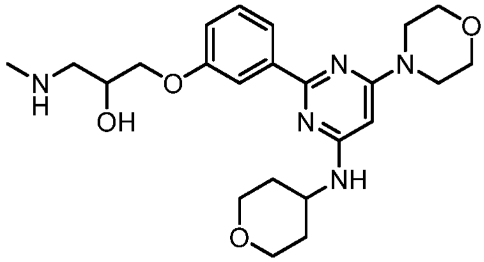
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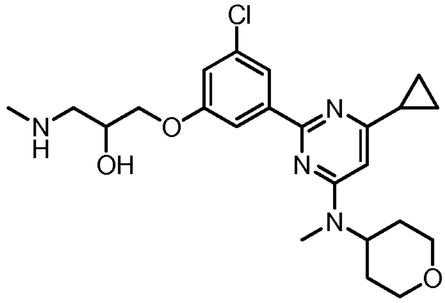
,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H
OH
O
N
N
N
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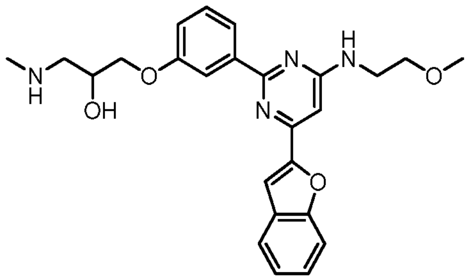
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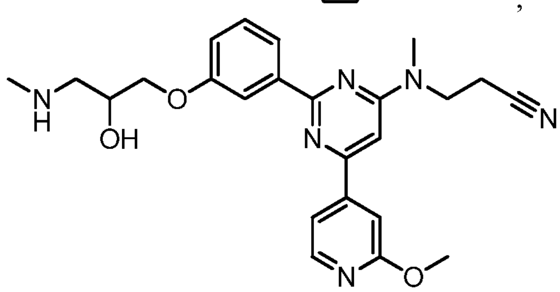
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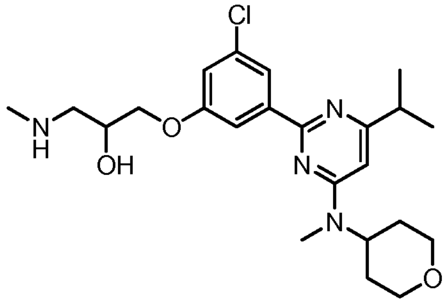
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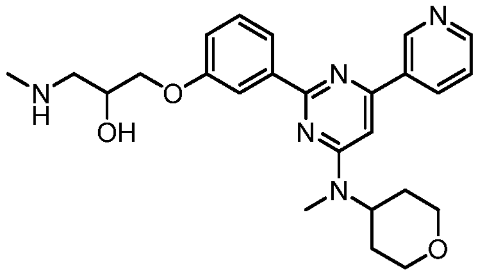

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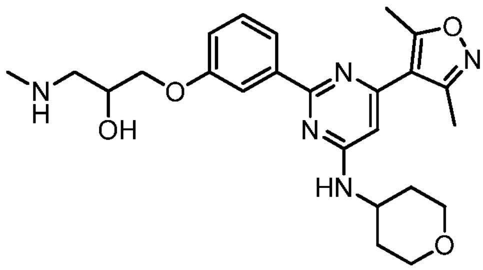

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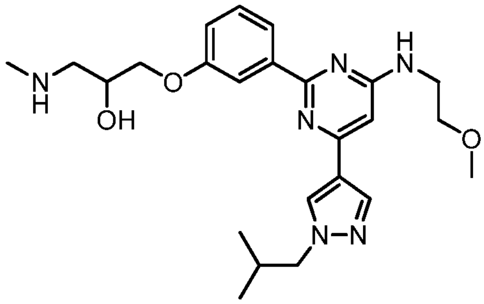

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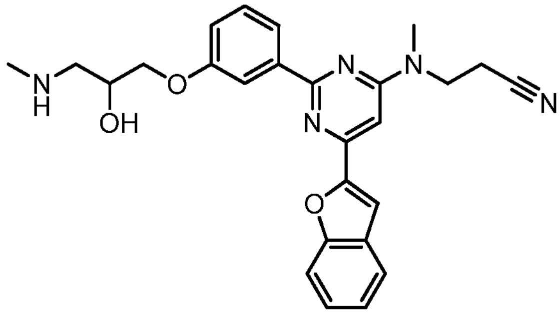

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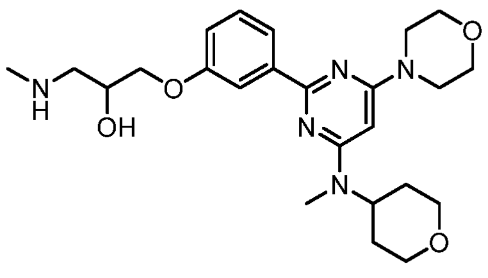

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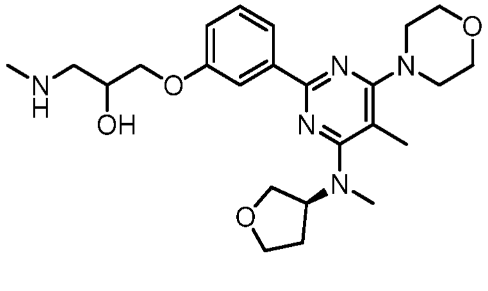

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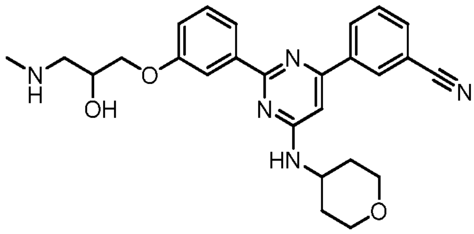

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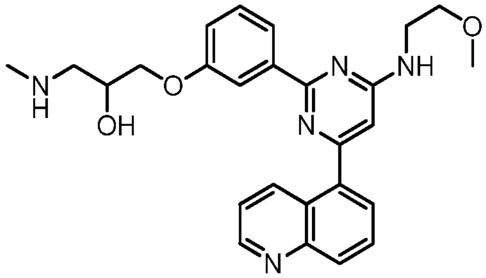

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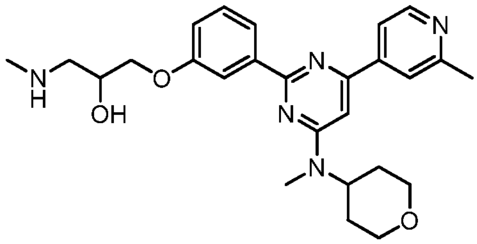

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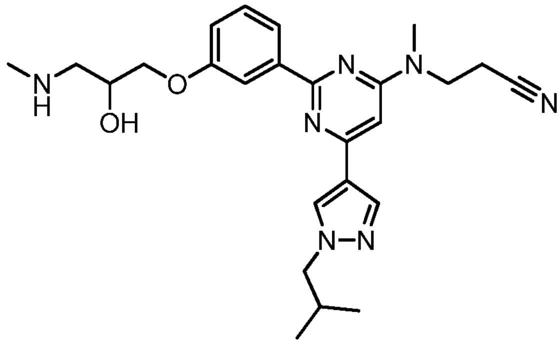

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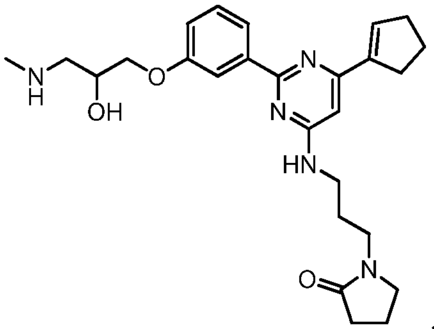

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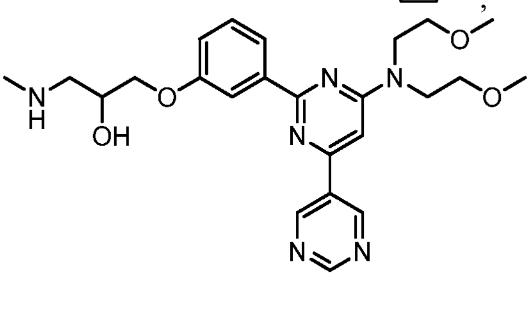

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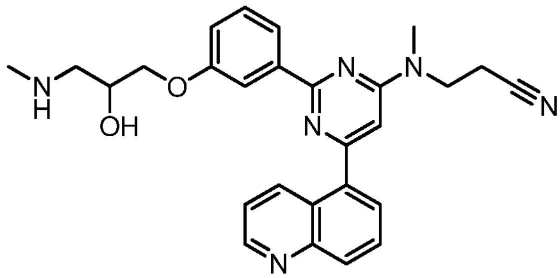

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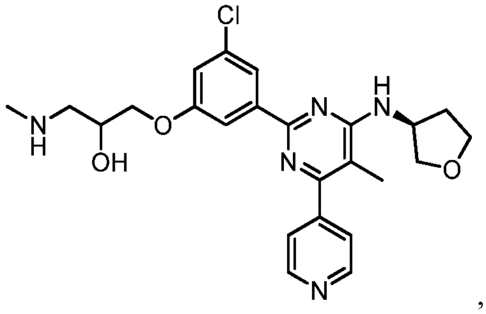

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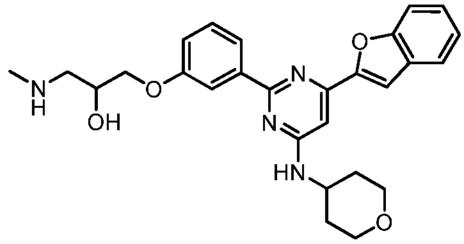

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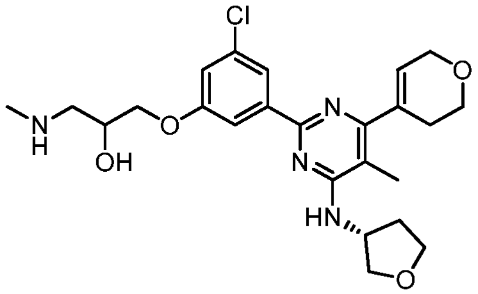

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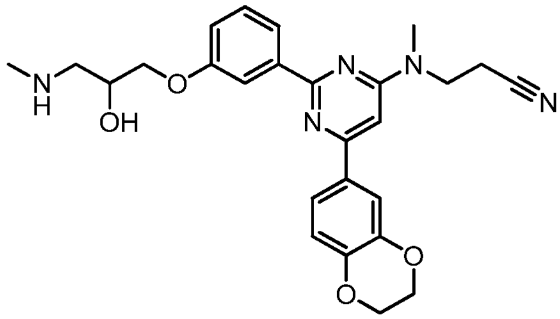

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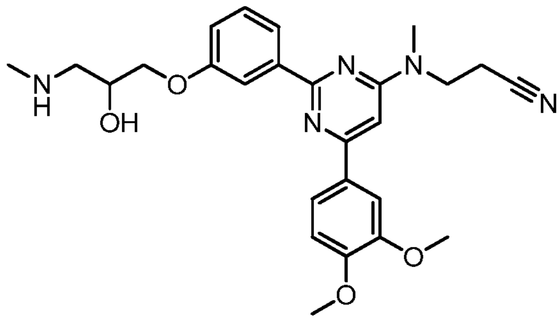

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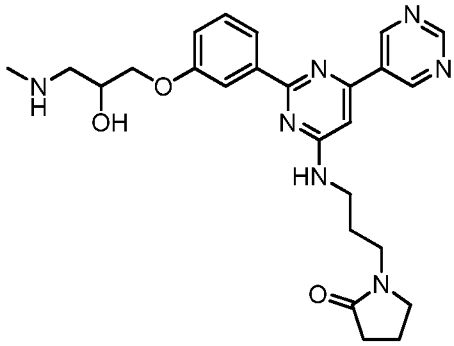
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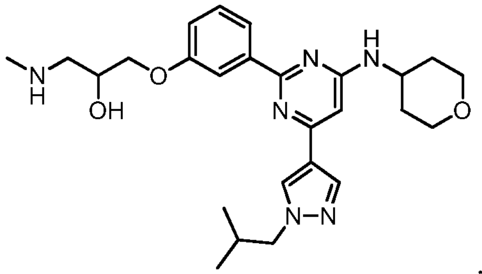
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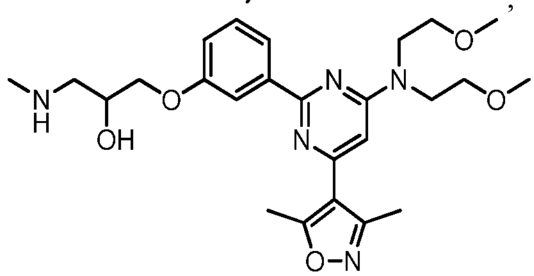
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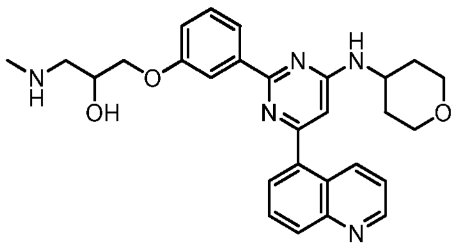
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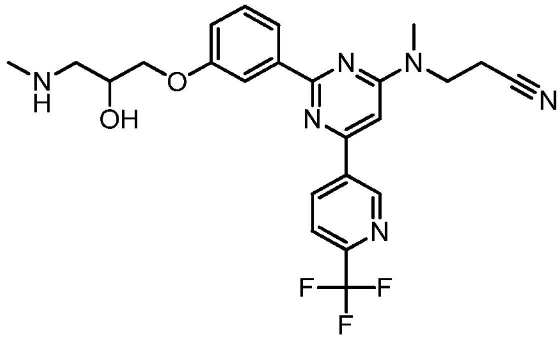
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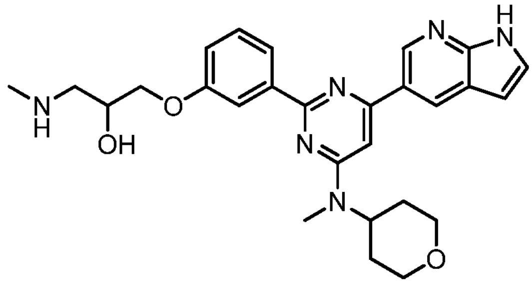
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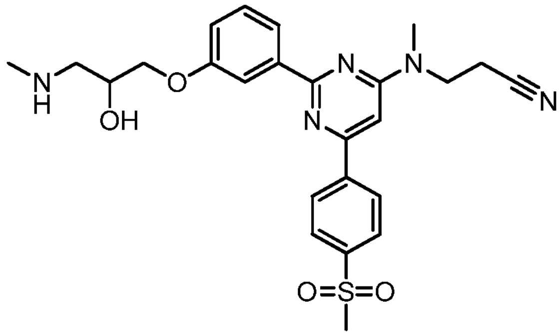
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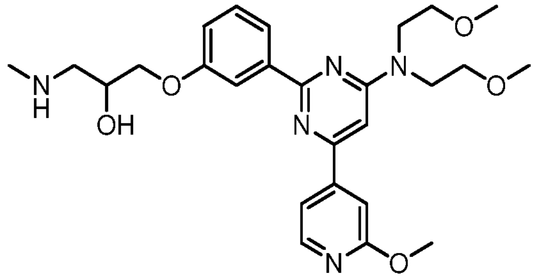
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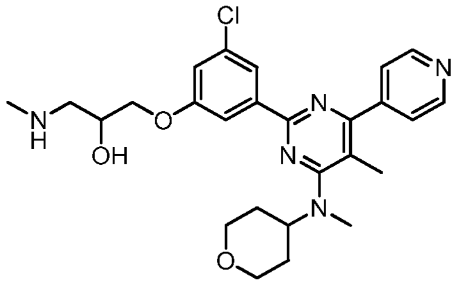
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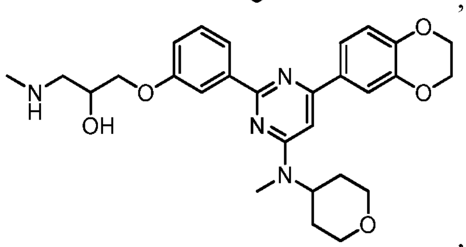
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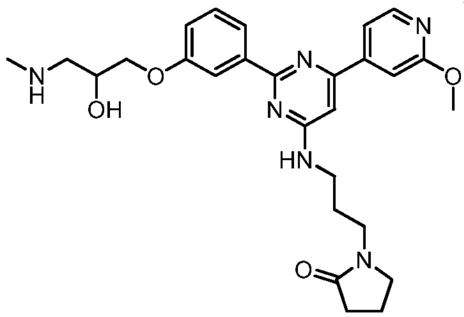
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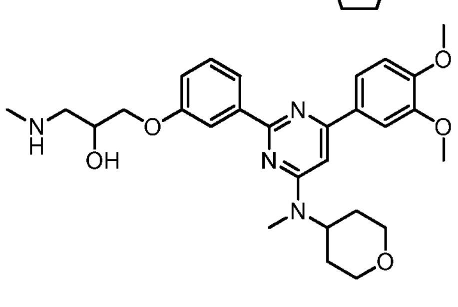
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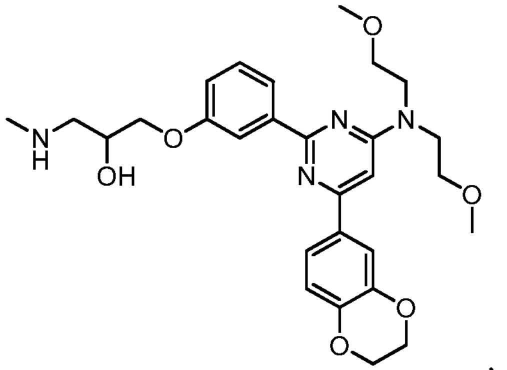

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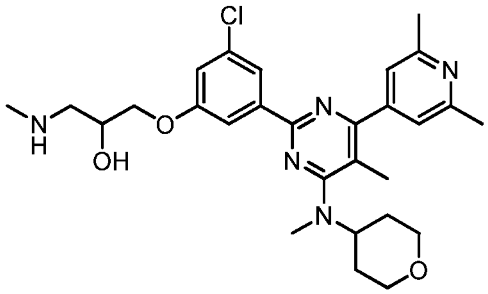

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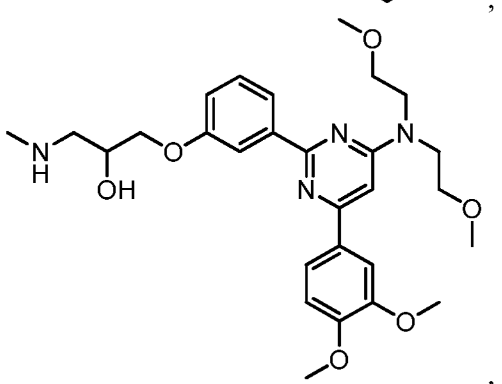

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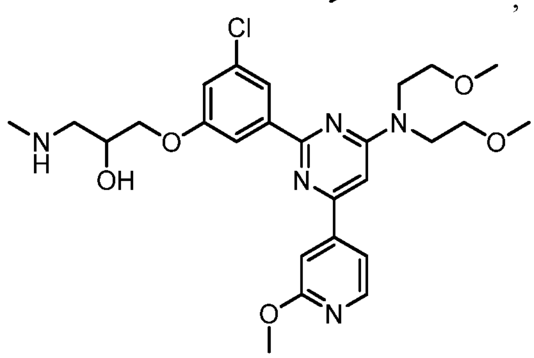

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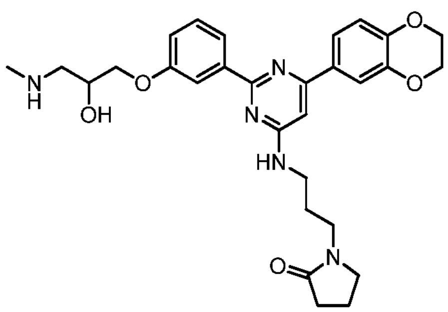

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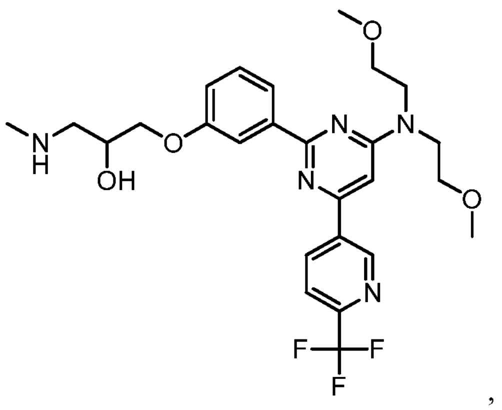

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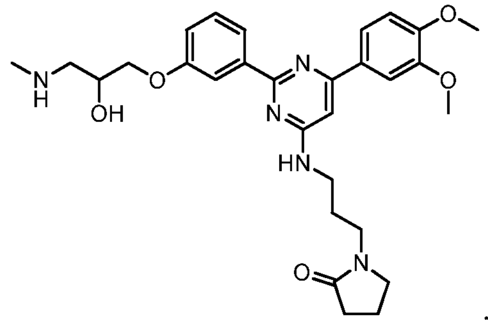

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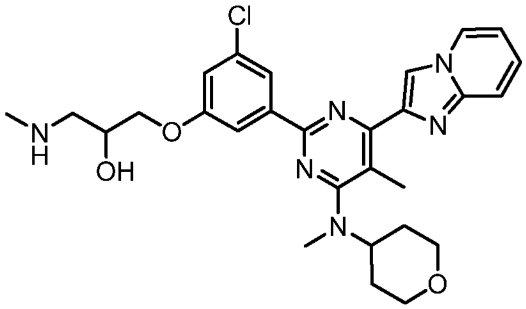

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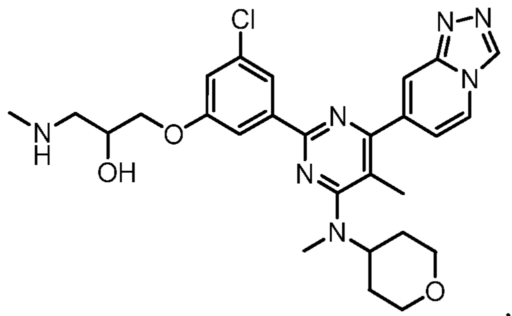

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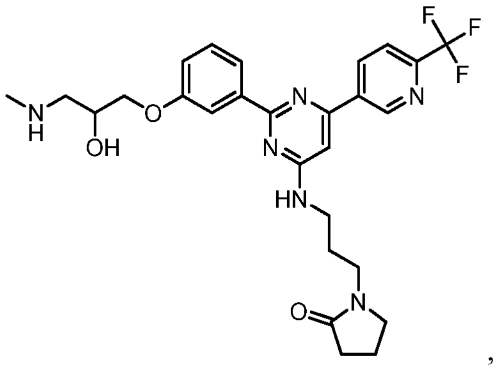

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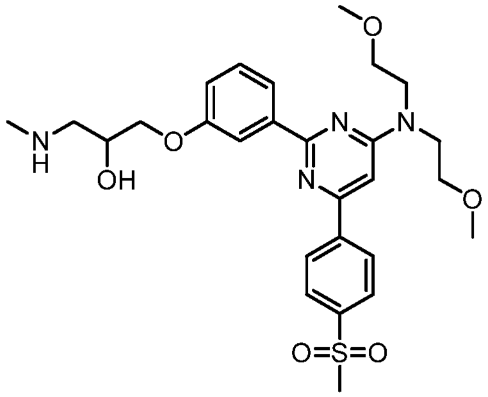

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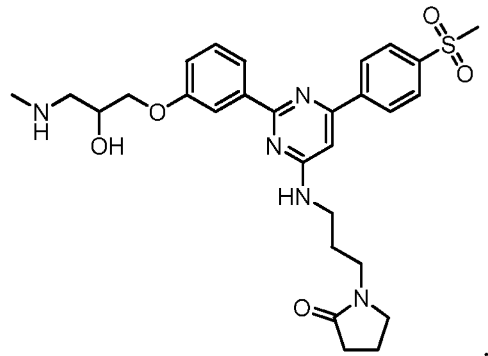

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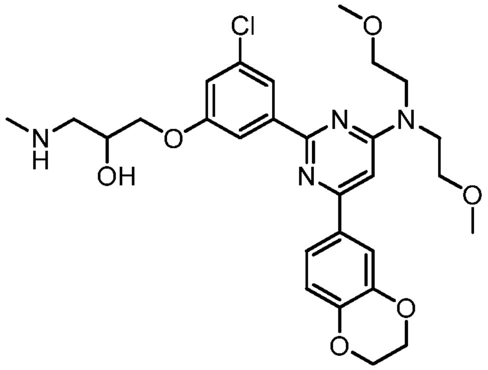

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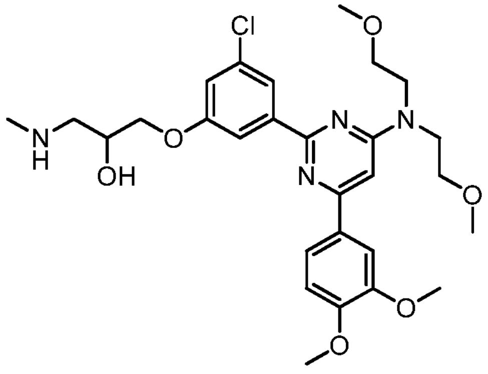

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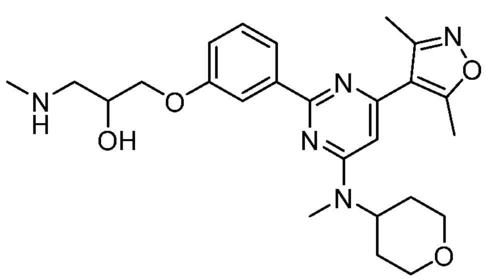

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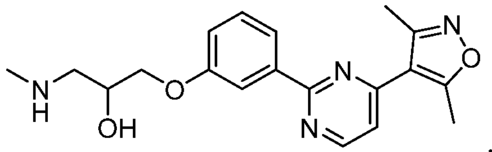
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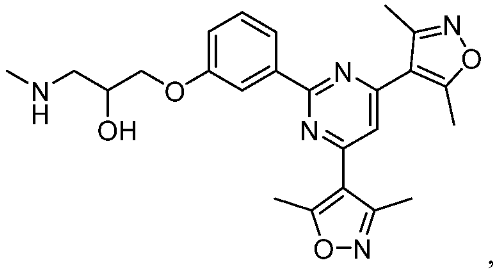
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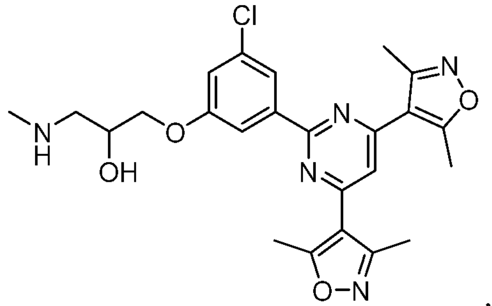
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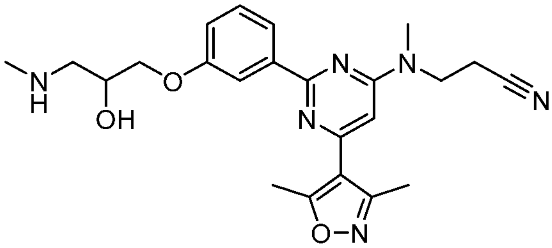
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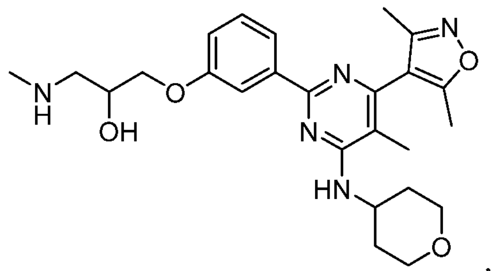
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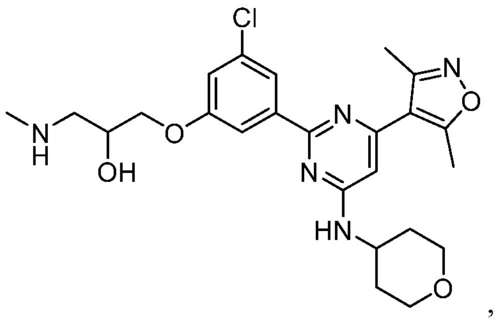
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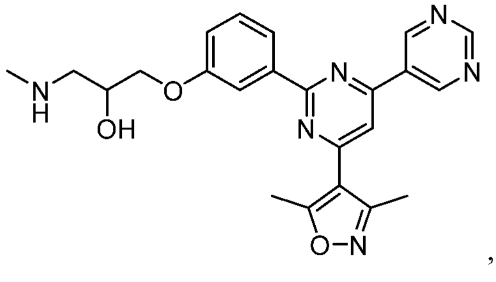
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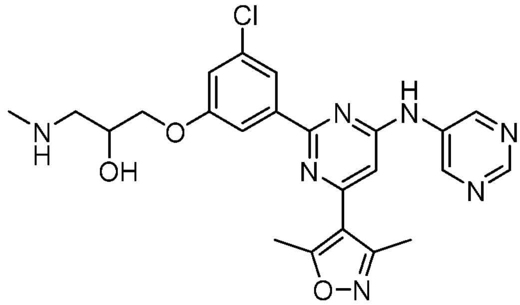

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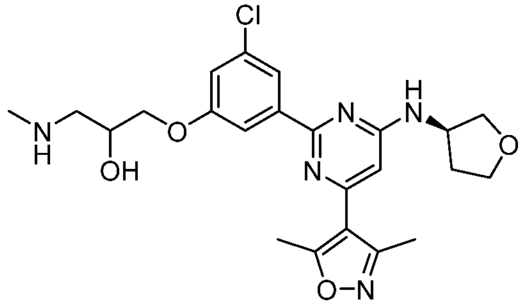

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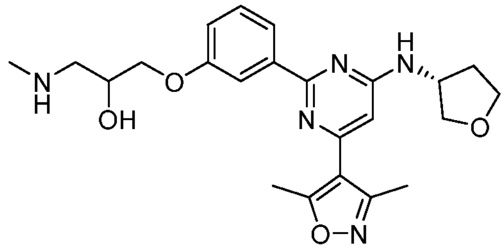

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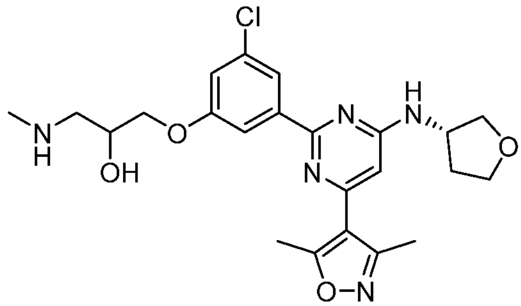

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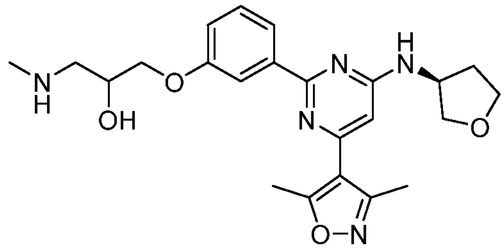

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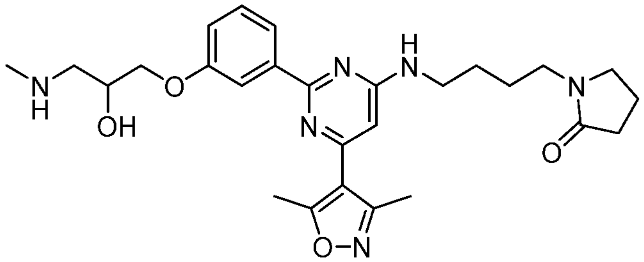

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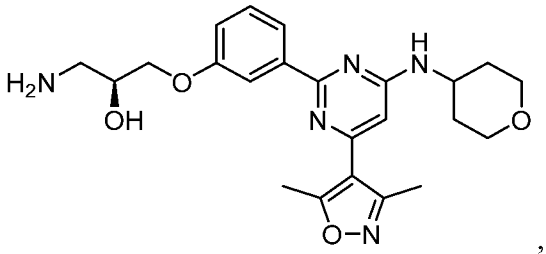
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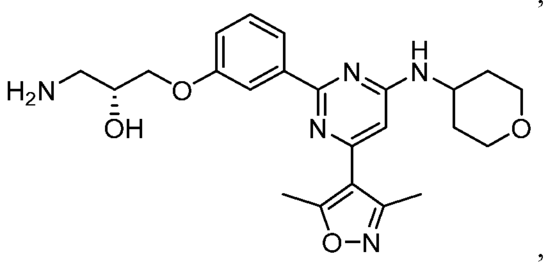
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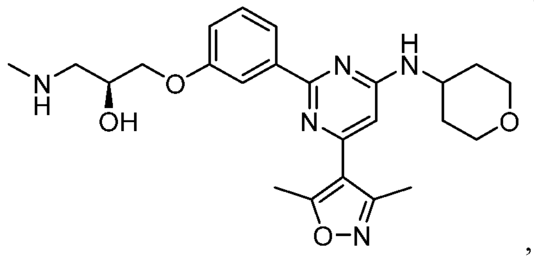
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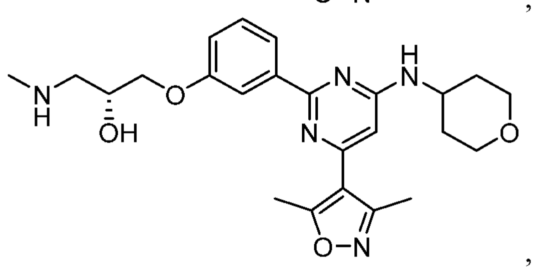
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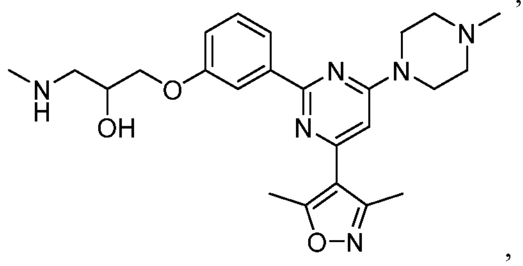
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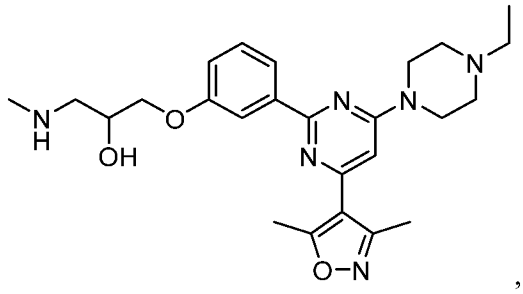
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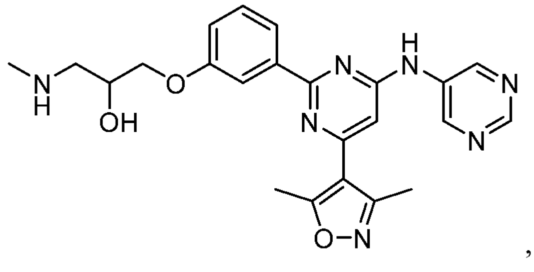
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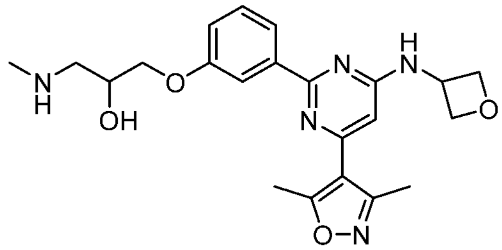

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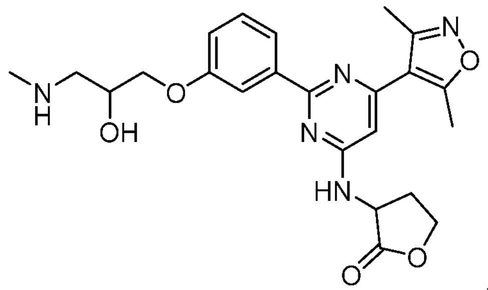

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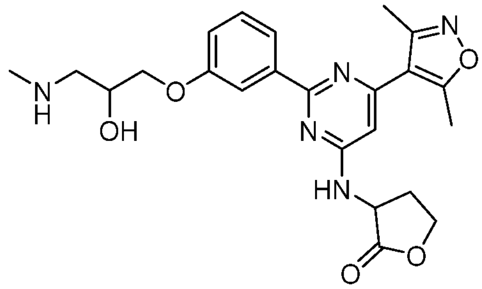

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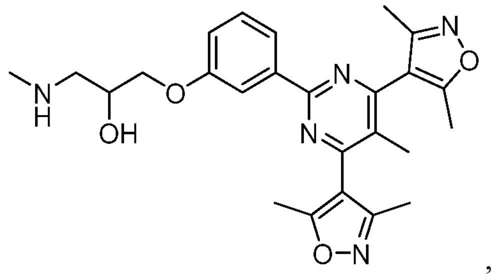

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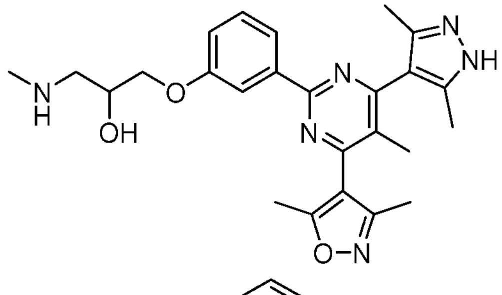

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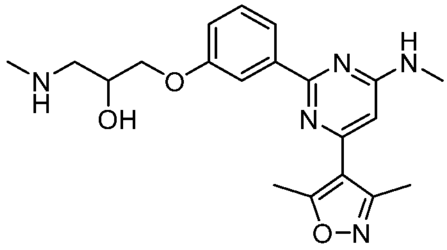

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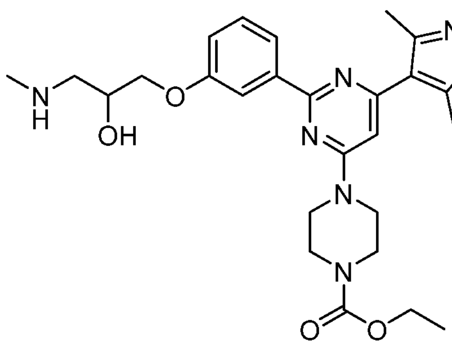

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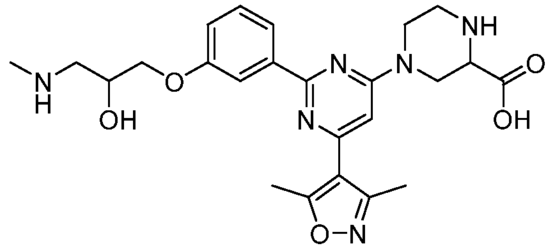

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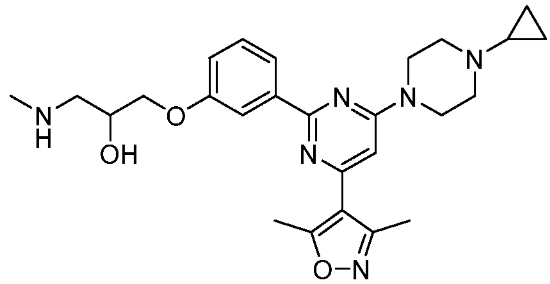

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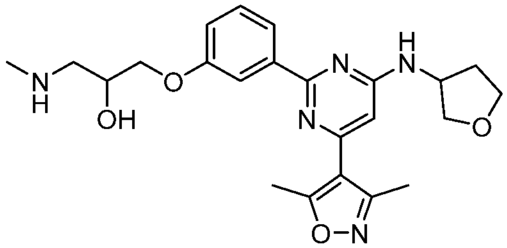

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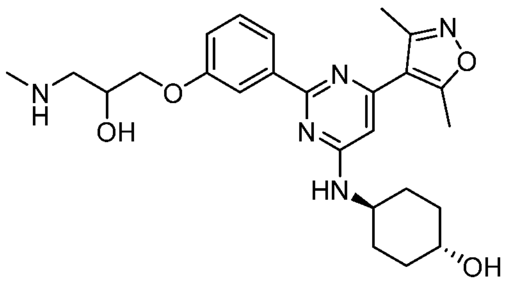

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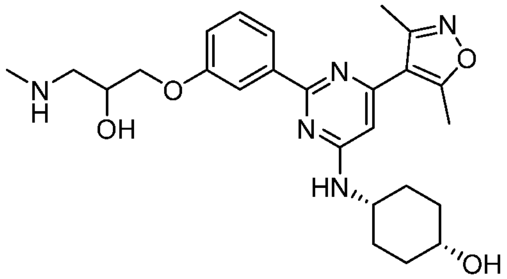

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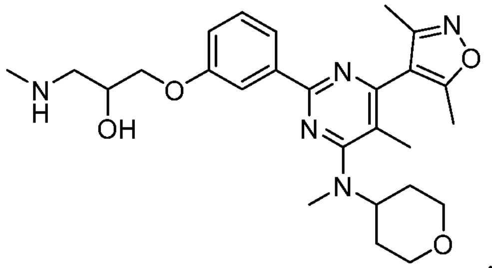
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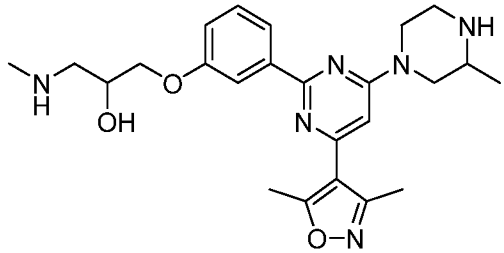
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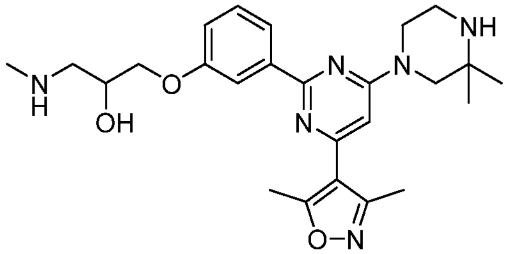
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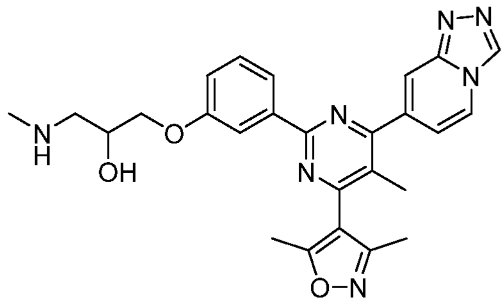
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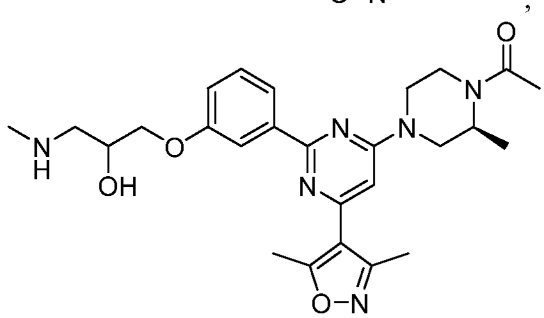
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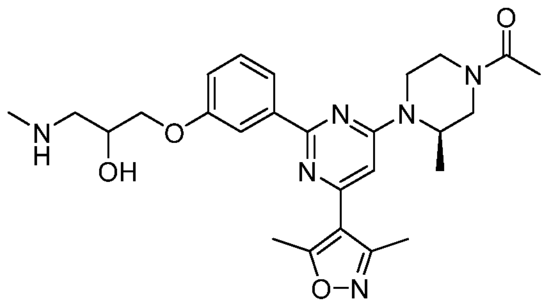
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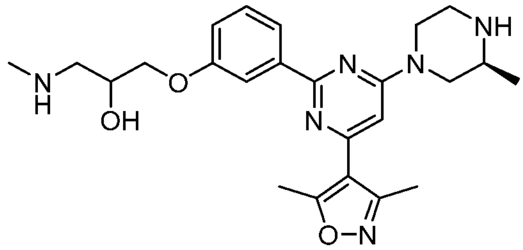

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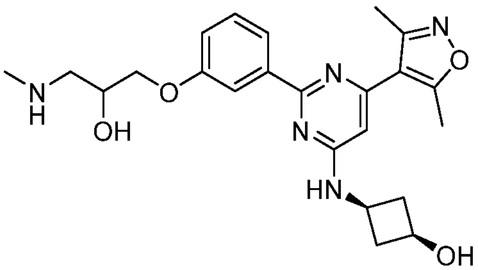

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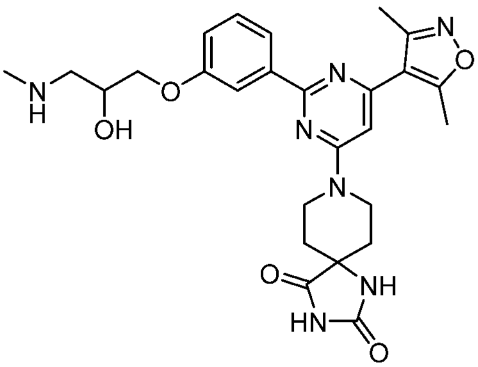

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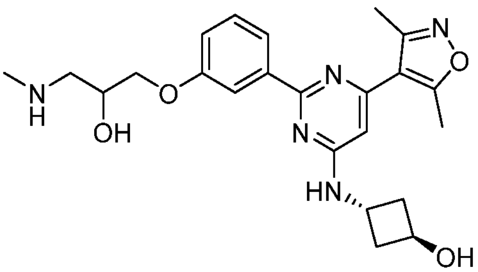

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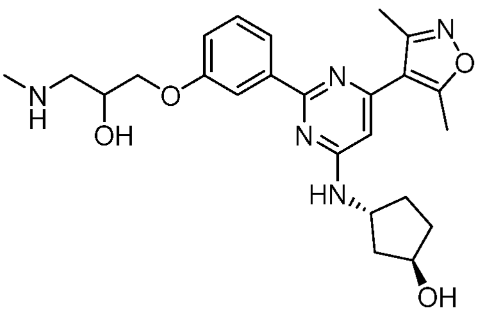

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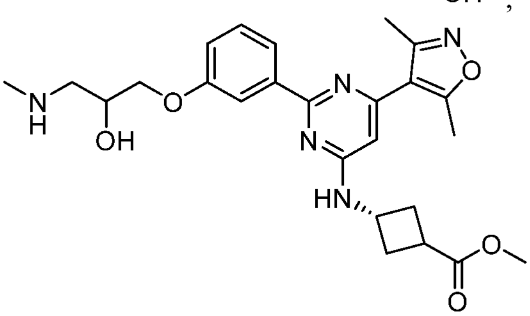

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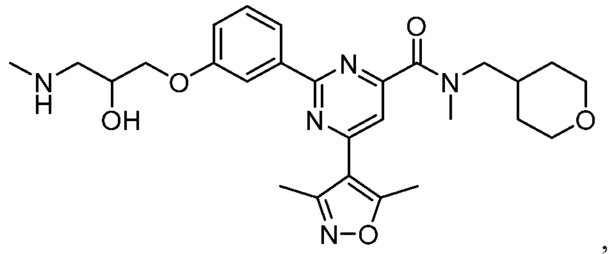

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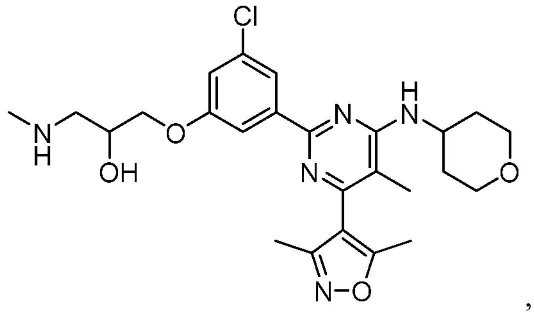

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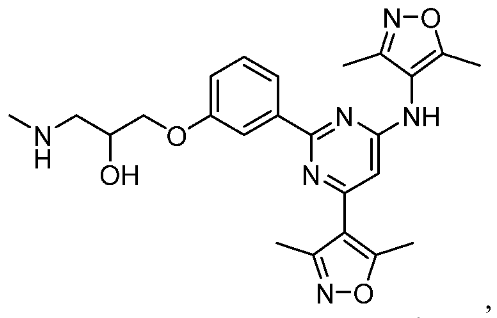

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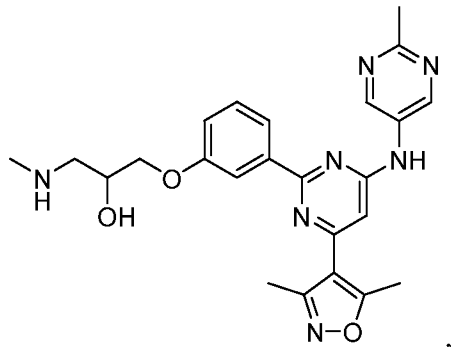

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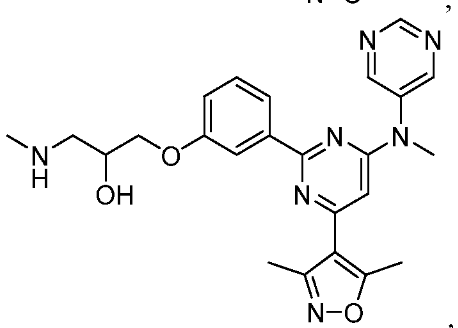

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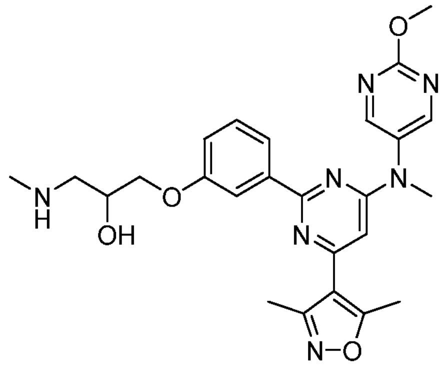

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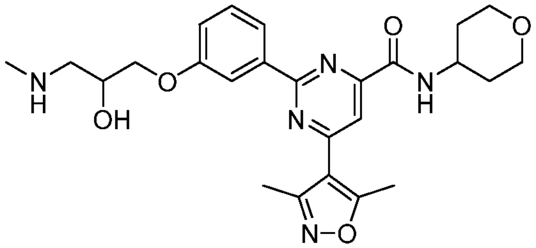

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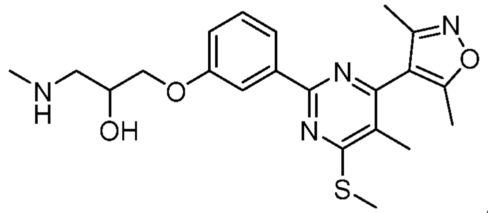

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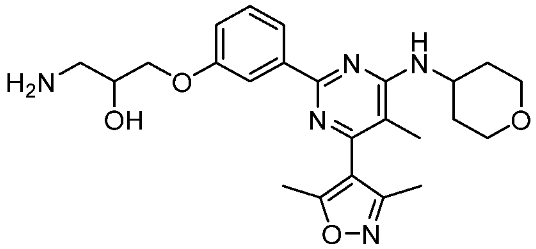

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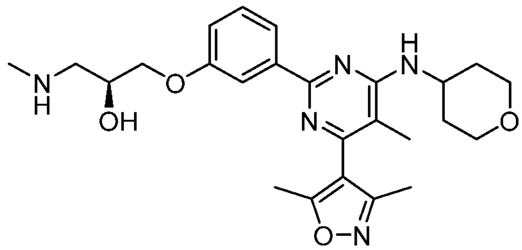

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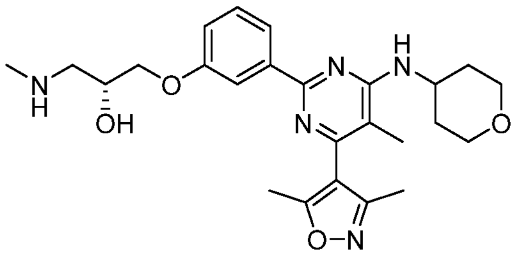

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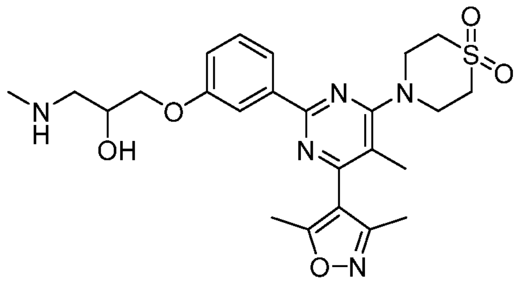

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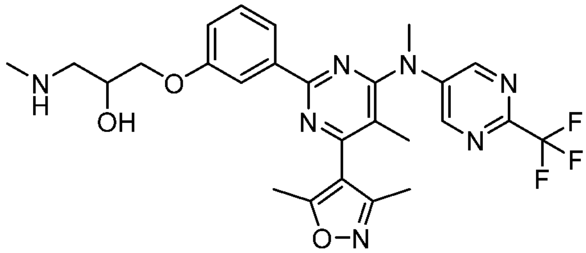

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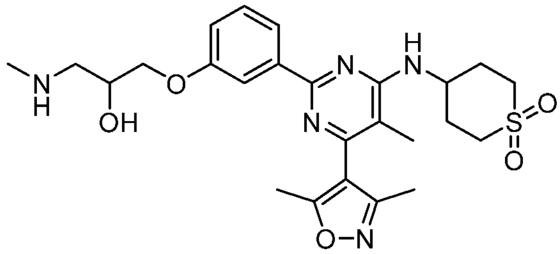

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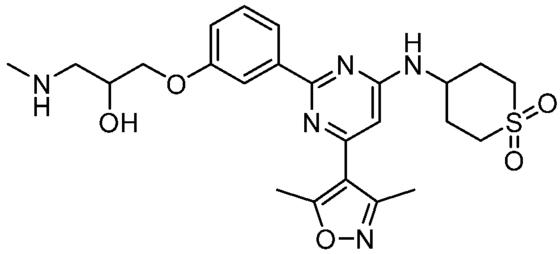

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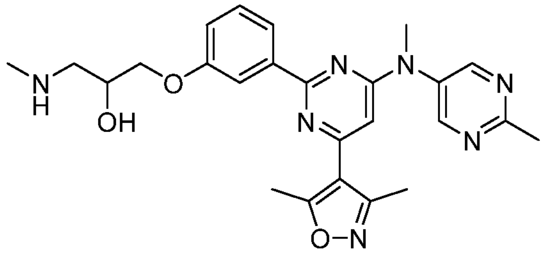

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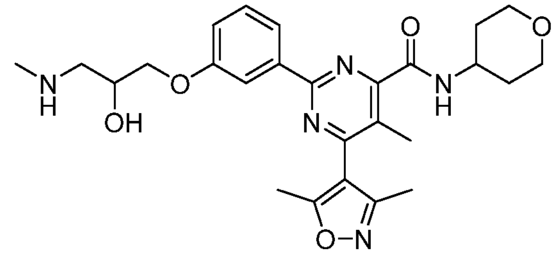

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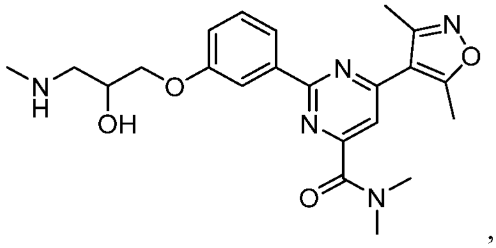

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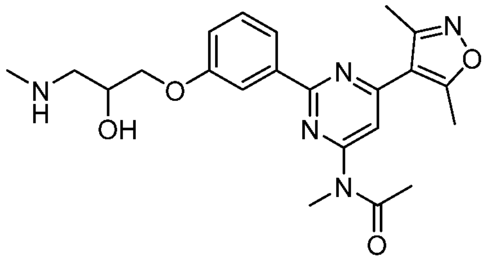

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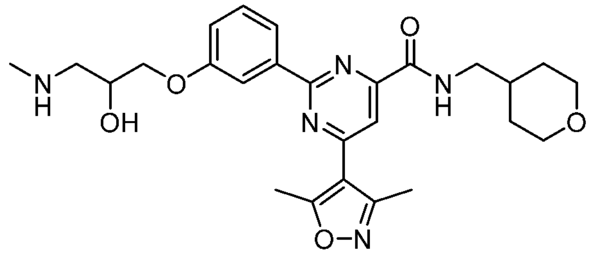

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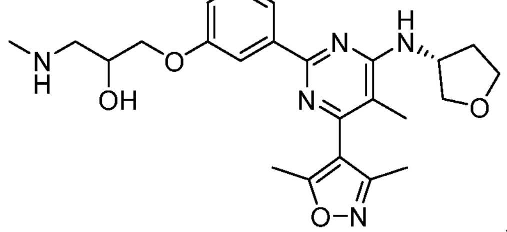

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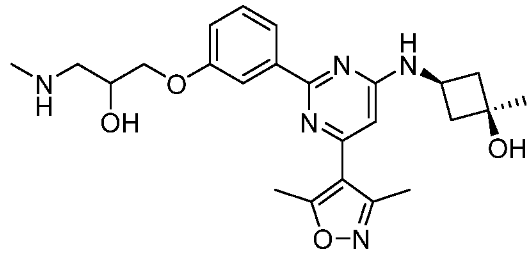

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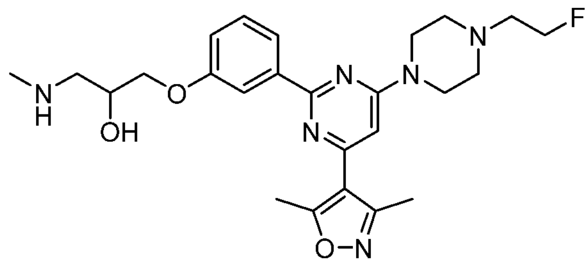

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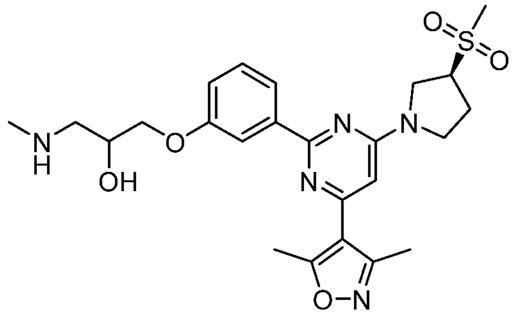

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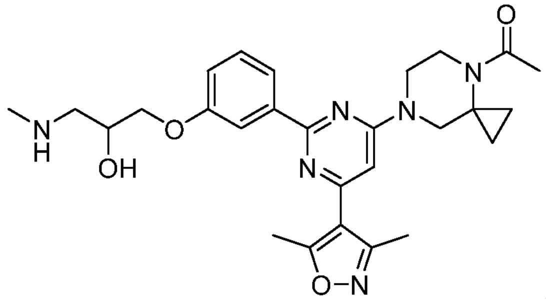

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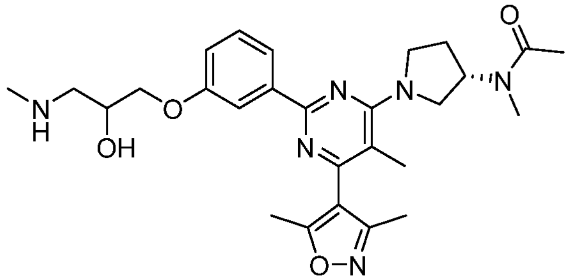

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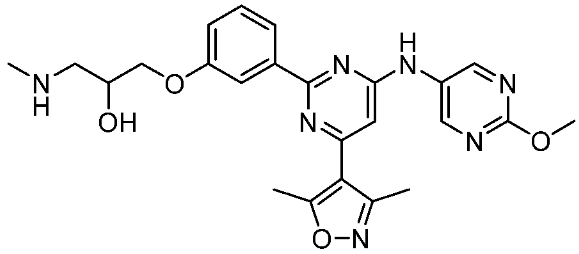

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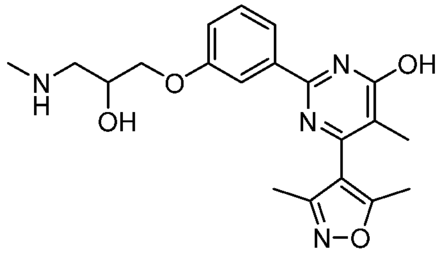

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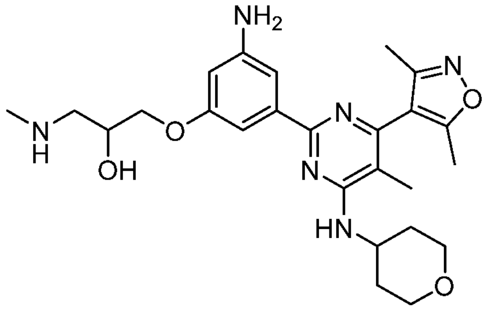

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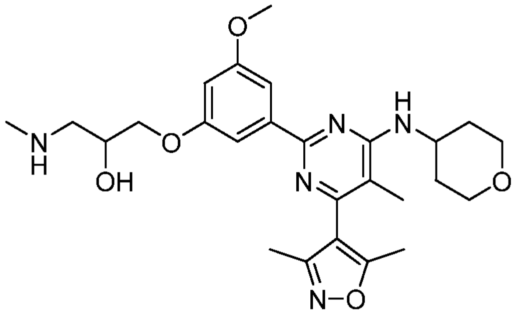

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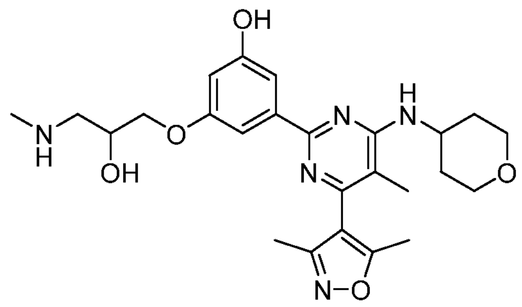

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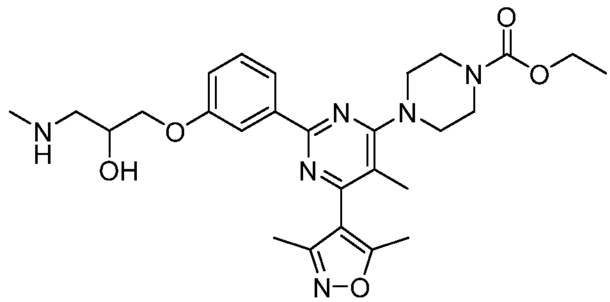

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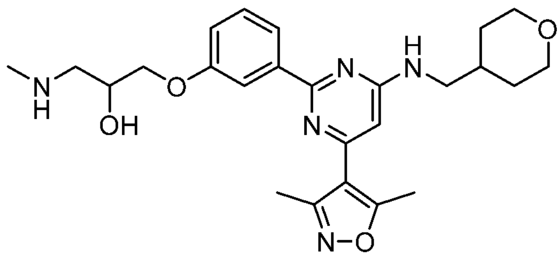

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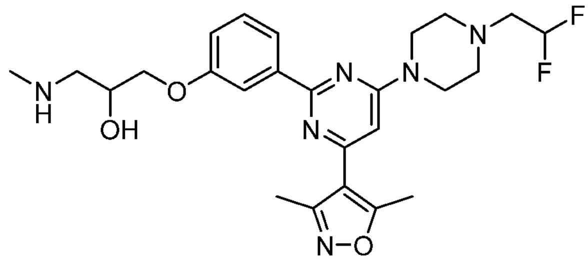

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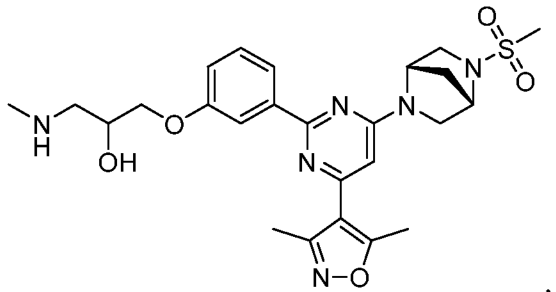

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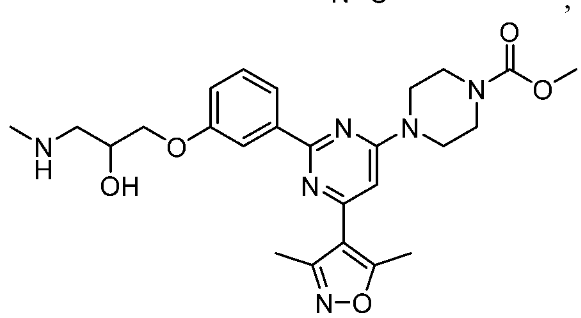

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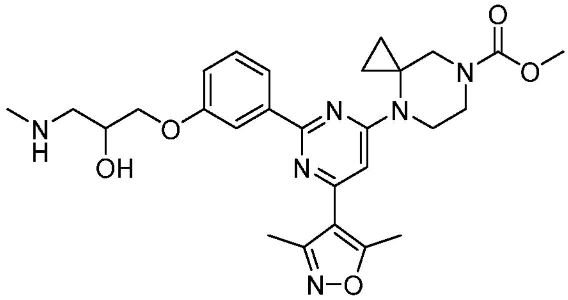

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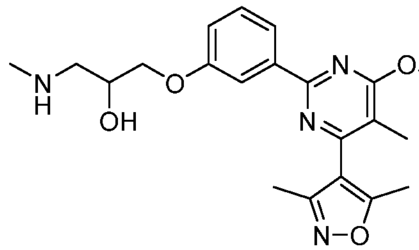

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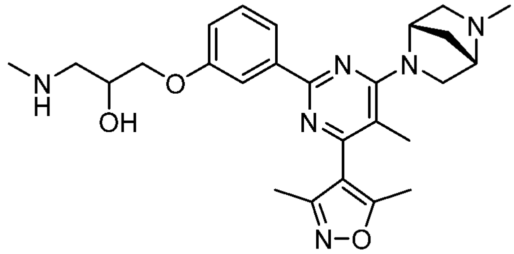

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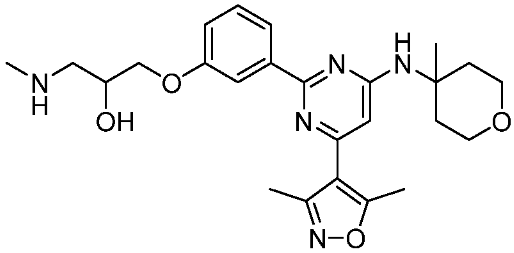

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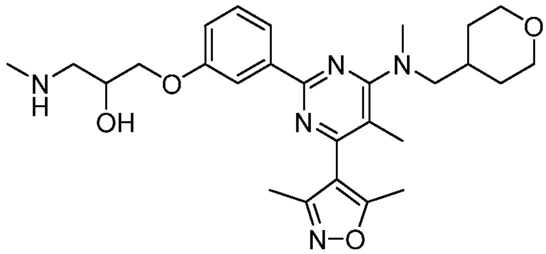

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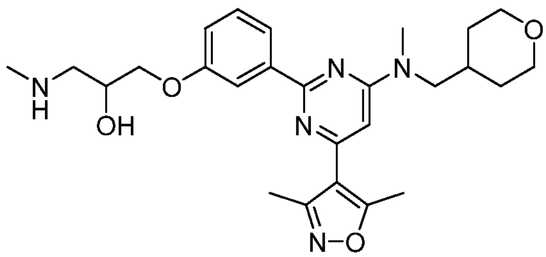

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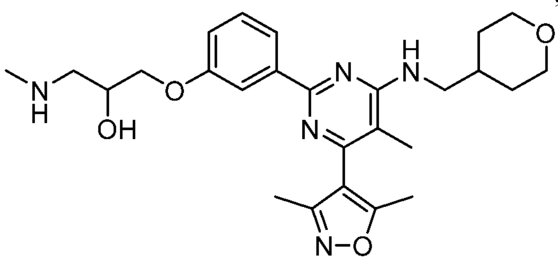

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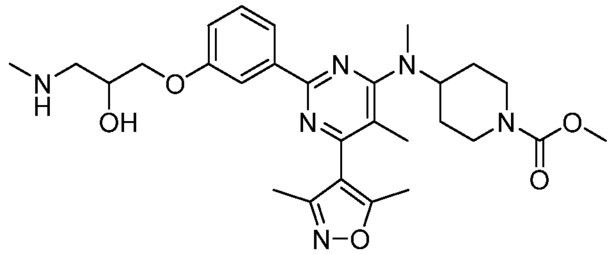

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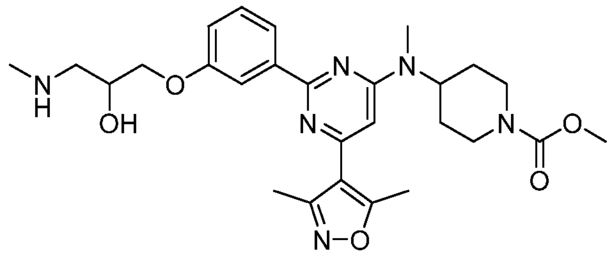

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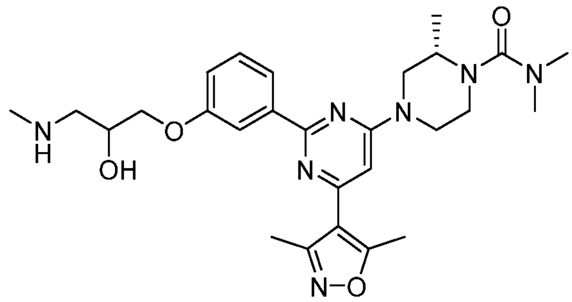

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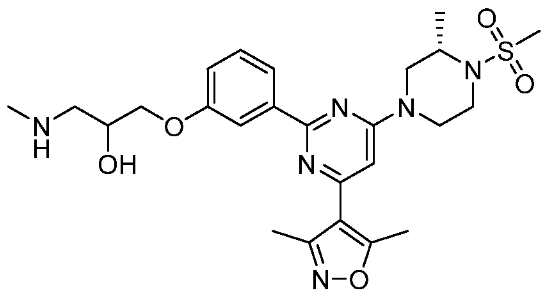

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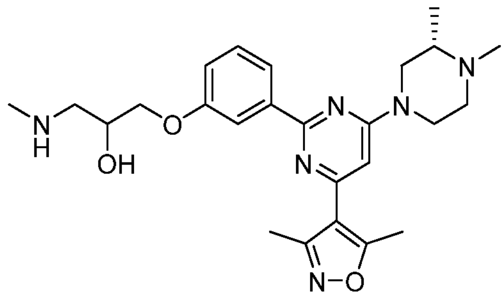

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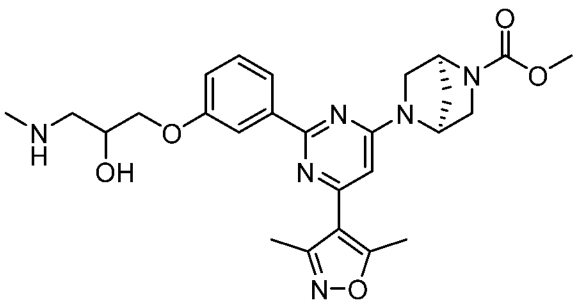

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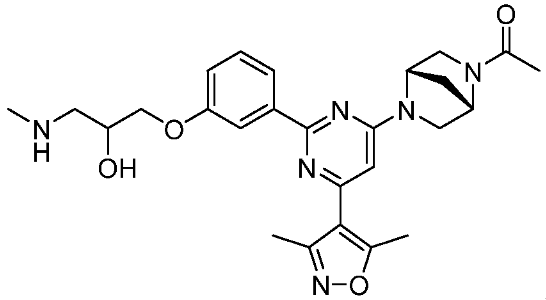

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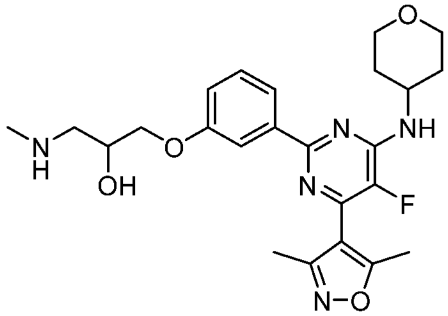

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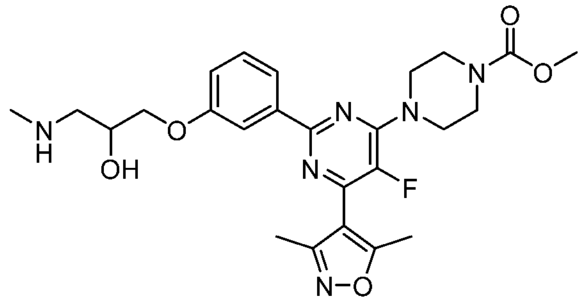

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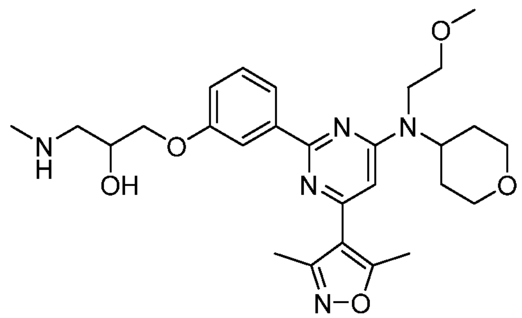

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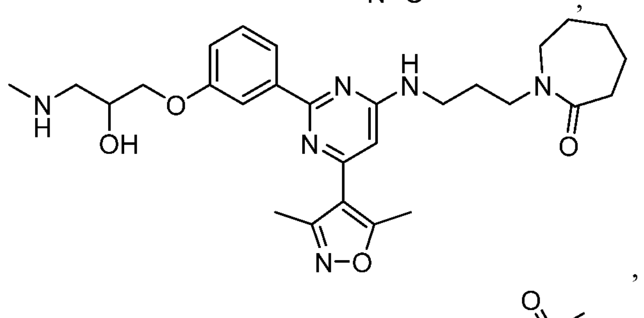

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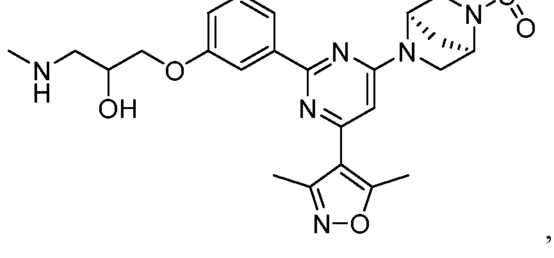

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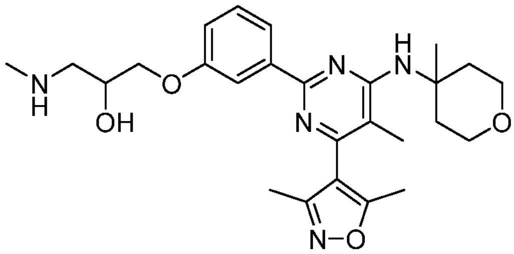

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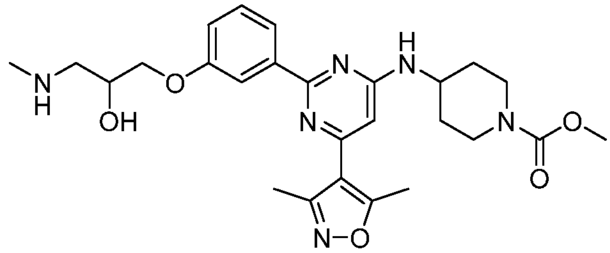

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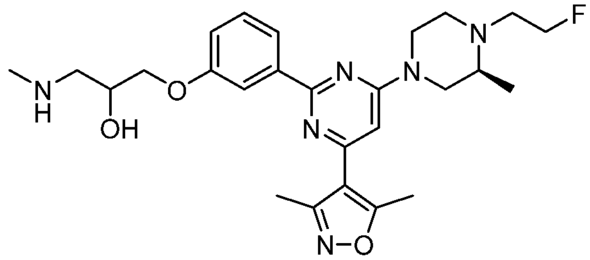

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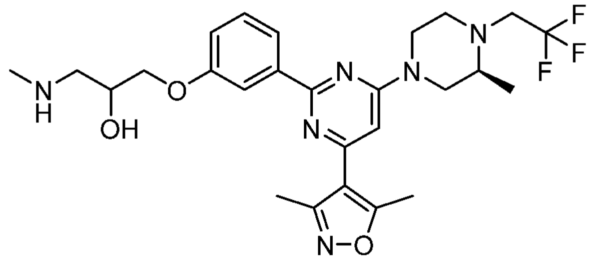

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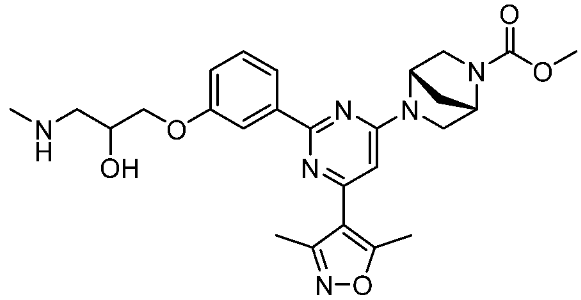

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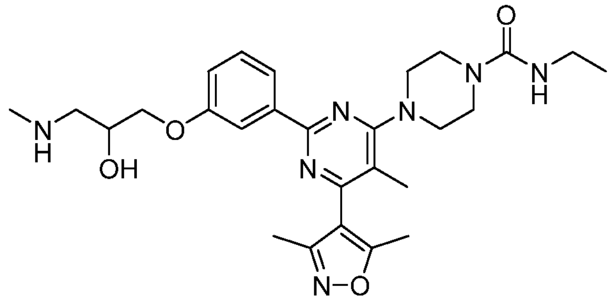

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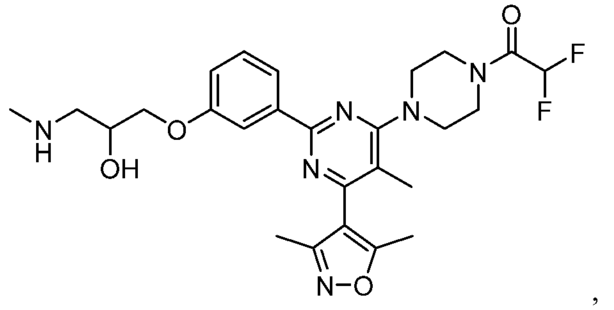

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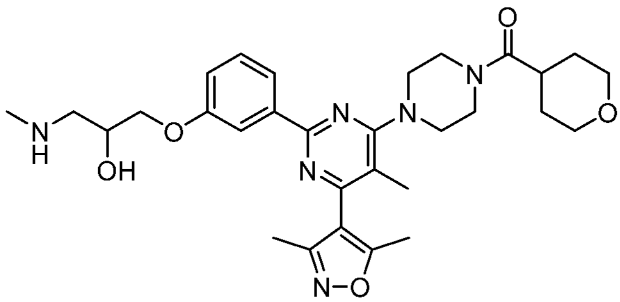

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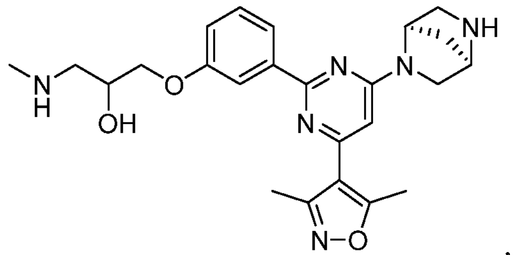

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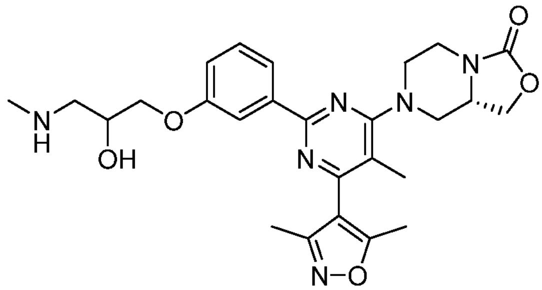

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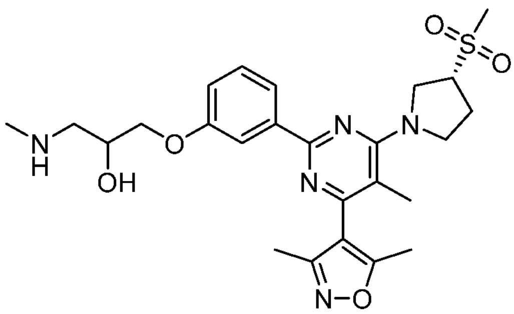

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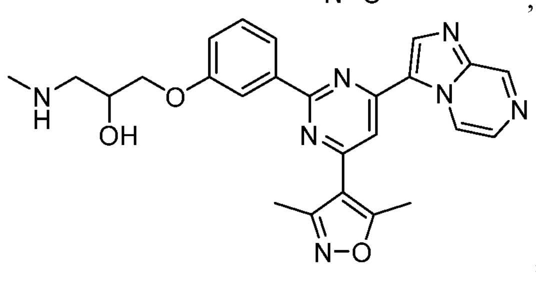

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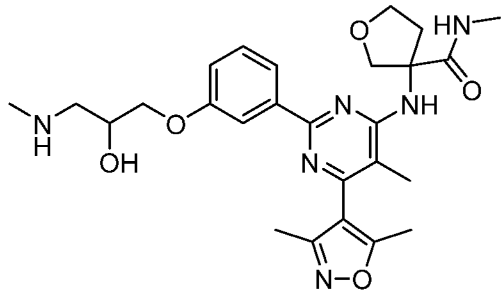

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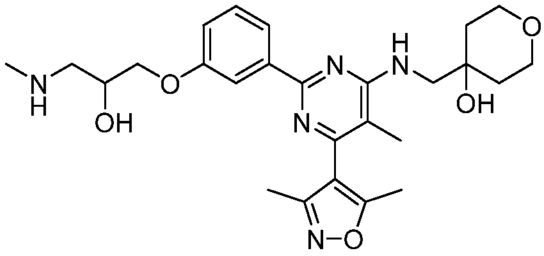

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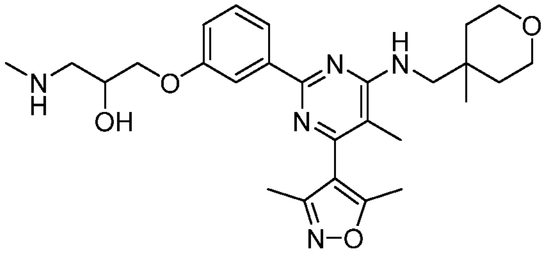

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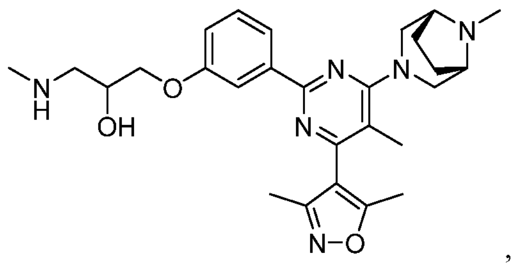

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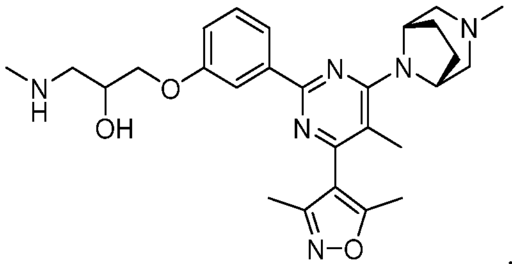

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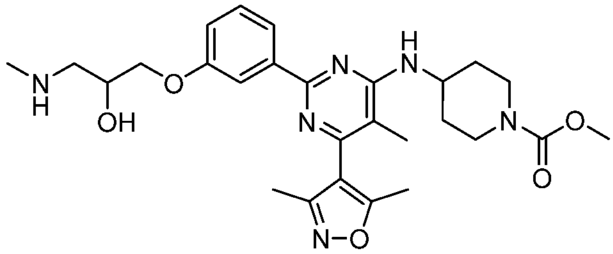

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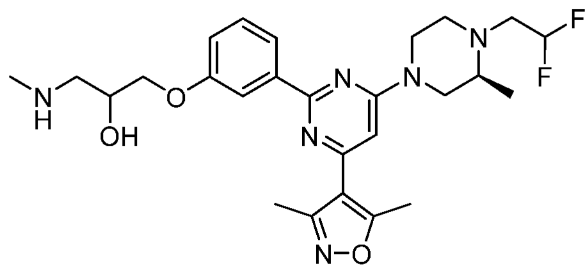
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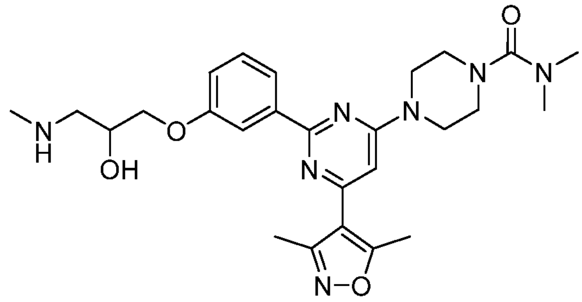
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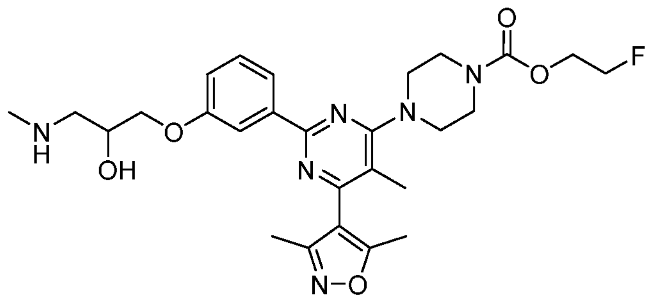
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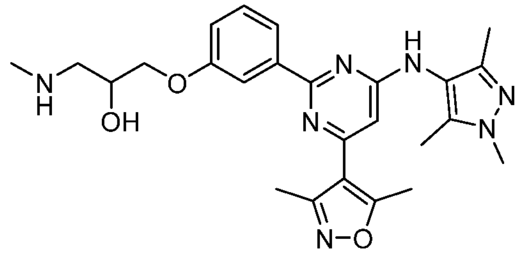
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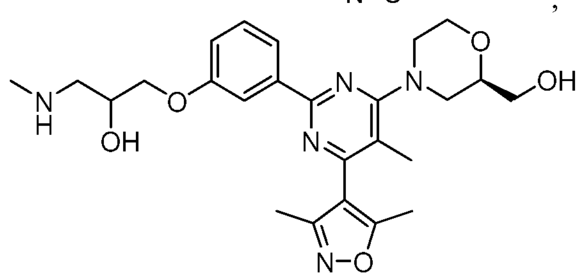
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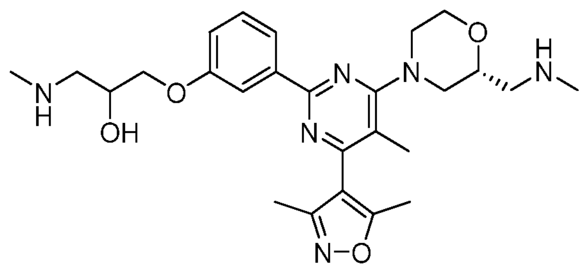
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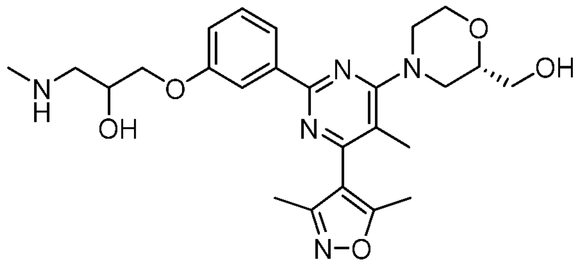

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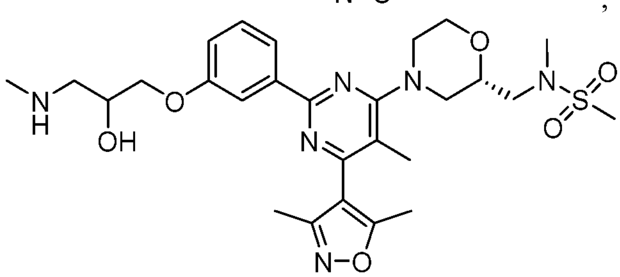

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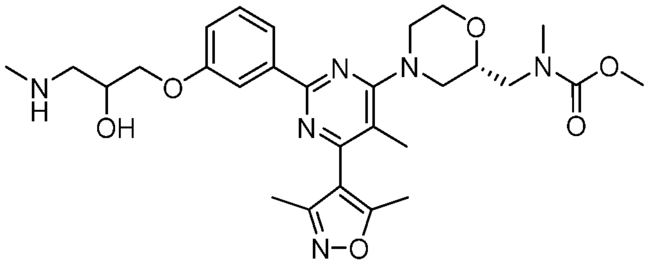

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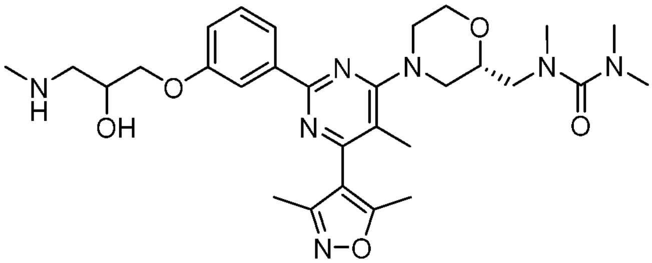

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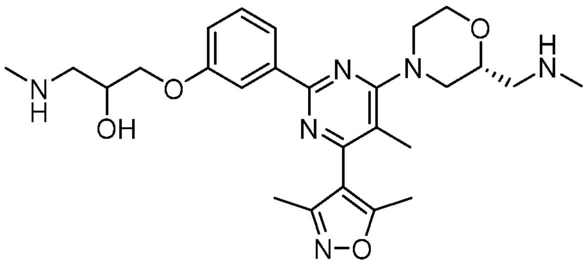

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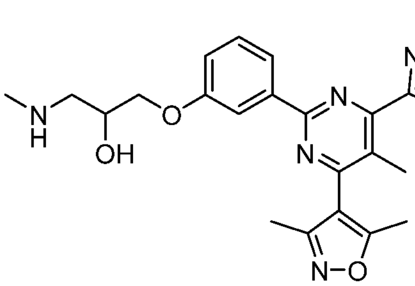

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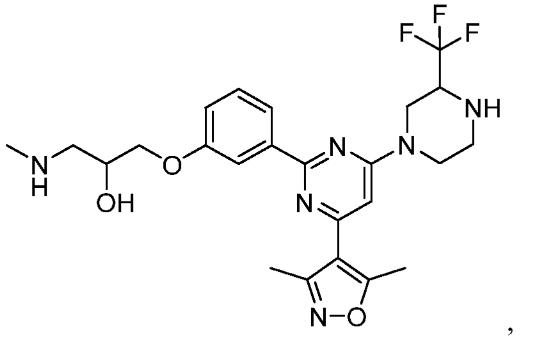
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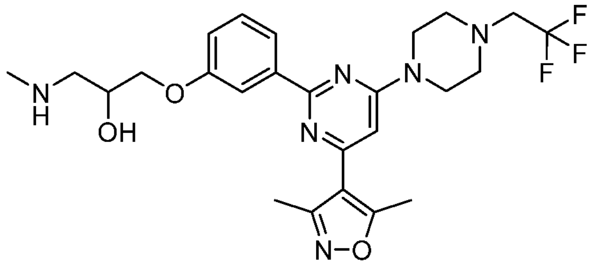
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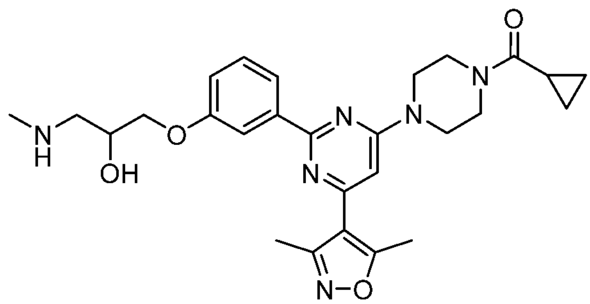
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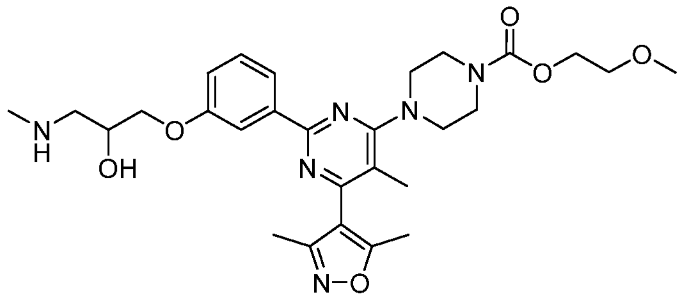
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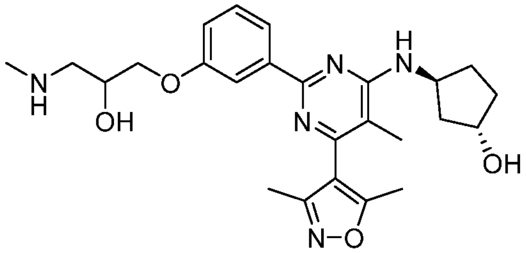
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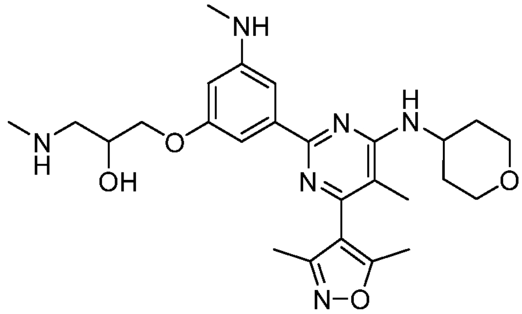
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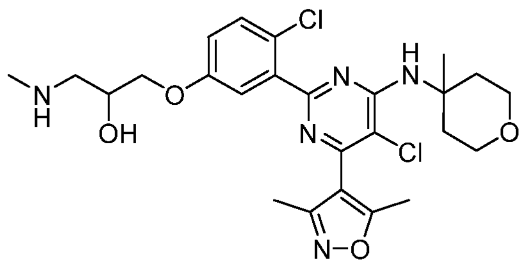
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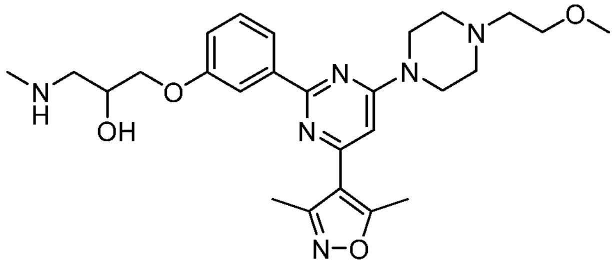
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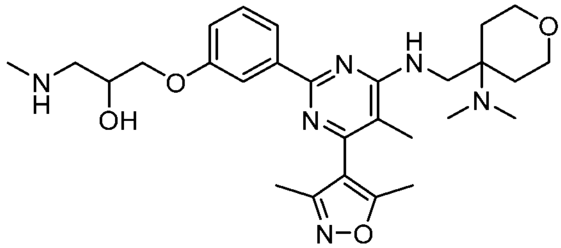
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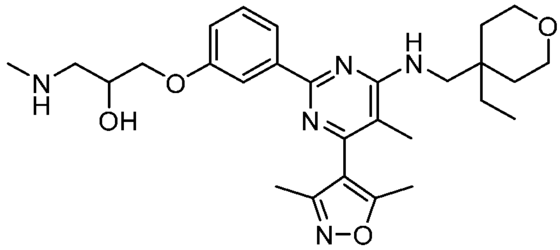
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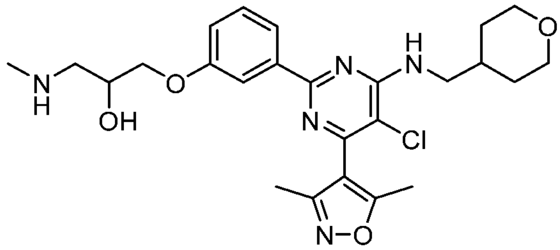
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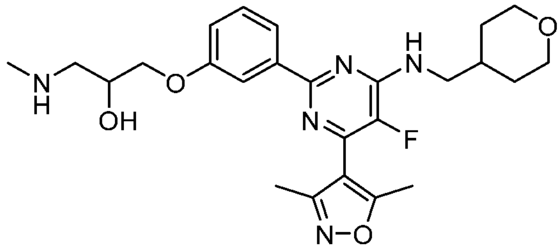
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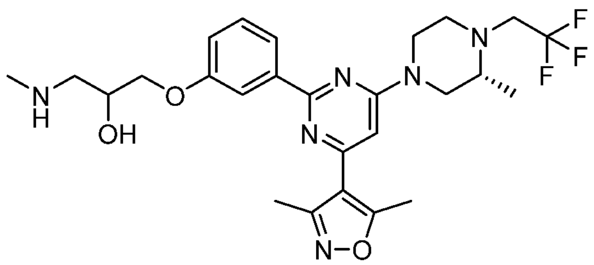
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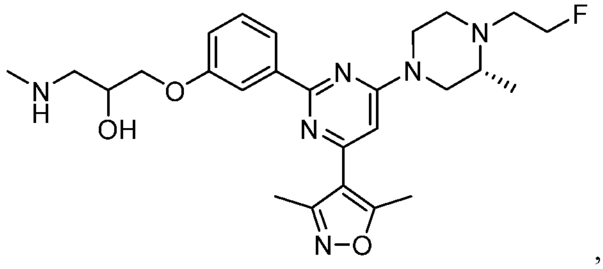

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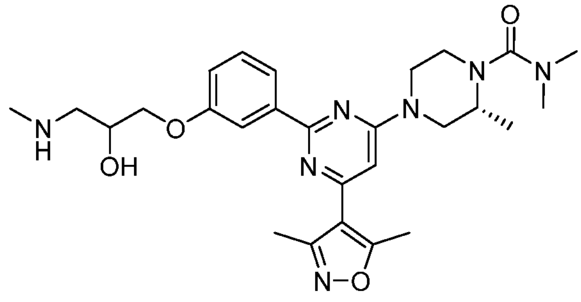

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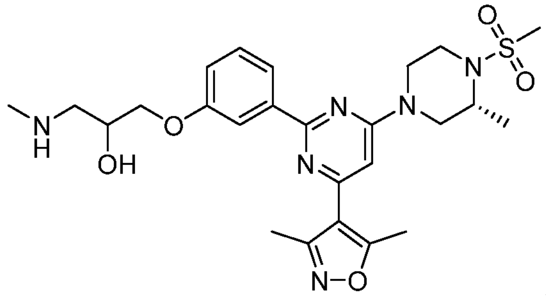

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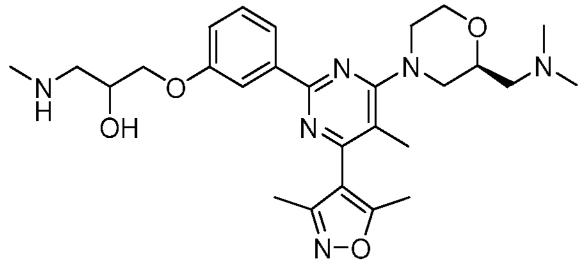

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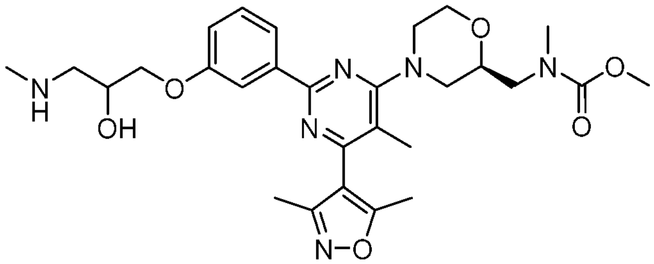

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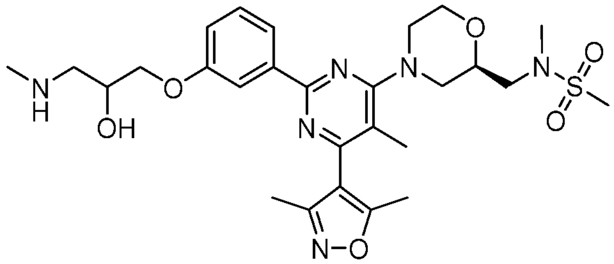

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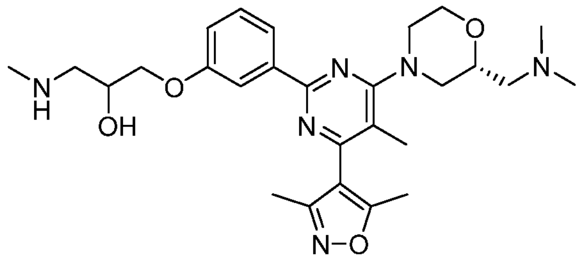
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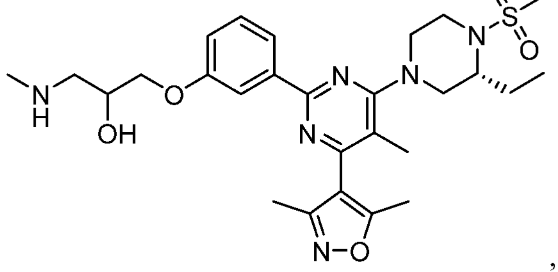
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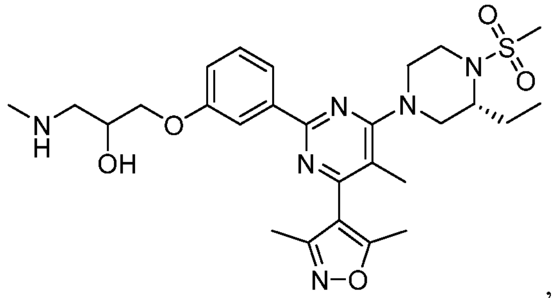
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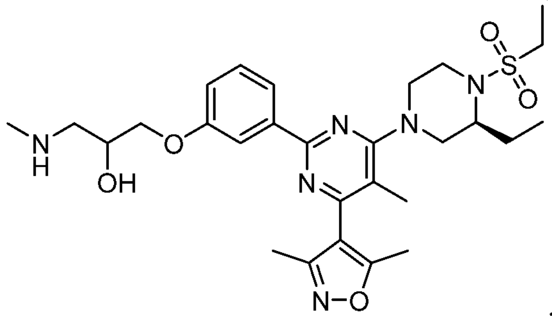
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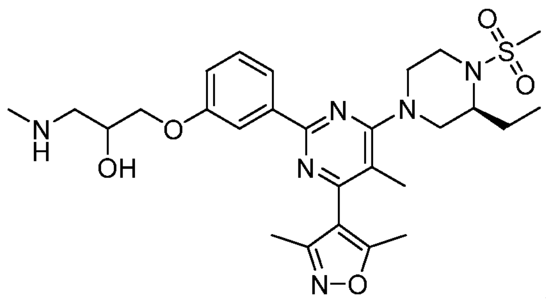
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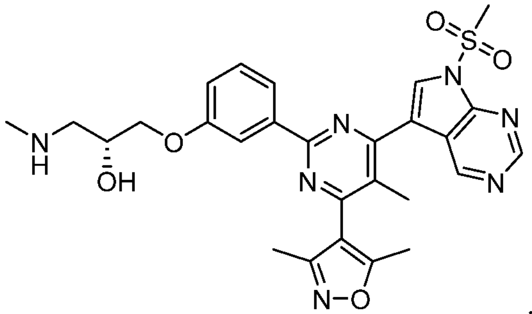
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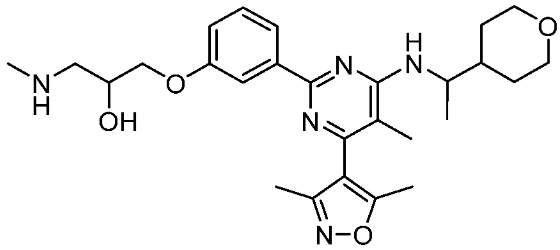

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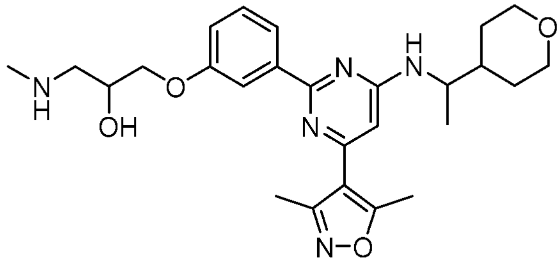

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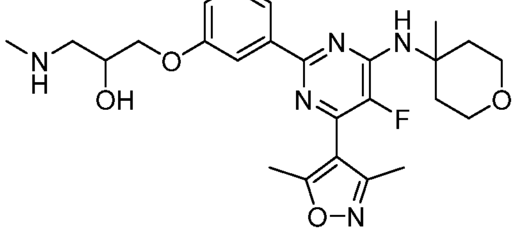

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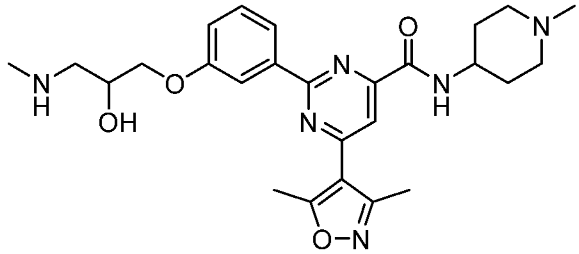

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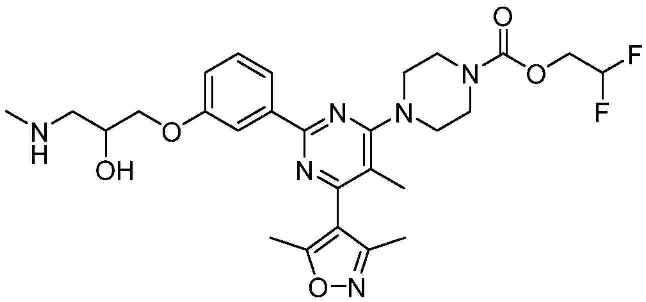

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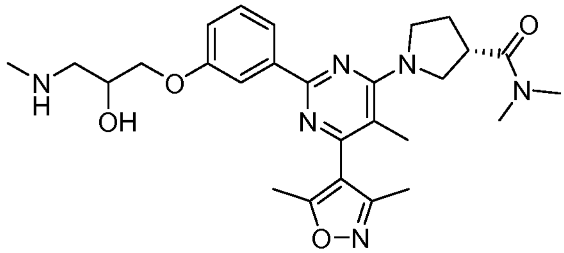

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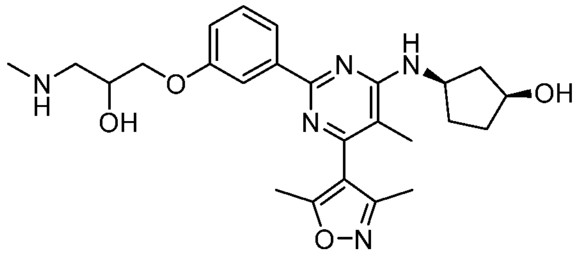
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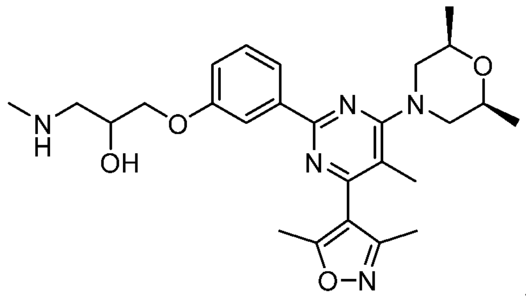
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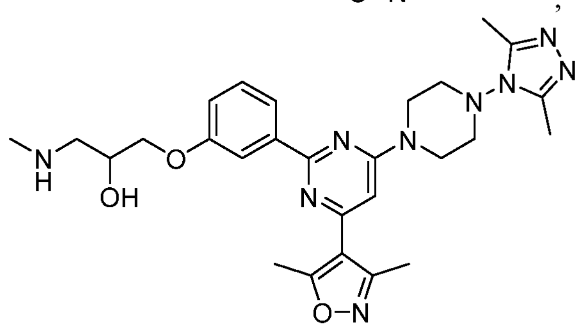
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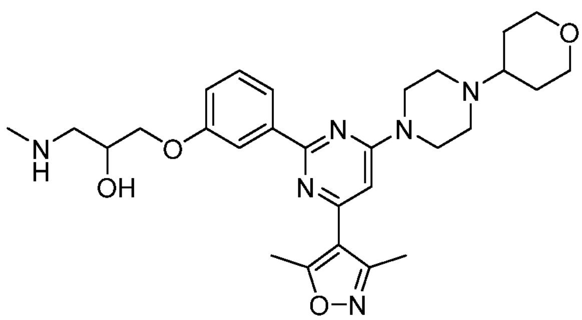
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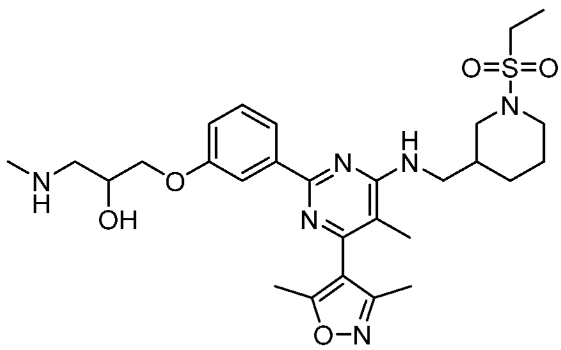
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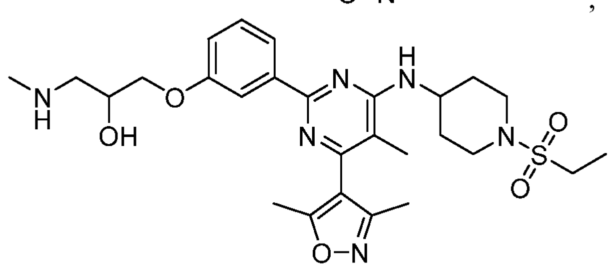
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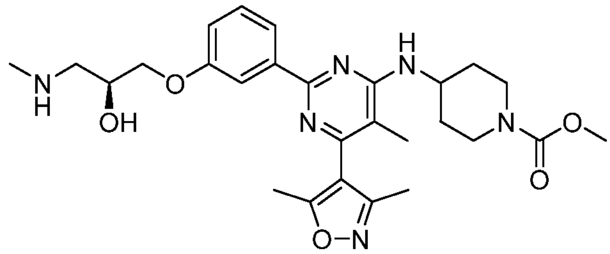

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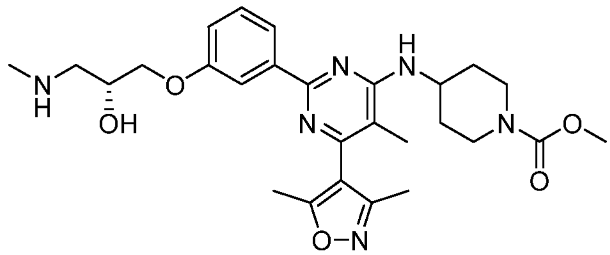

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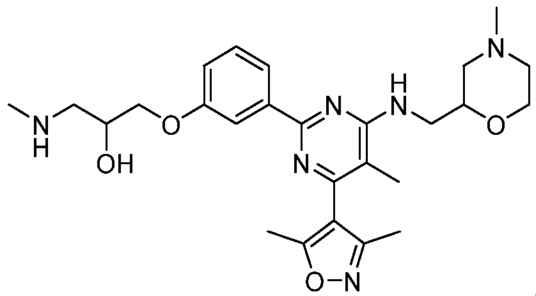

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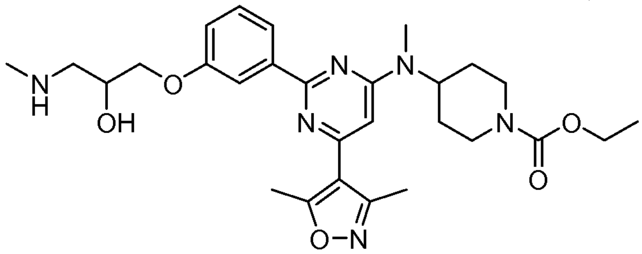

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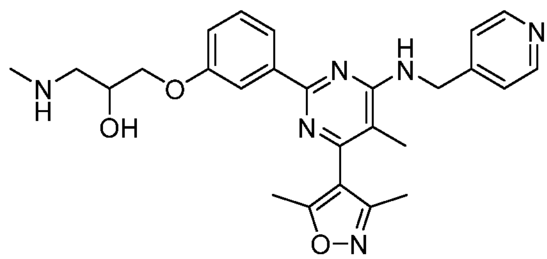

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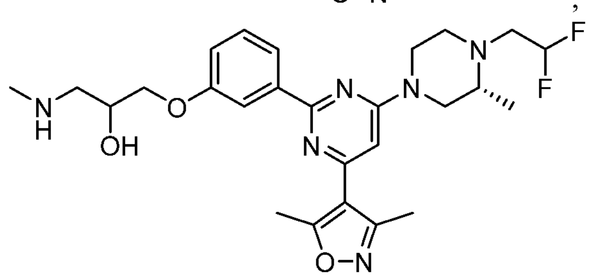

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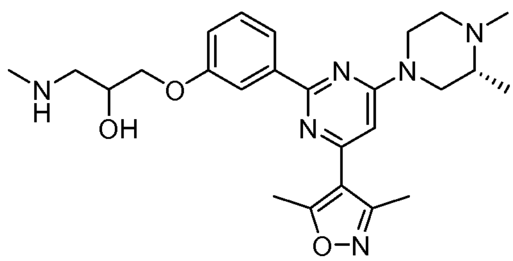

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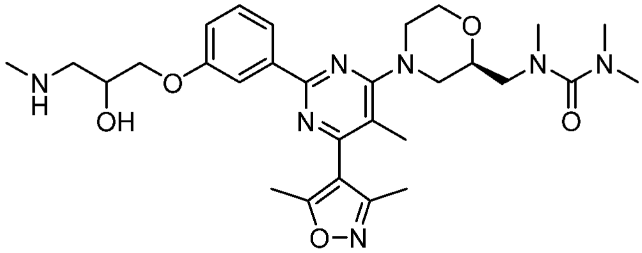

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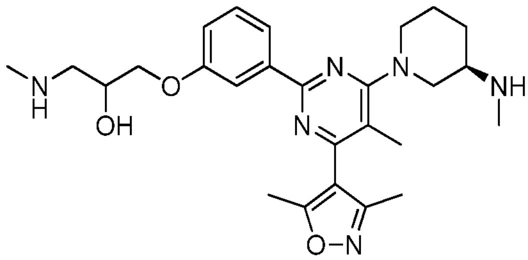

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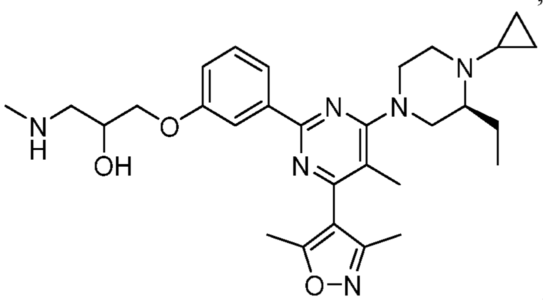

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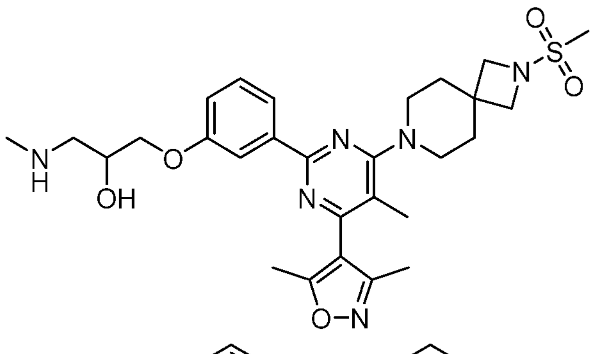

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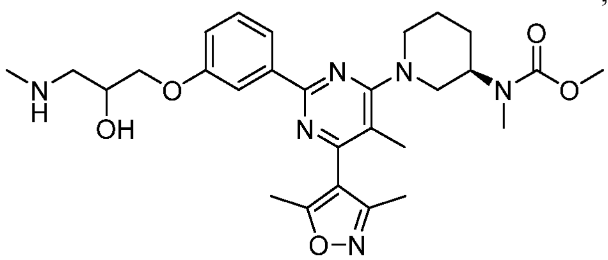

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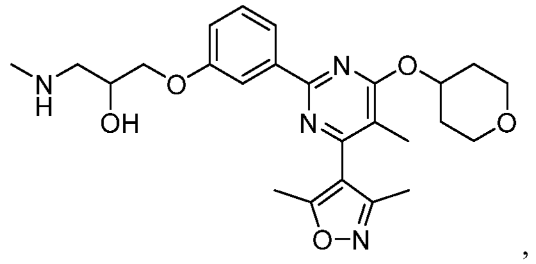

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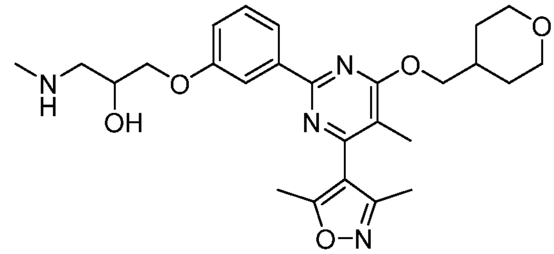

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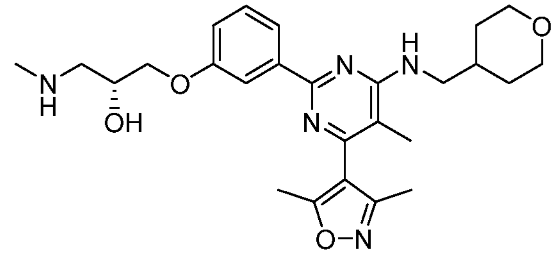

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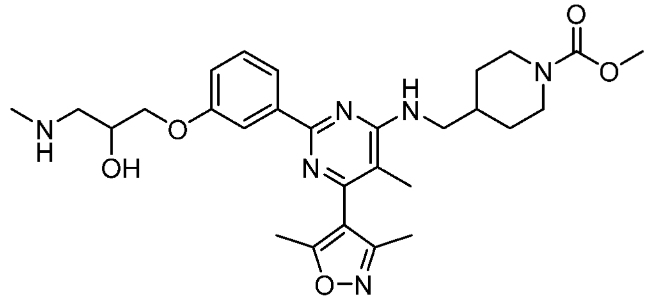

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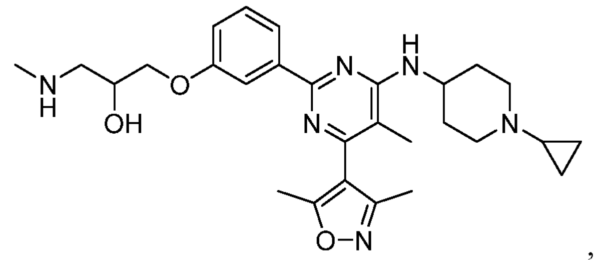

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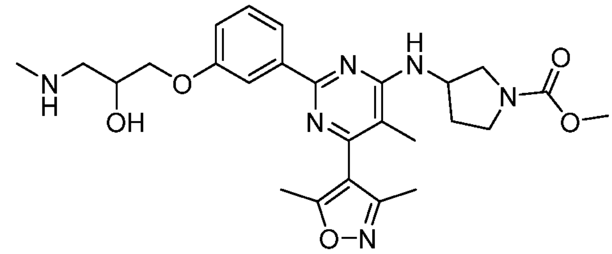

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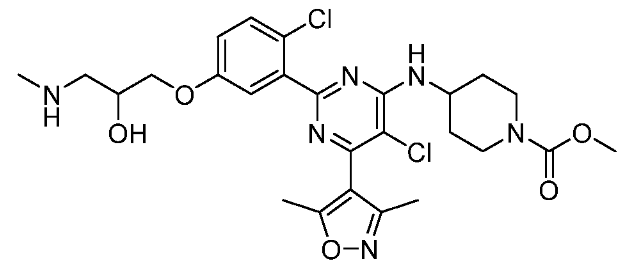

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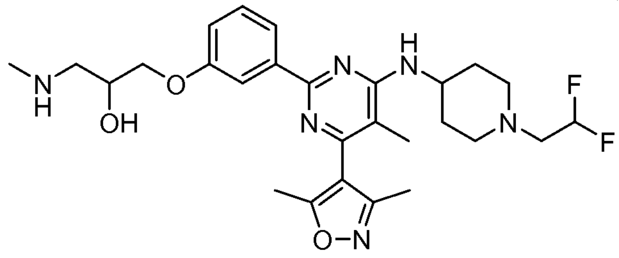

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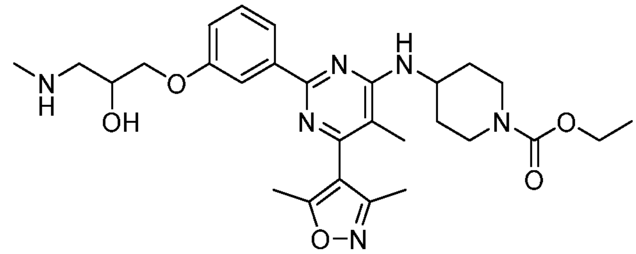

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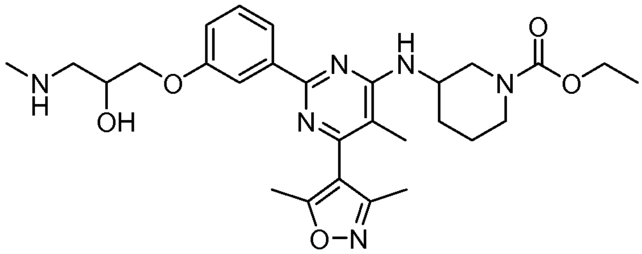

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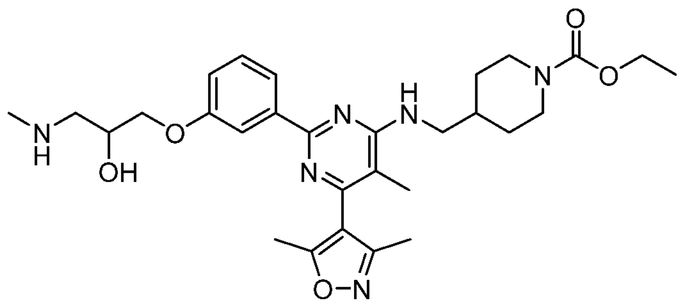

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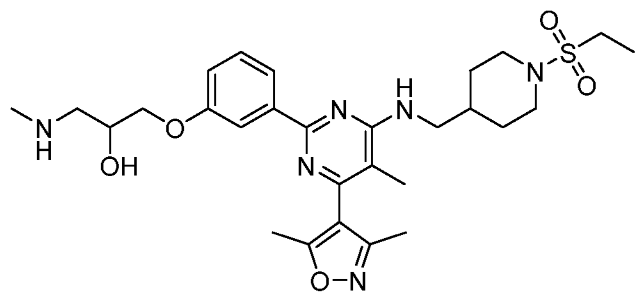

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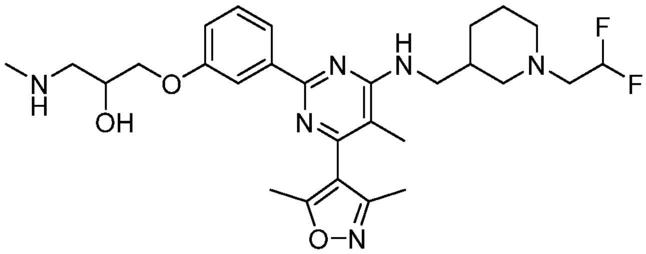

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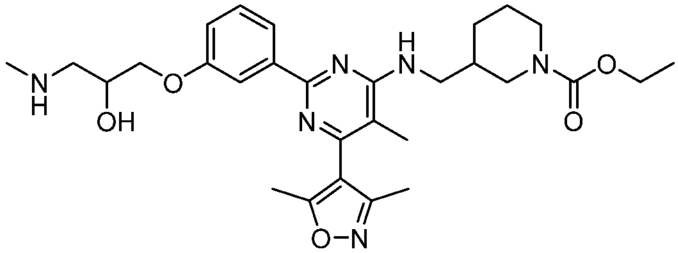

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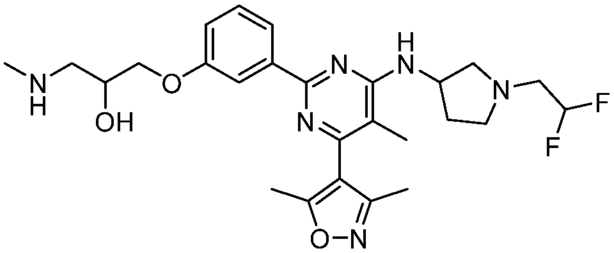

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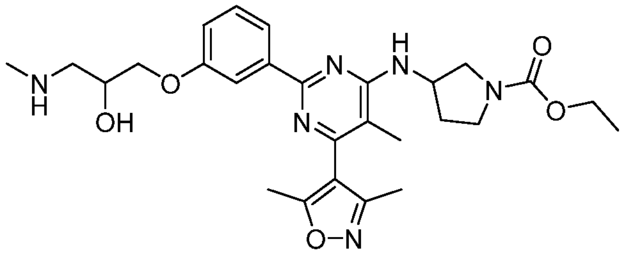

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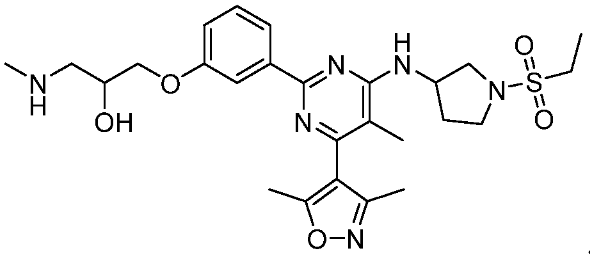

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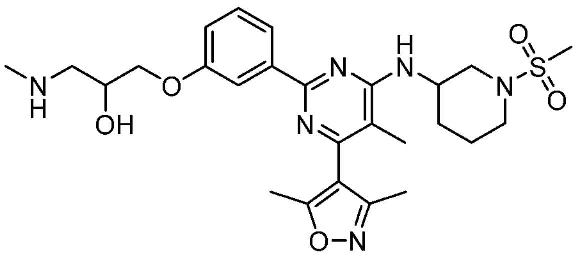

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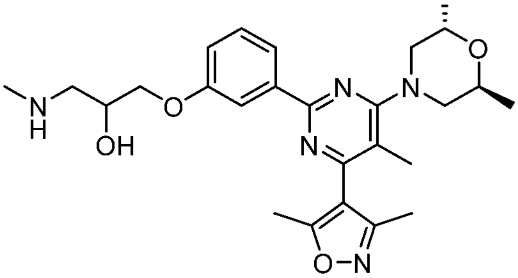

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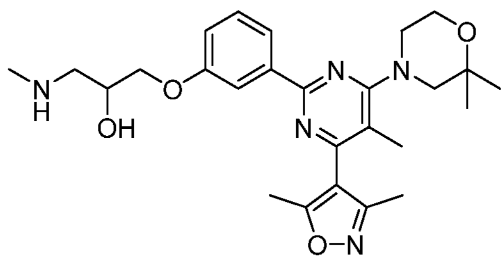

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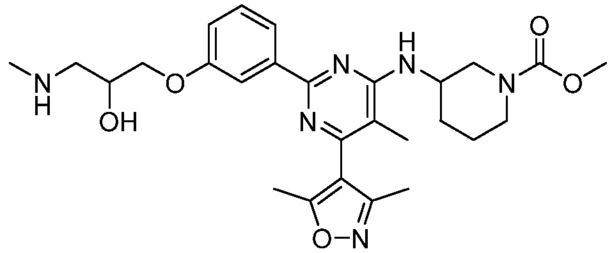

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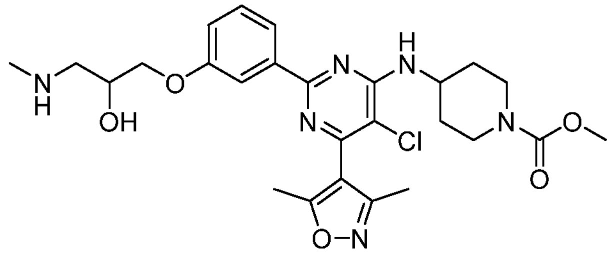

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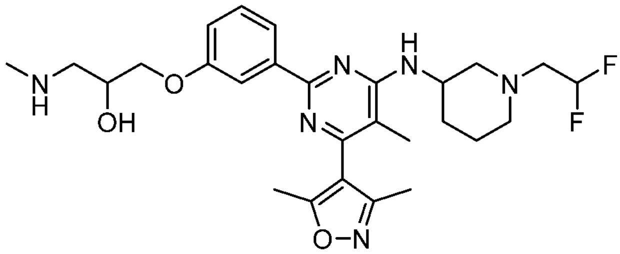

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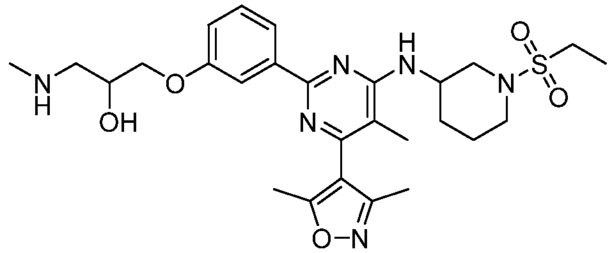

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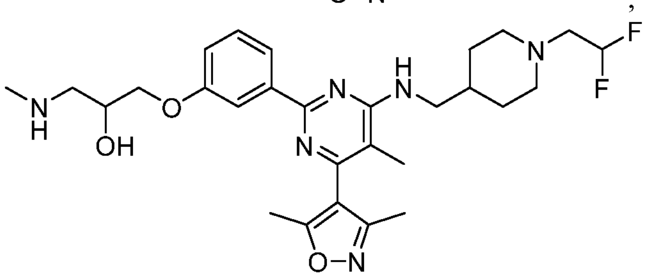

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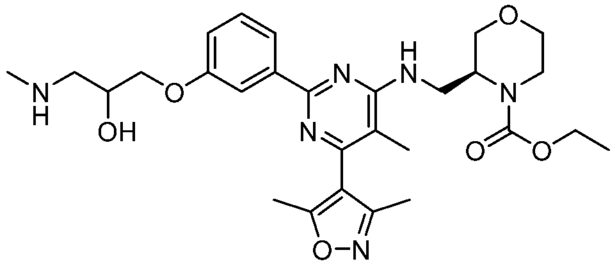

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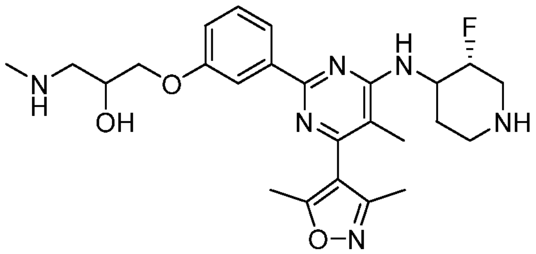

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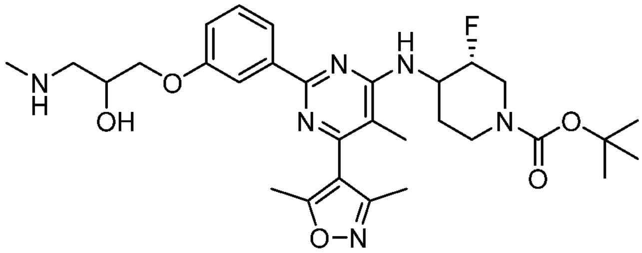

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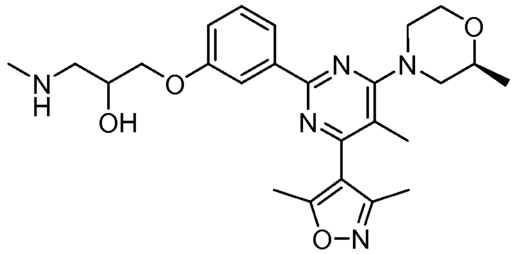

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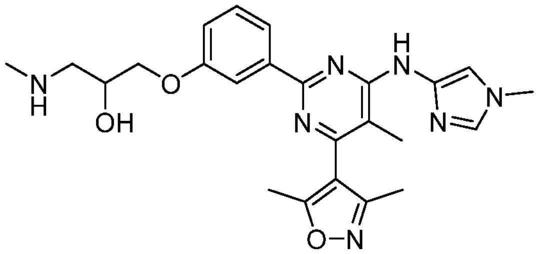

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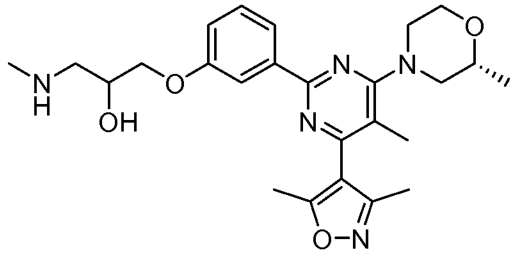

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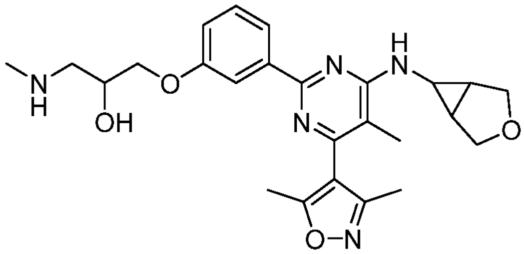

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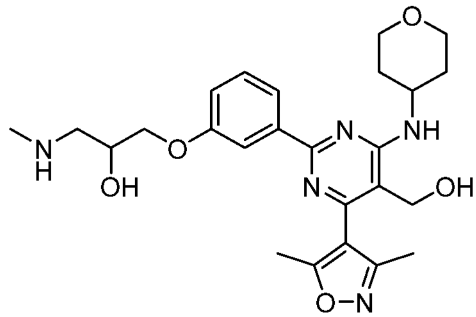
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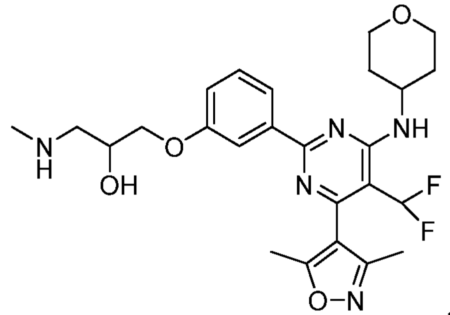
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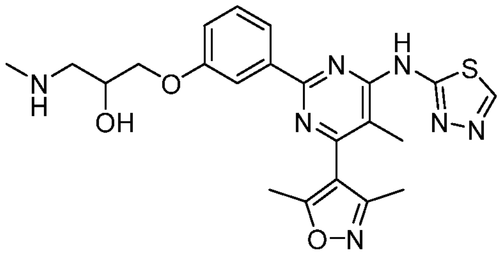
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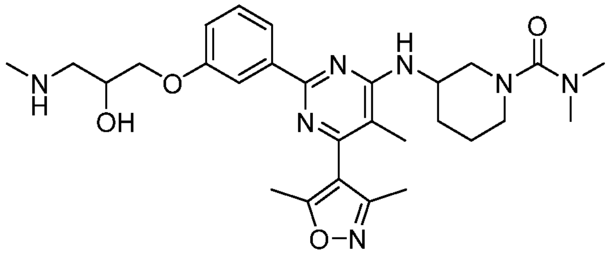
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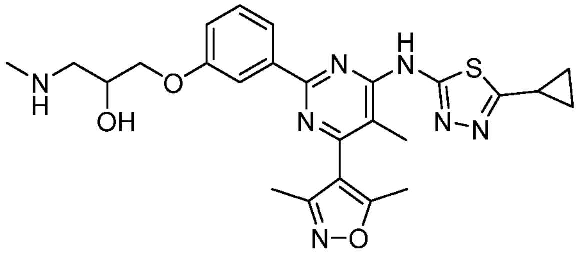
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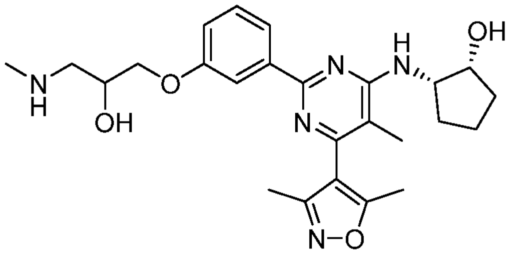
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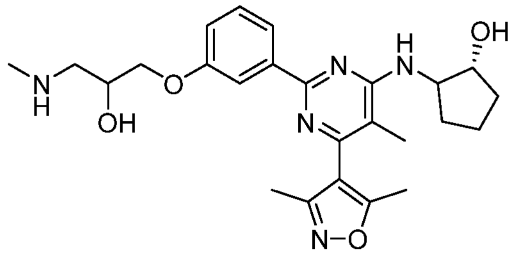
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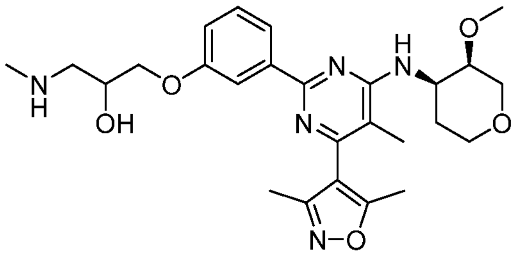
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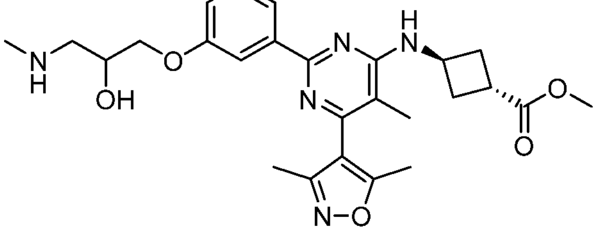
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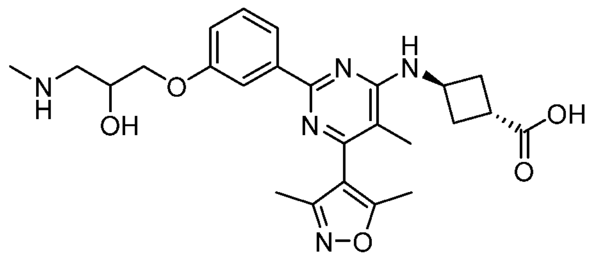
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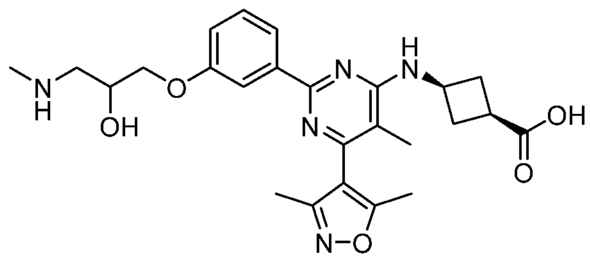
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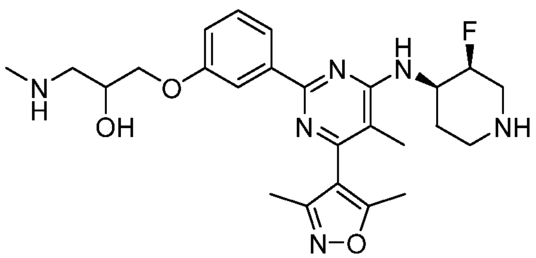
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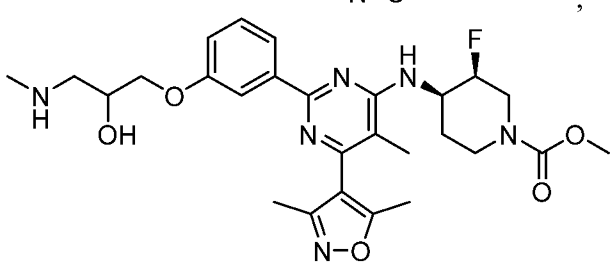
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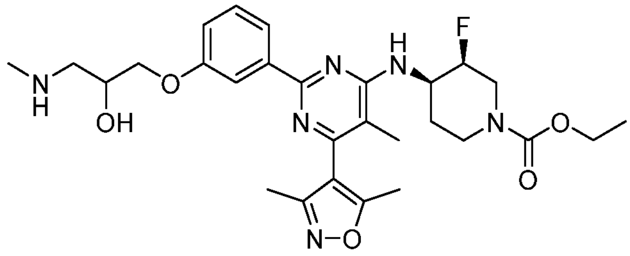

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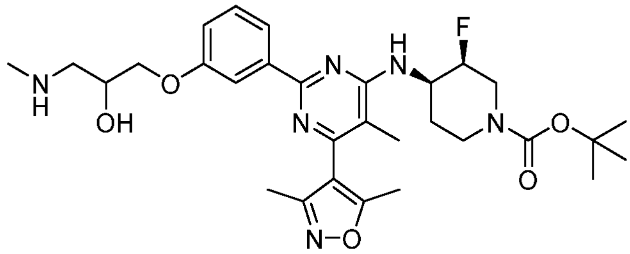

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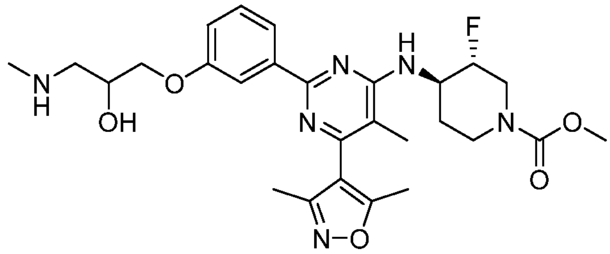

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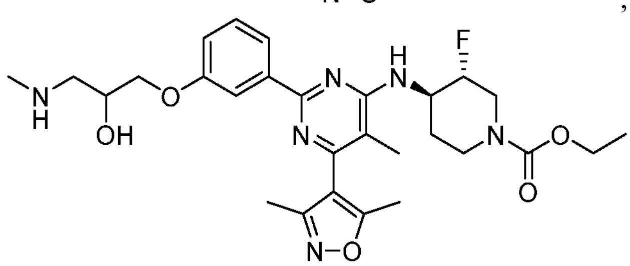

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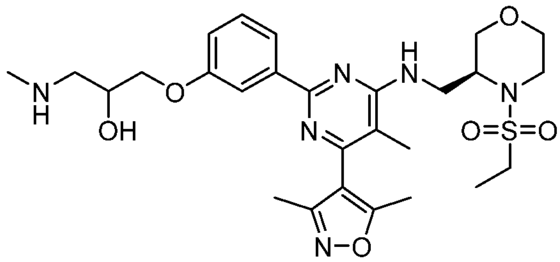

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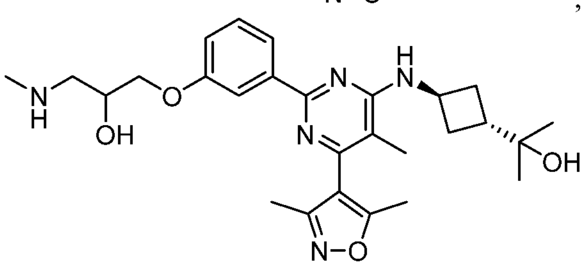

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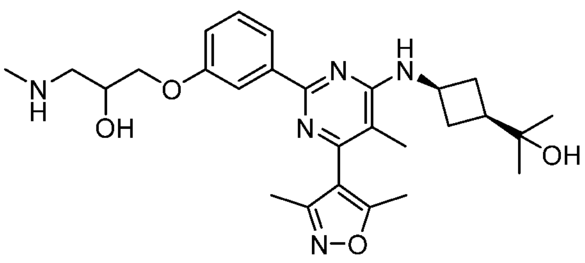

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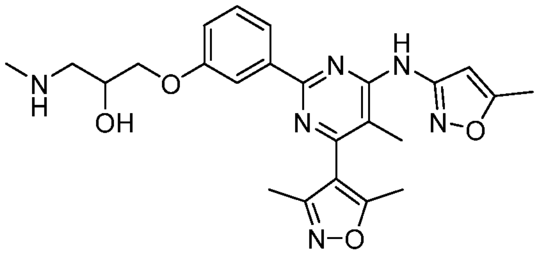

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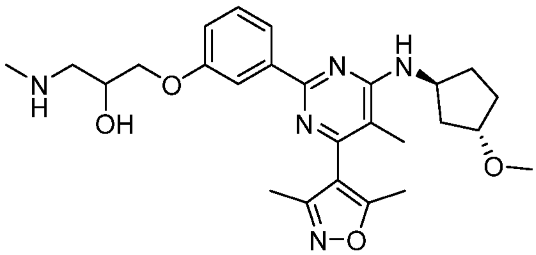

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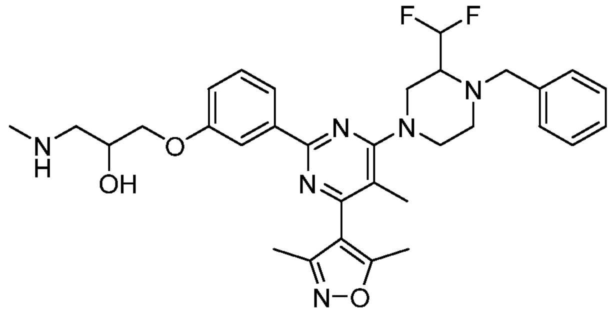

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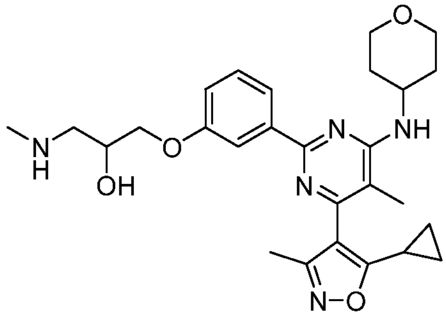

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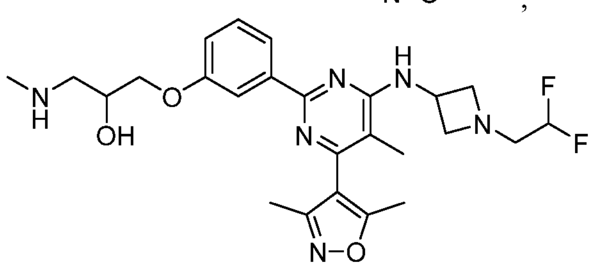

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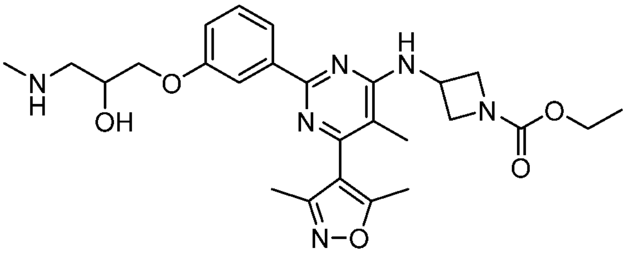

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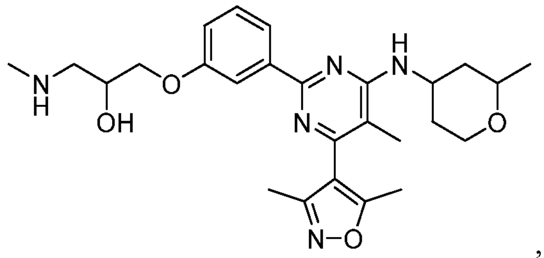
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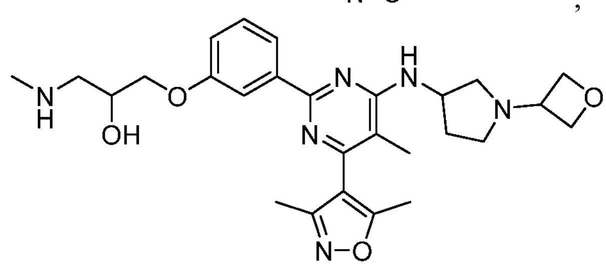
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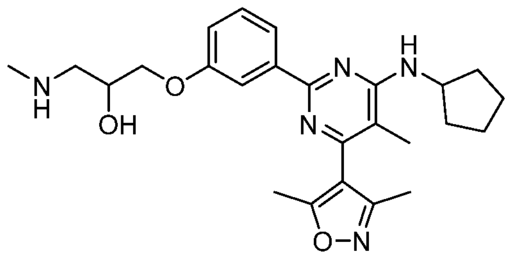
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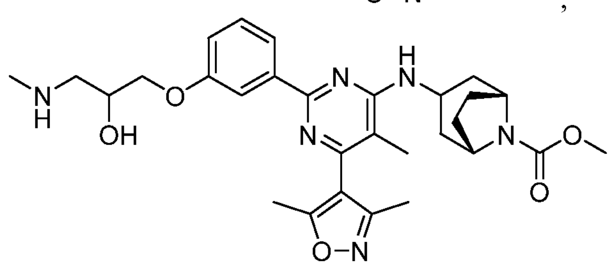
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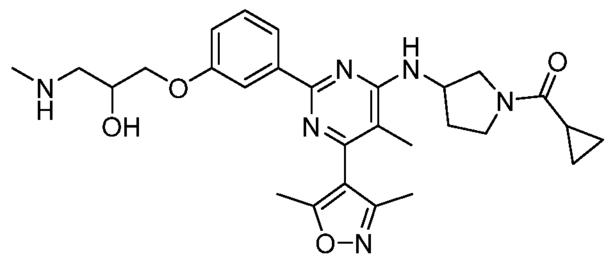
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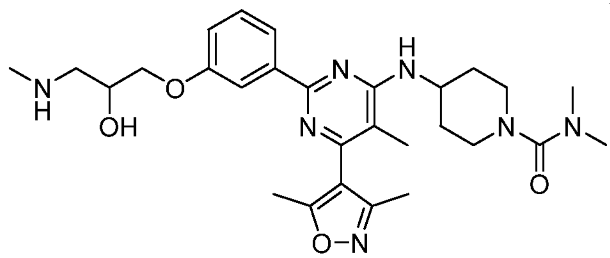
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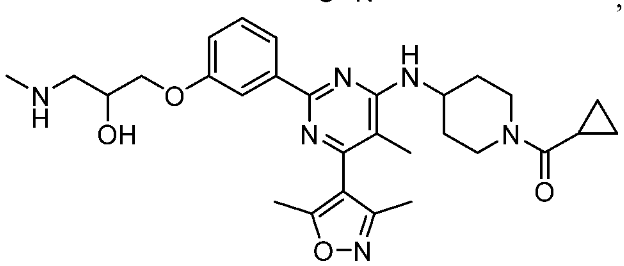
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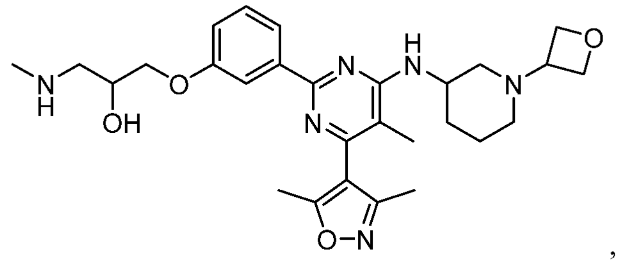

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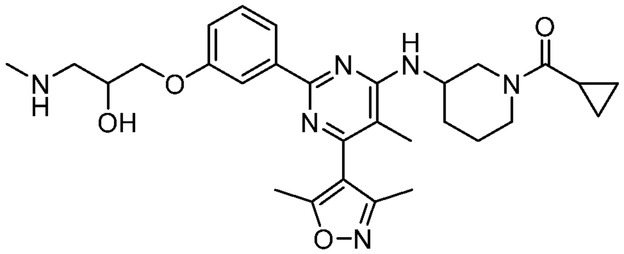

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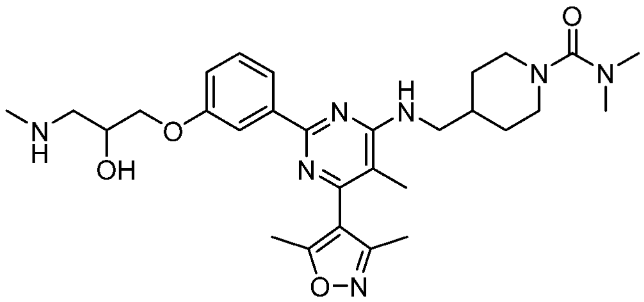

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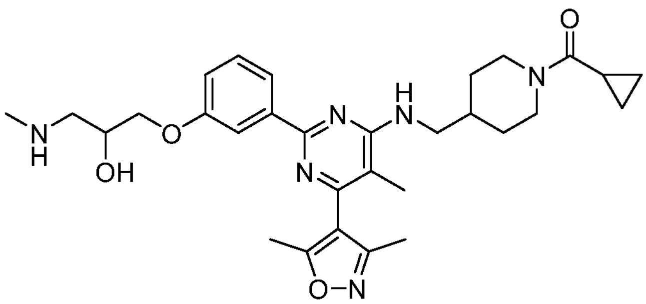

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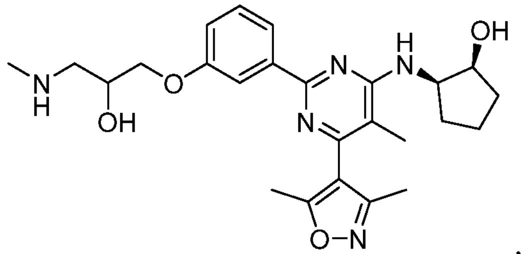

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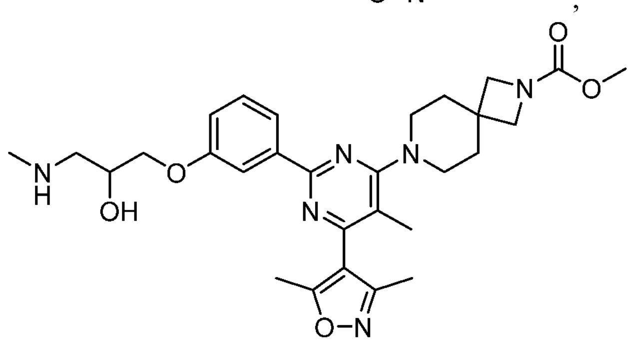

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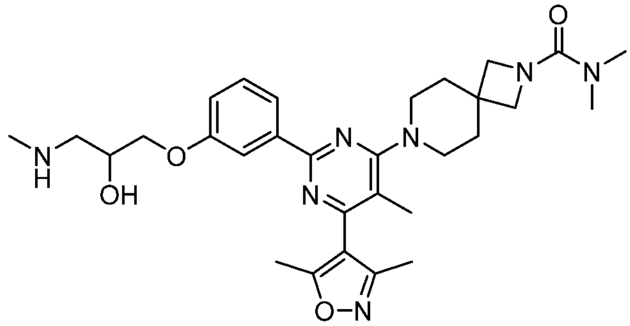

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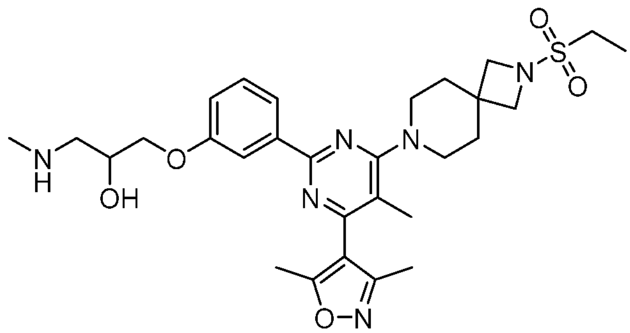

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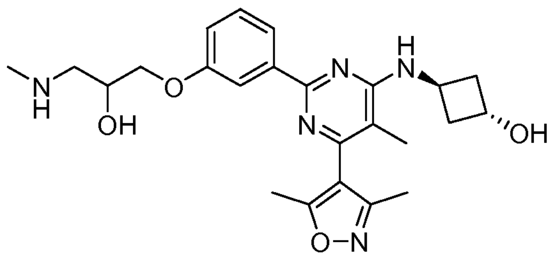

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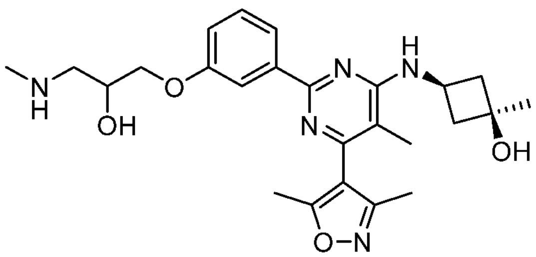

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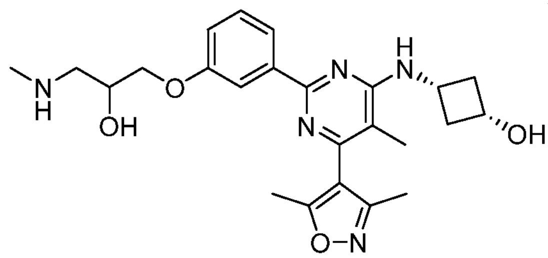

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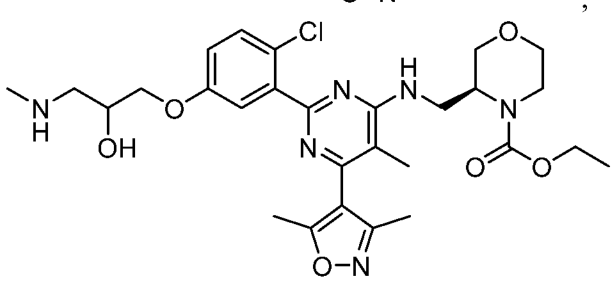

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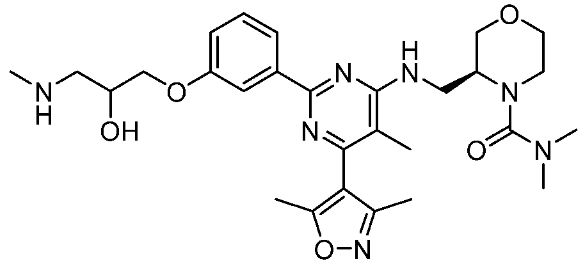

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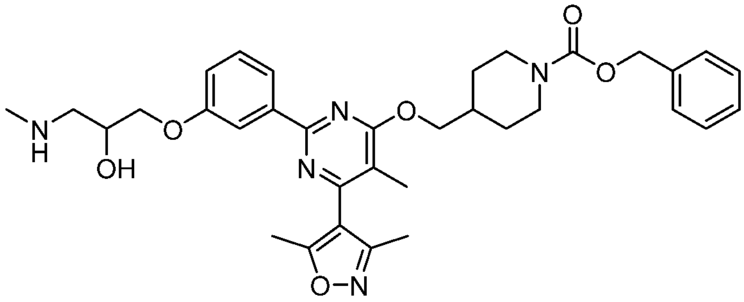

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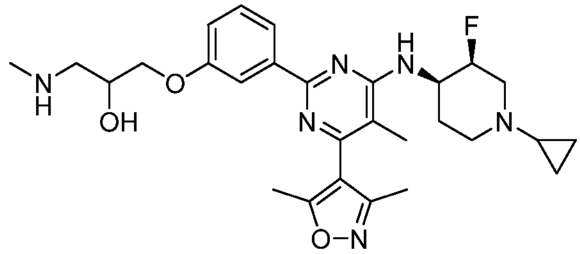

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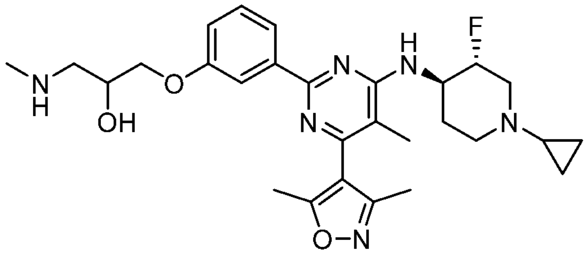

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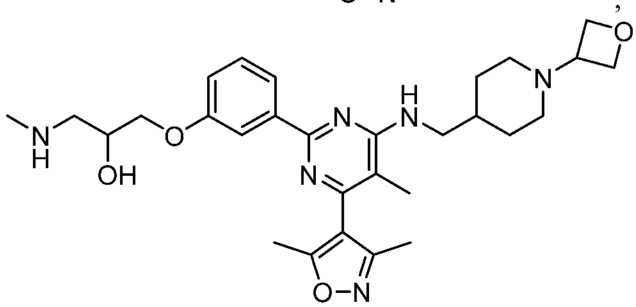

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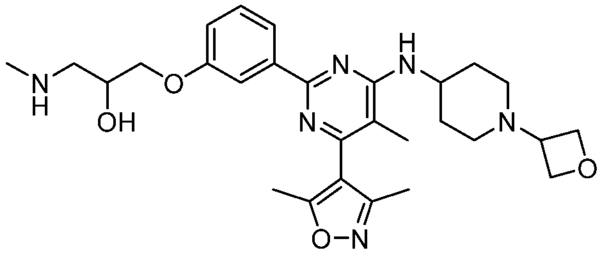

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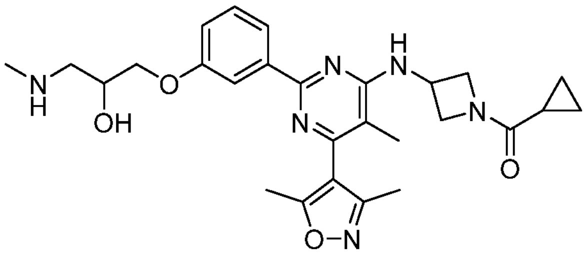

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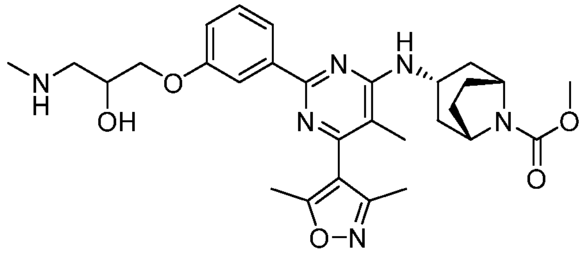

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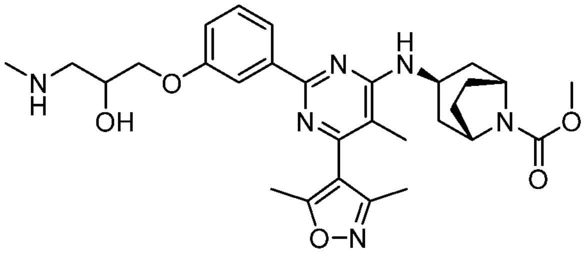

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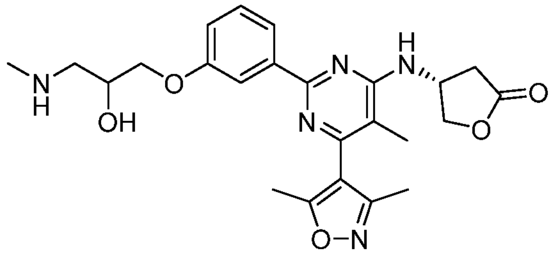

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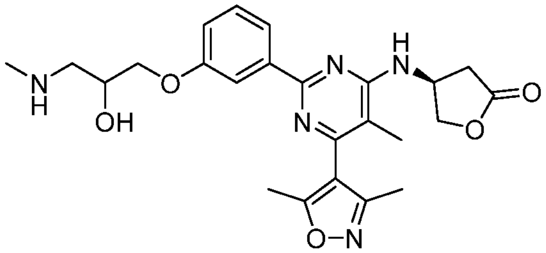

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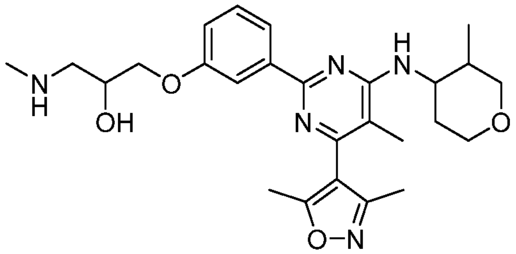

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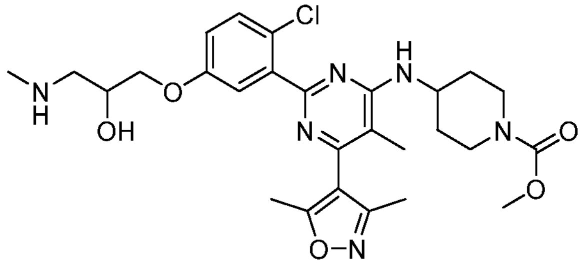

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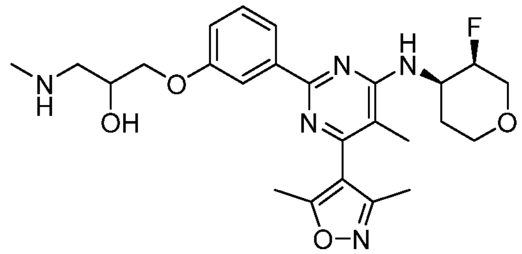

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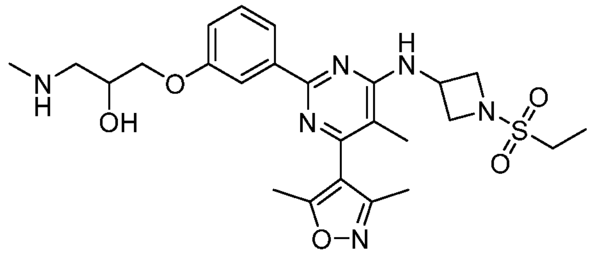

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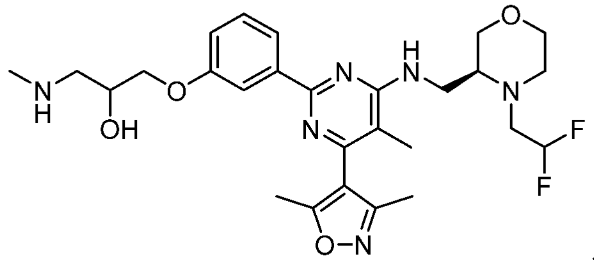

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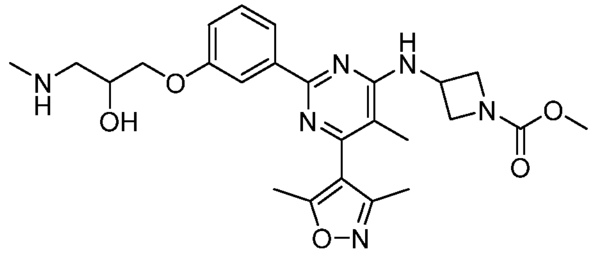

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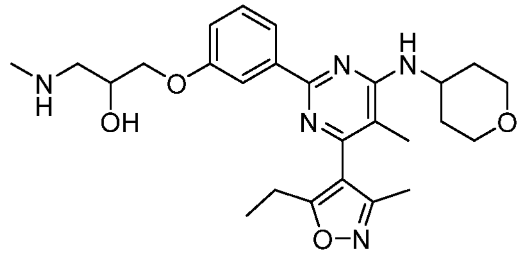

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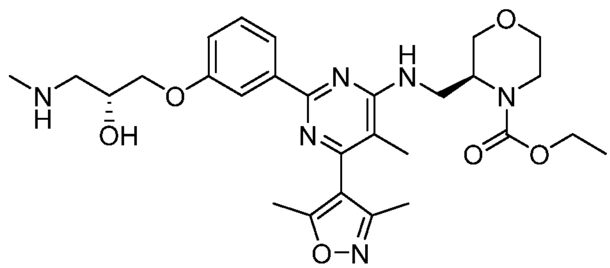

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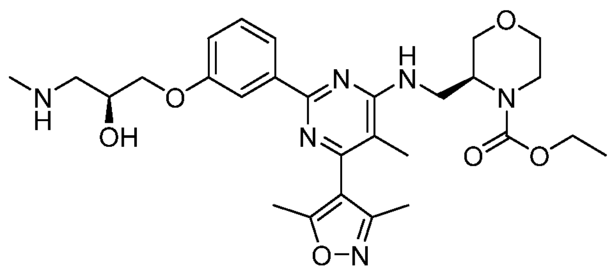

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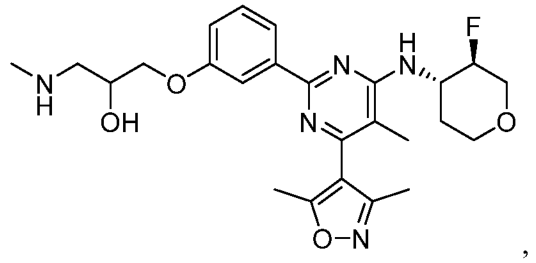
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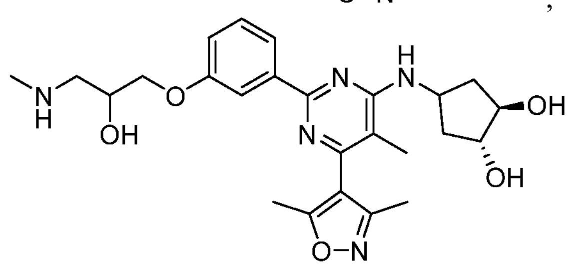
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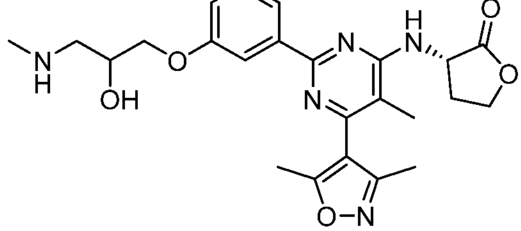
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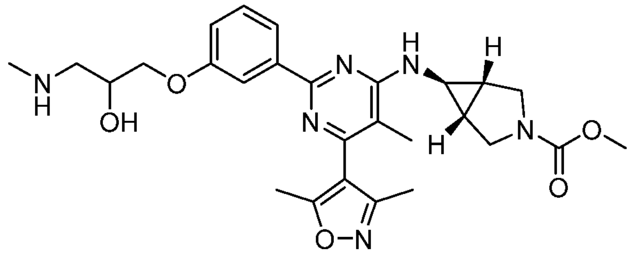
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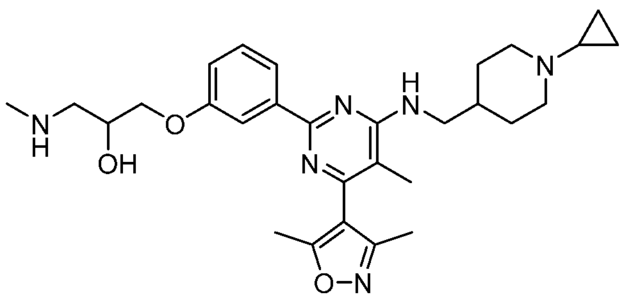
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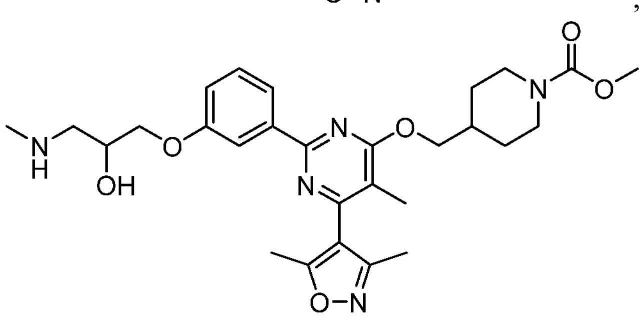
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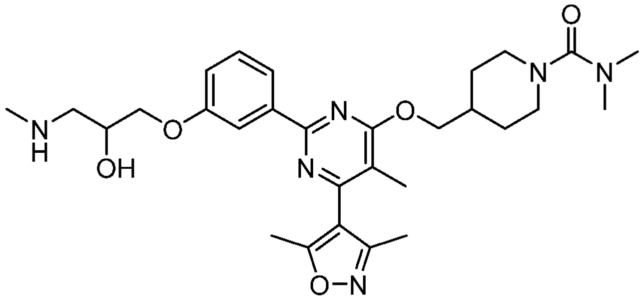

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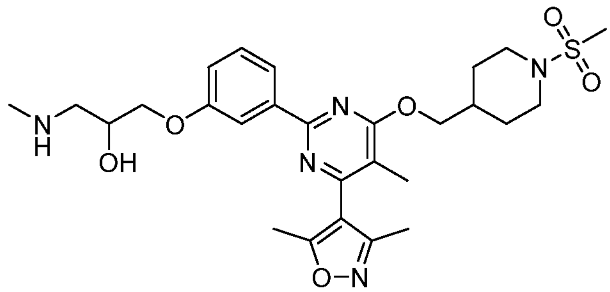

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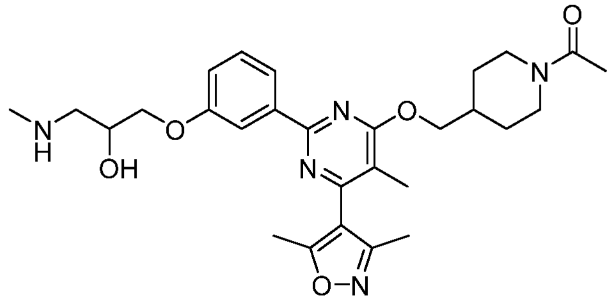

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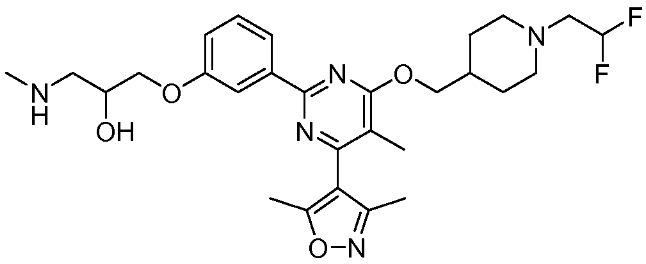

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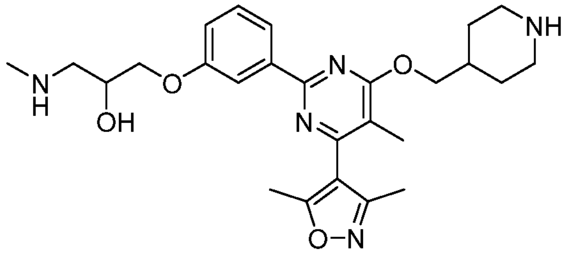

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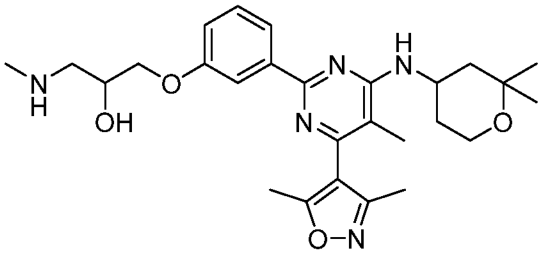

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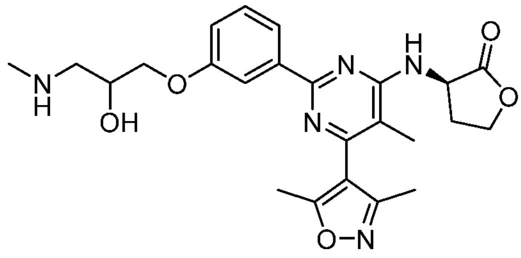

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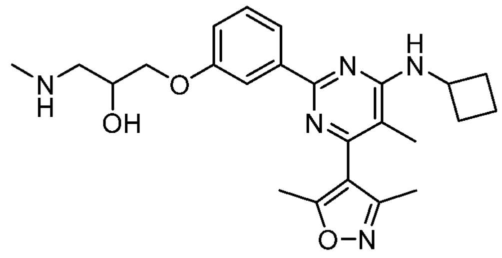

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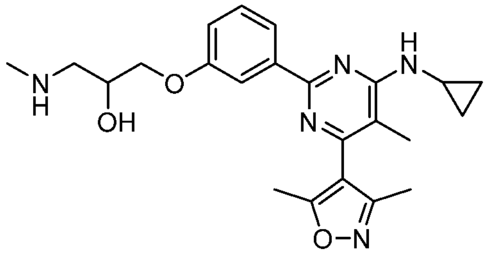

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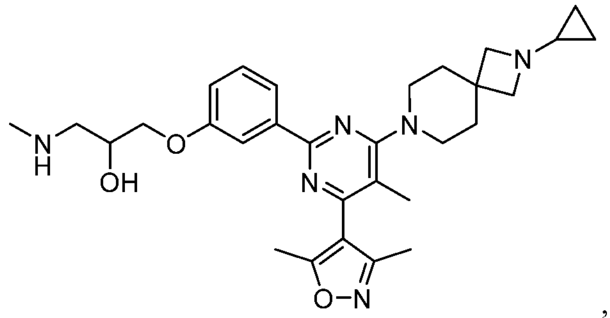

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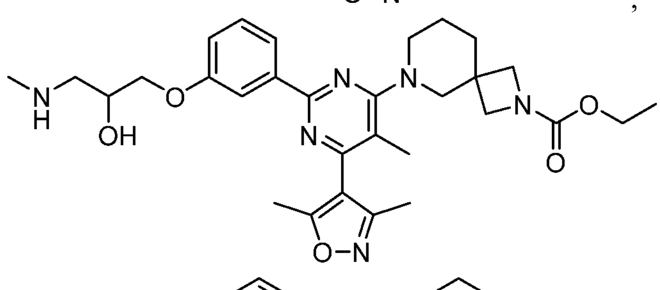

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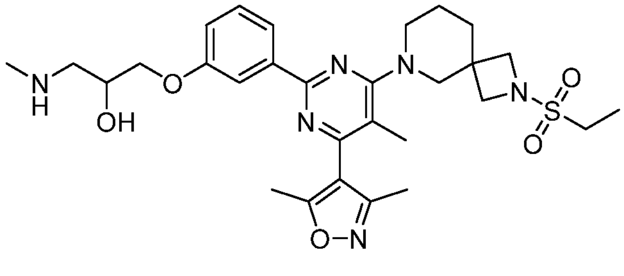

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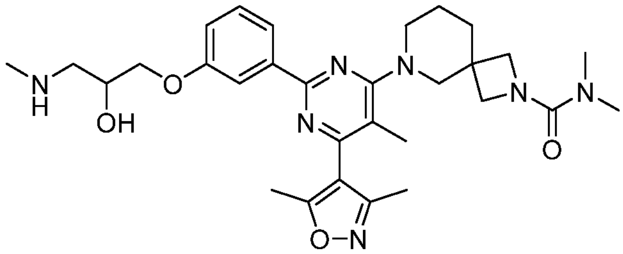

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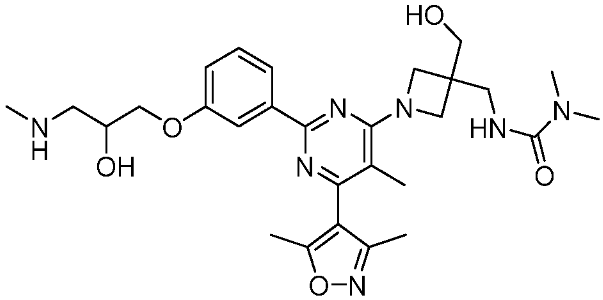

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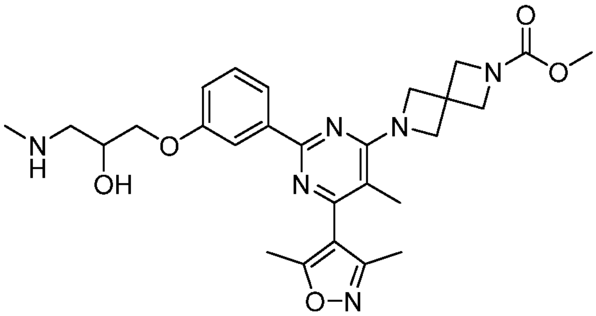

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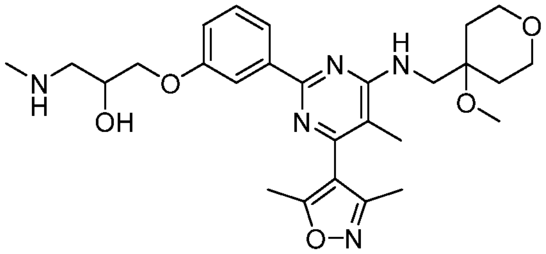

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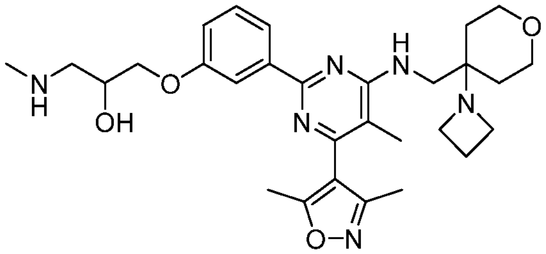

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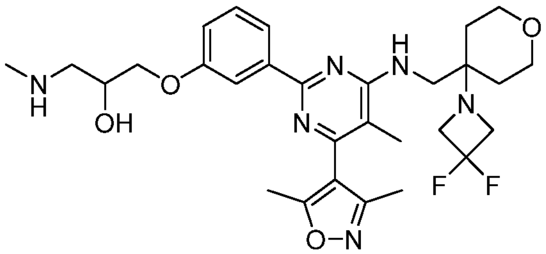

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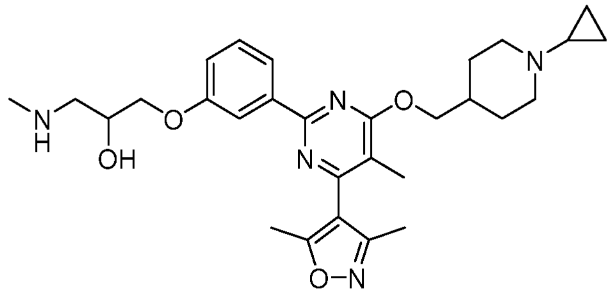

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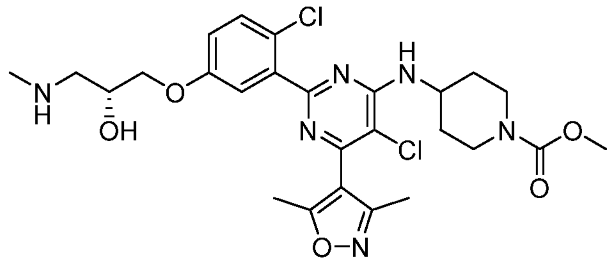

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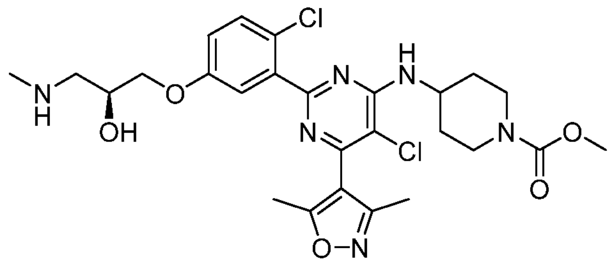

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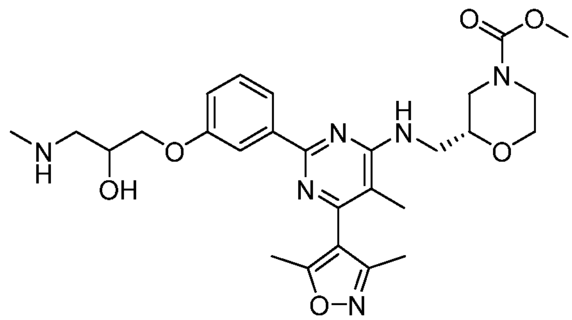

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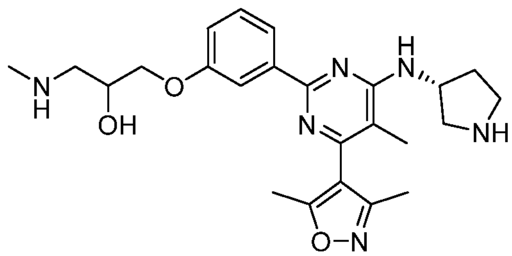

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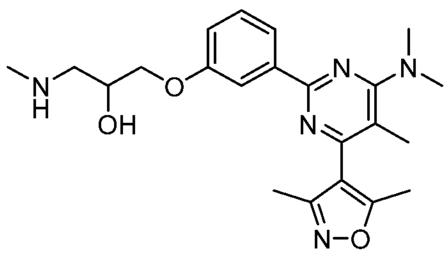

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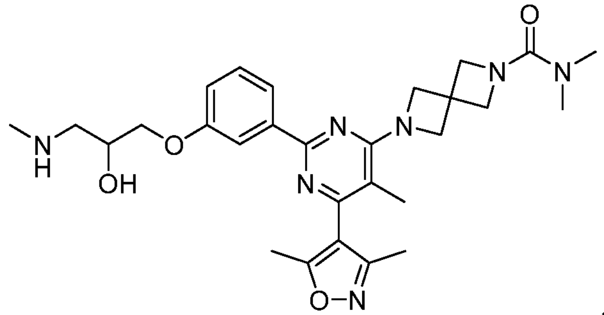
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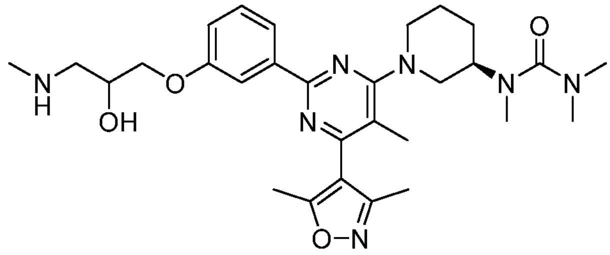
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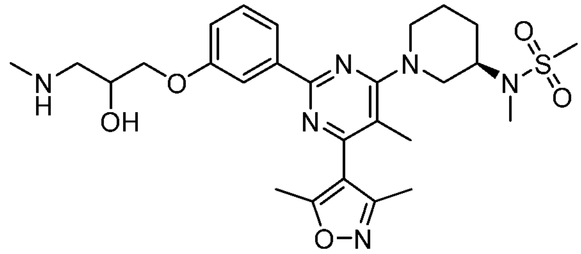
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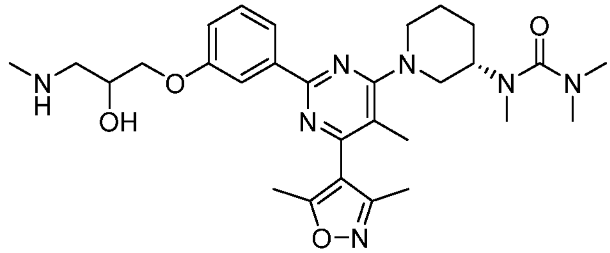
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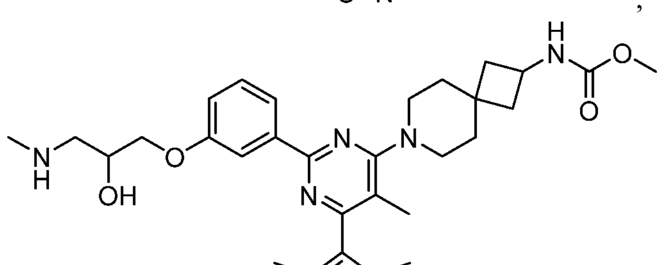
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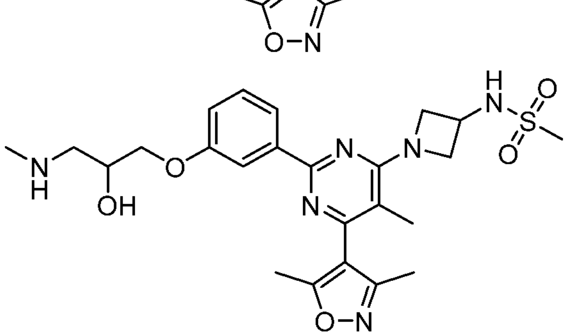
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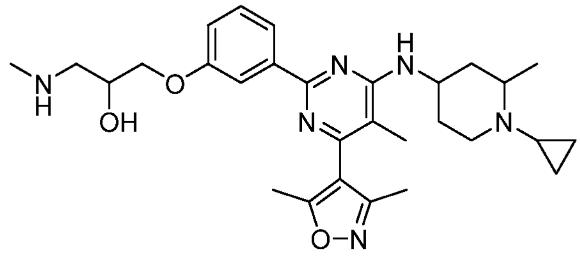
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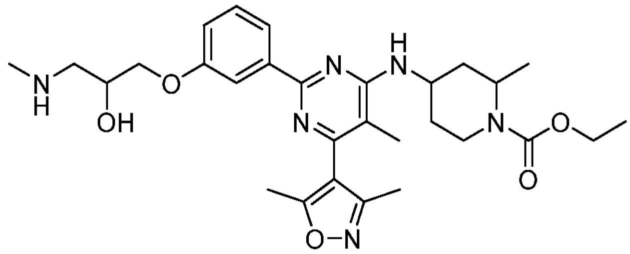
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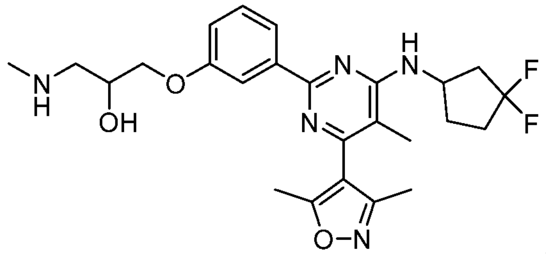
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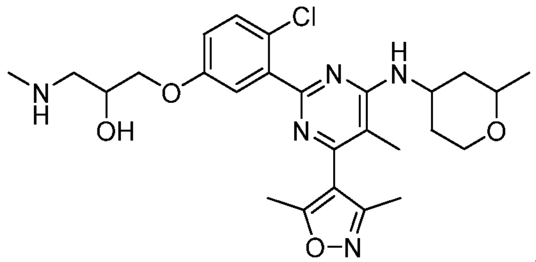
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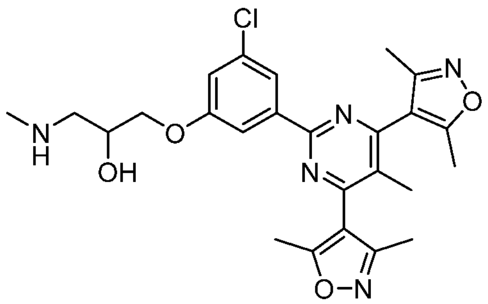
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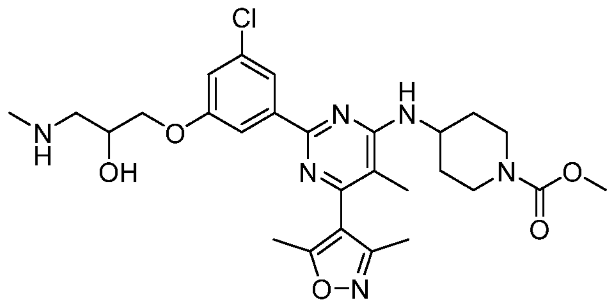
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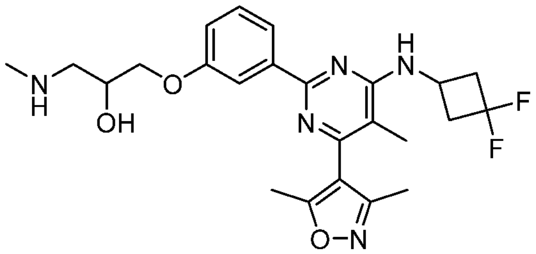

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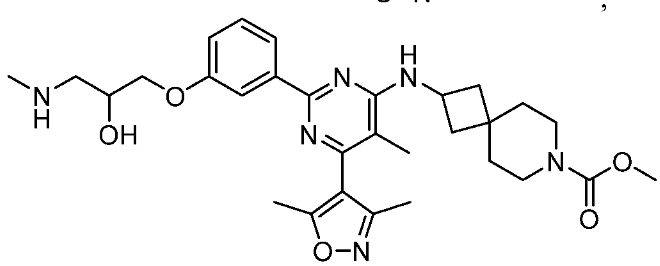

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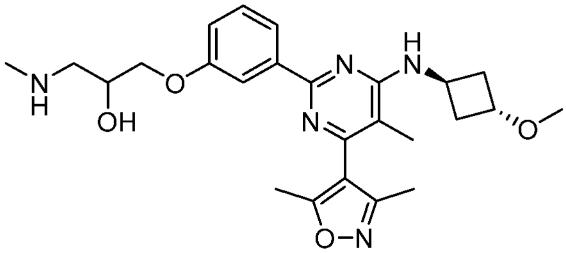

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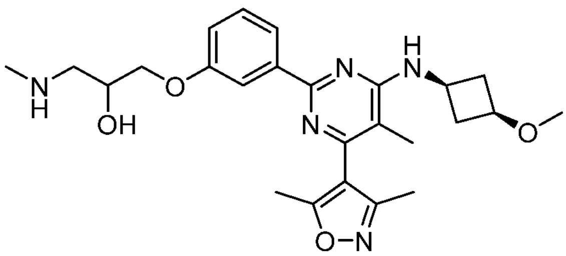

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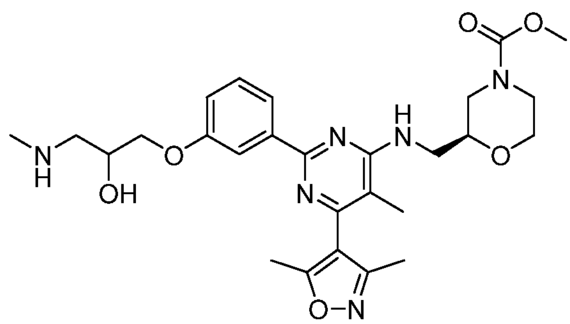

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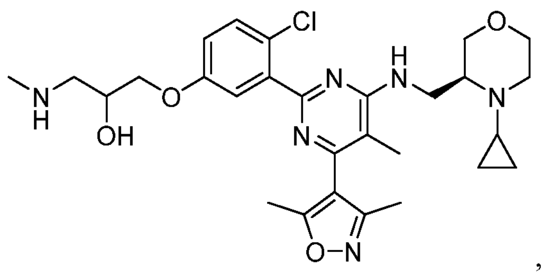

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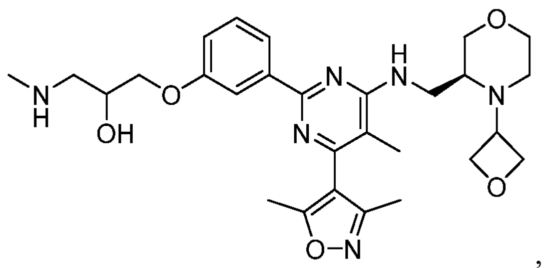

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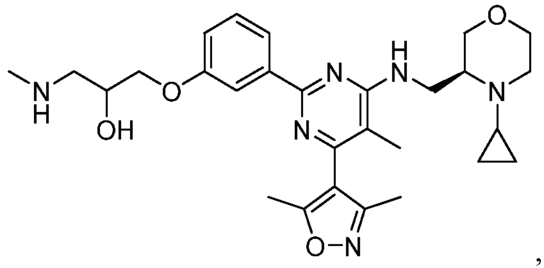

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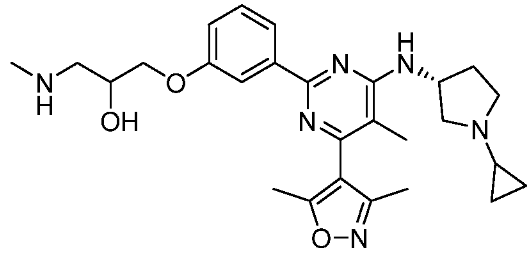

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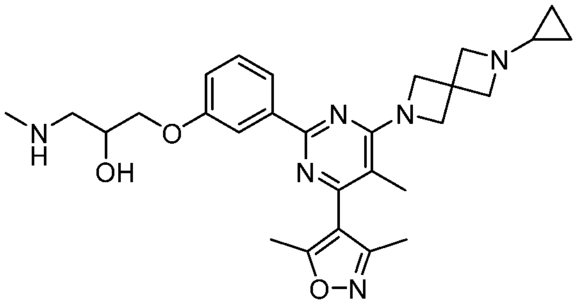

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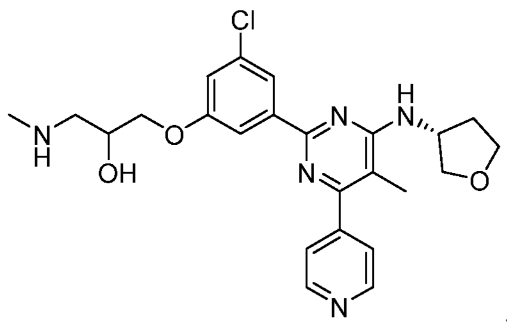

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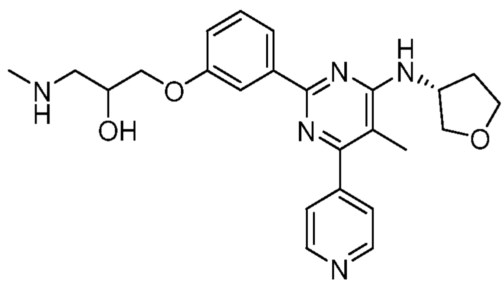

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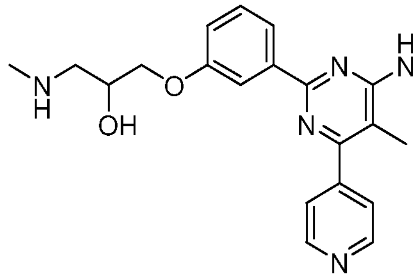

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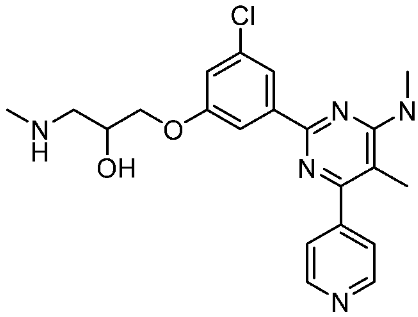

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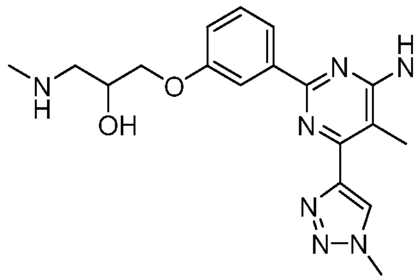

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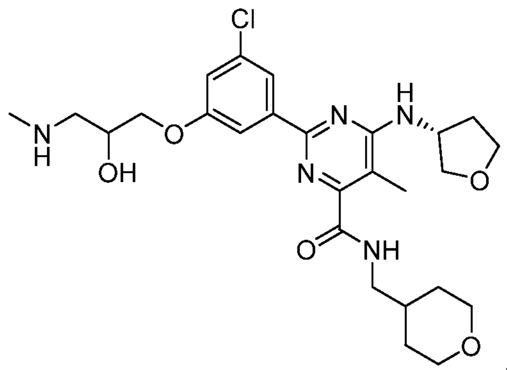

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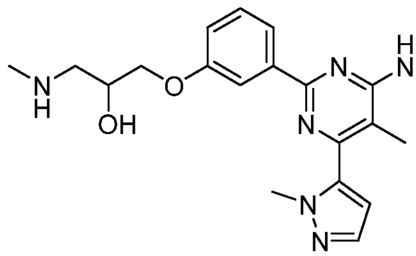

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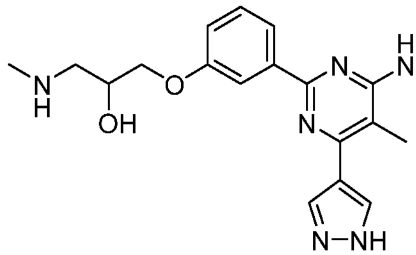

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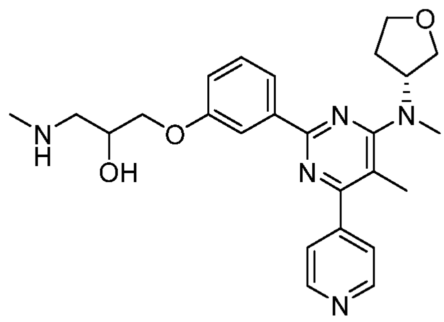

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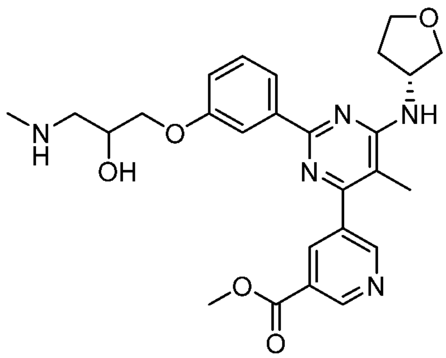

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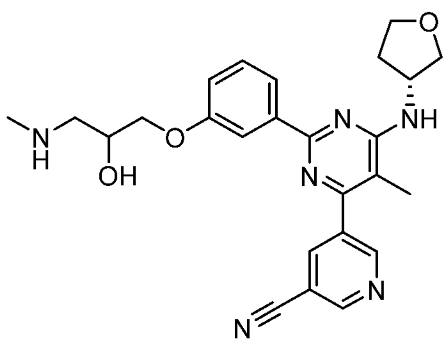

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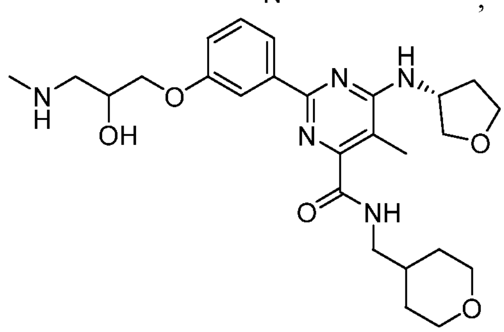

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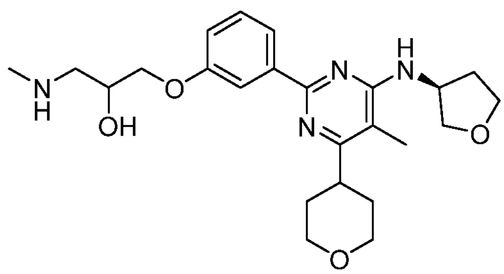

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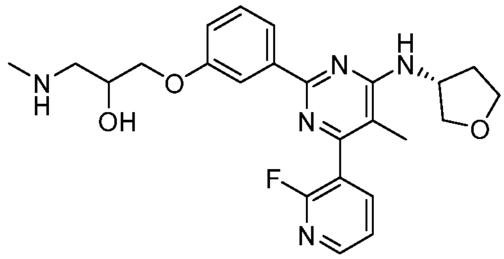

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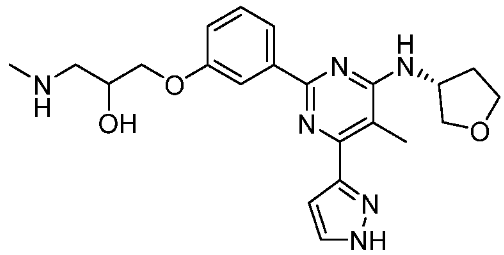

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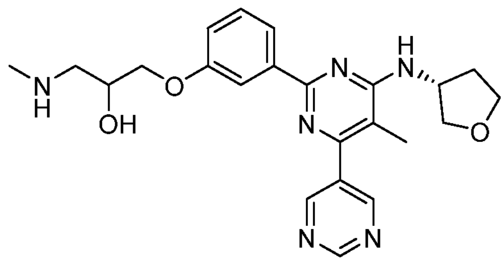

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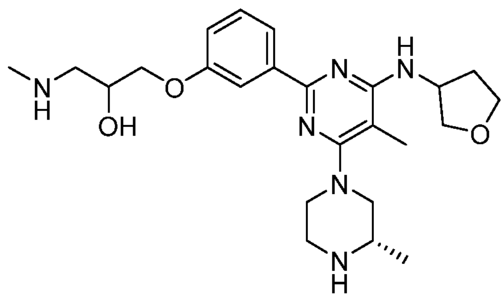

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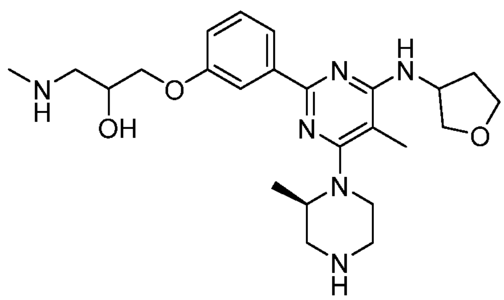

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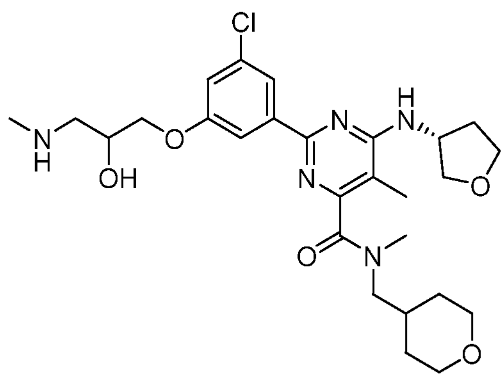

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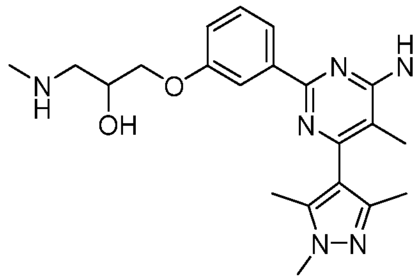

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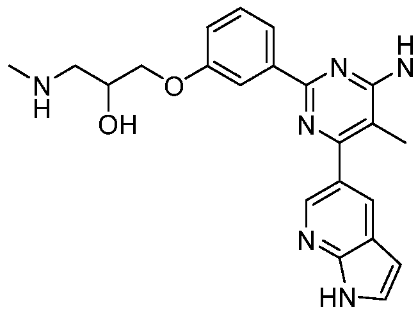

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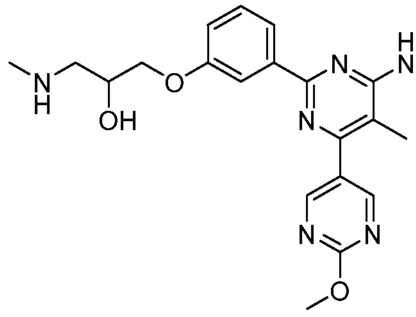

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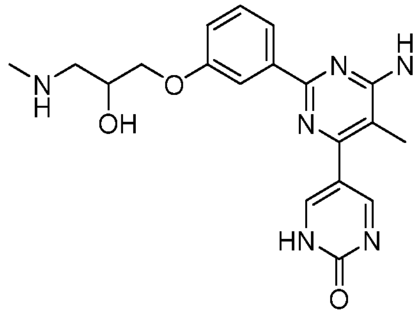

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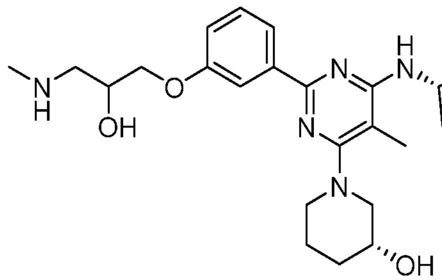

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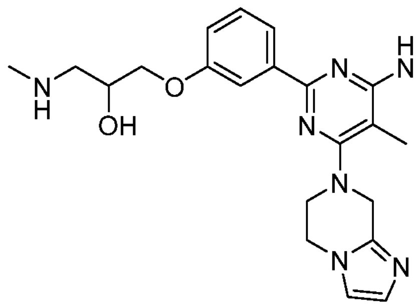

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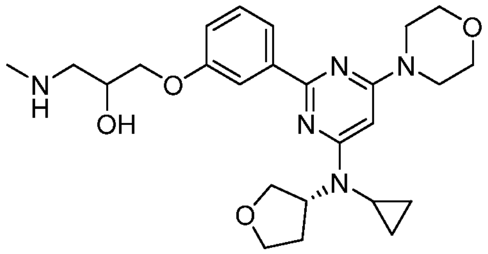
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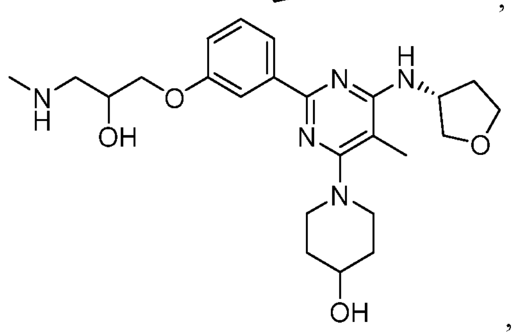
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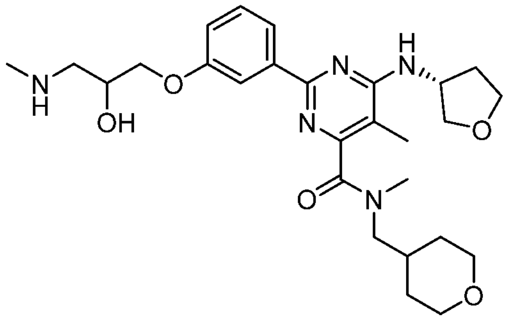
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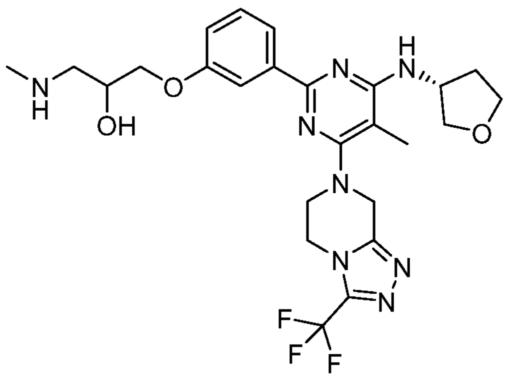
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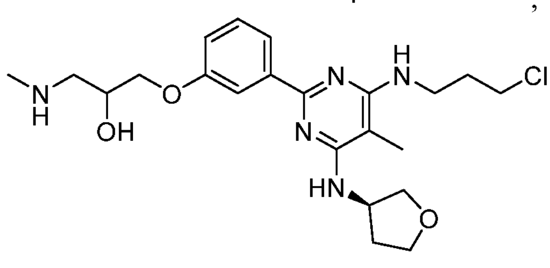
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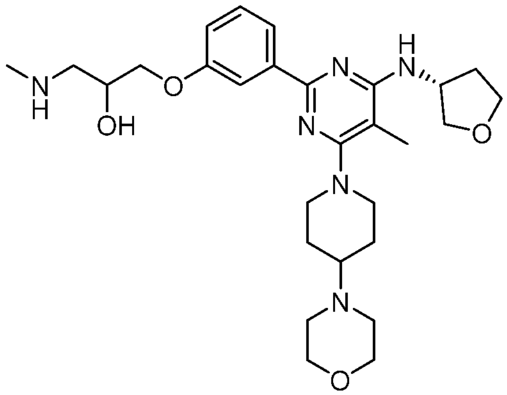

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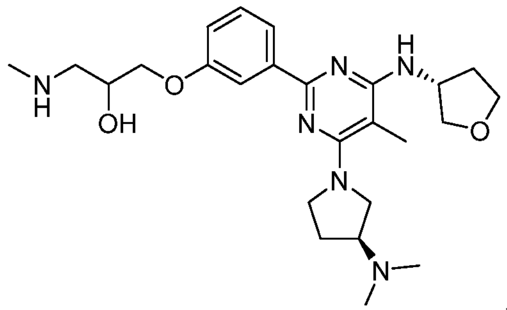

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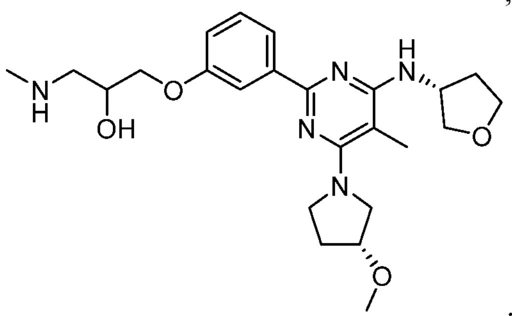

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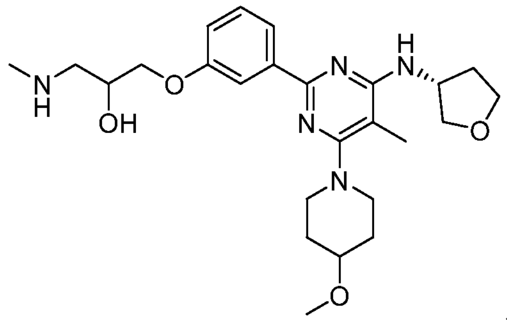

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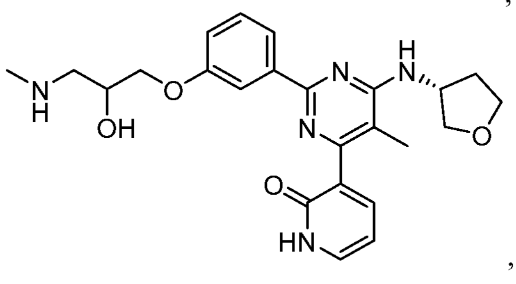

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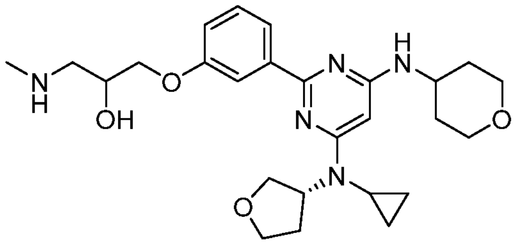

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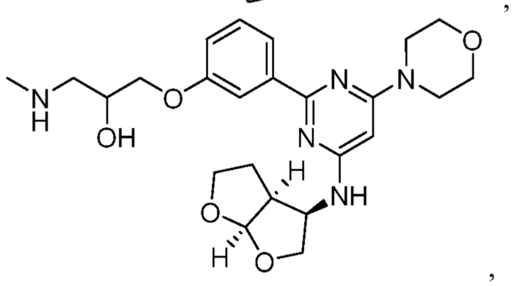

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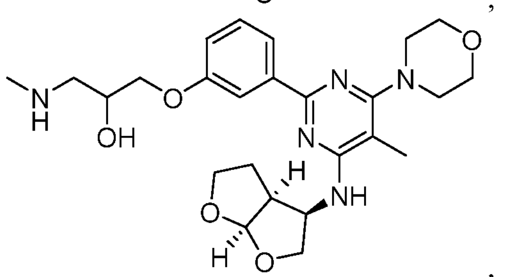

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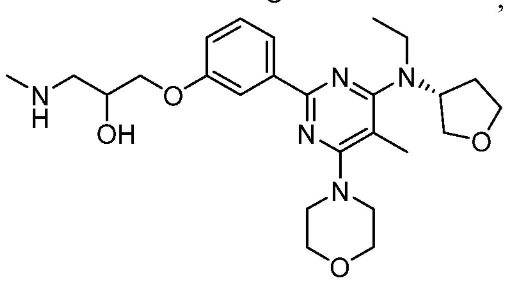

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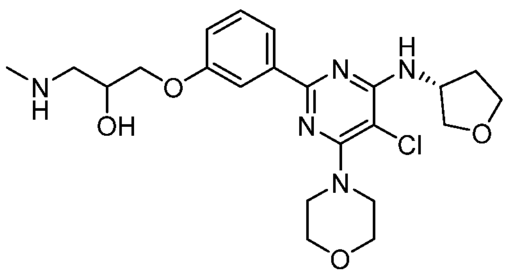

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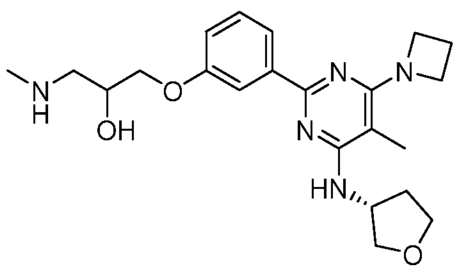

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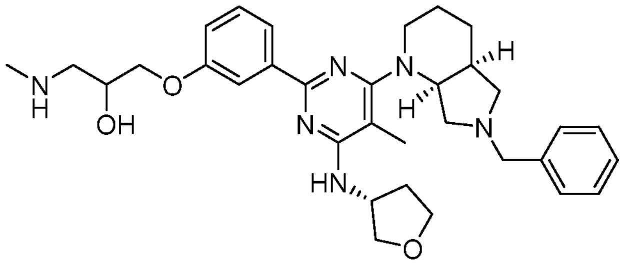

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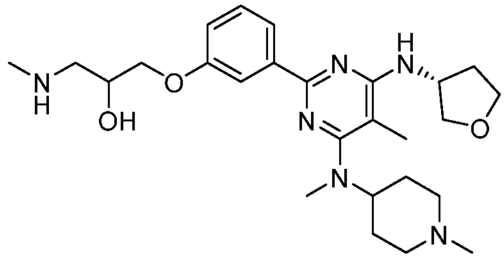

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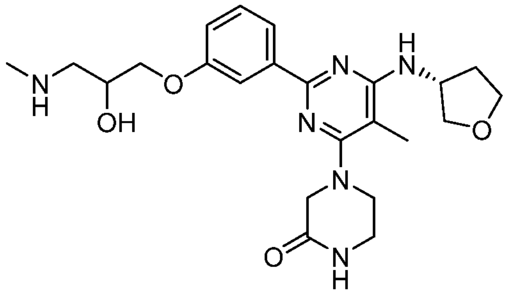

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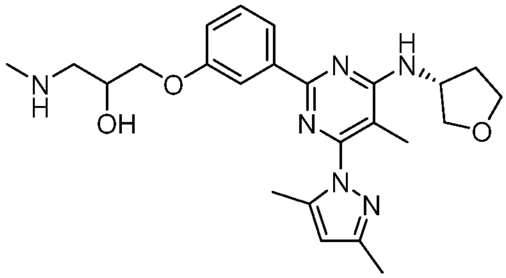

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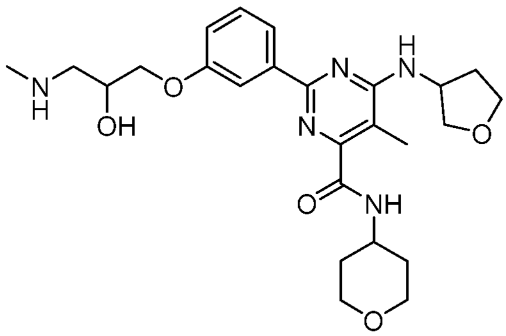

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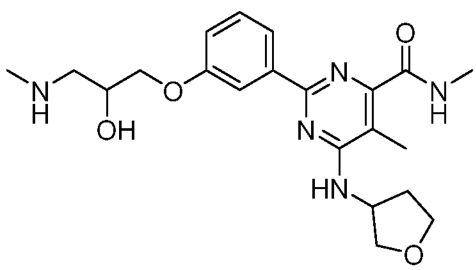

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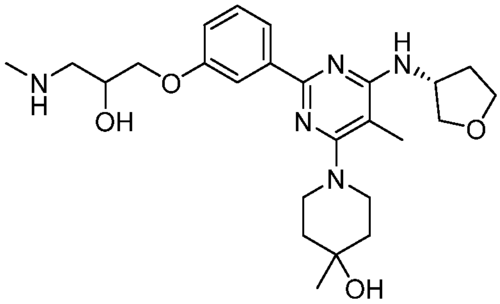

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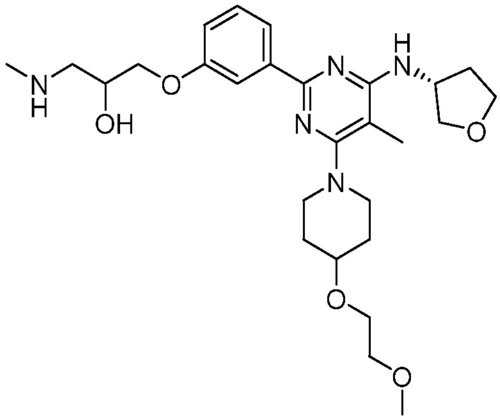

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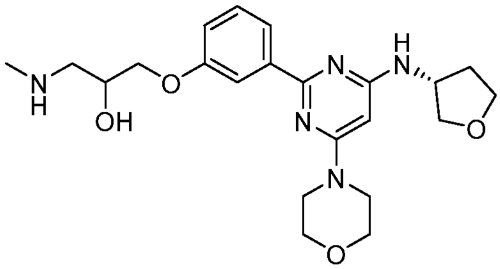

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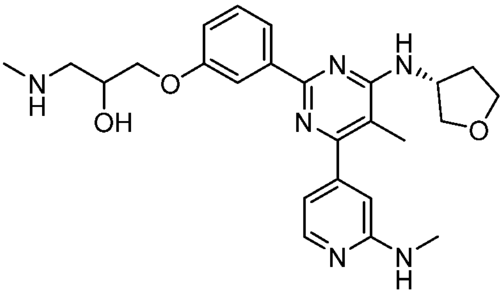

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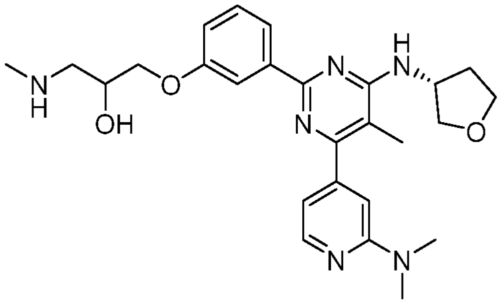

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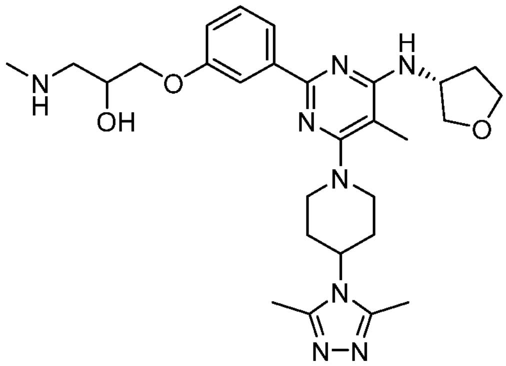

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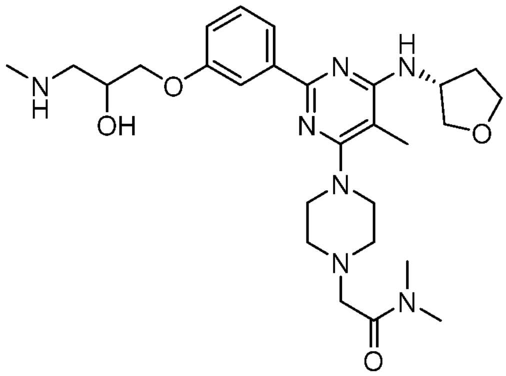

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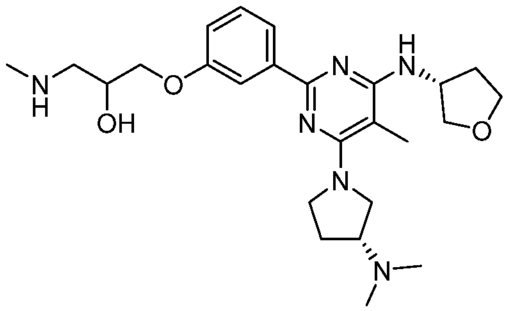

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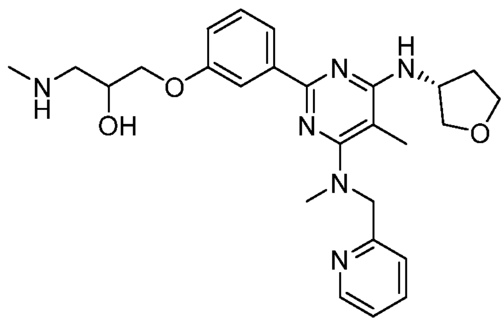

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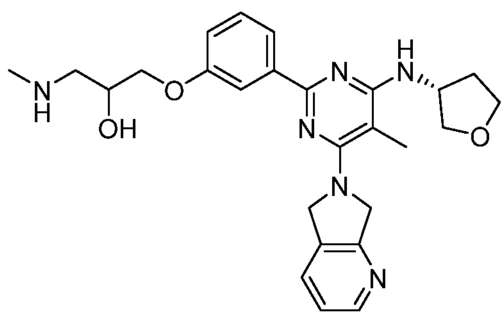

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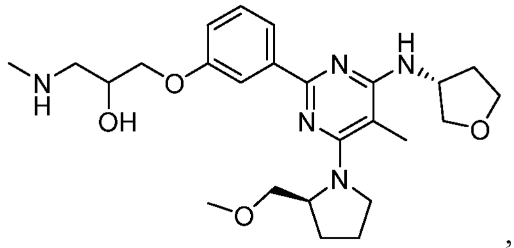
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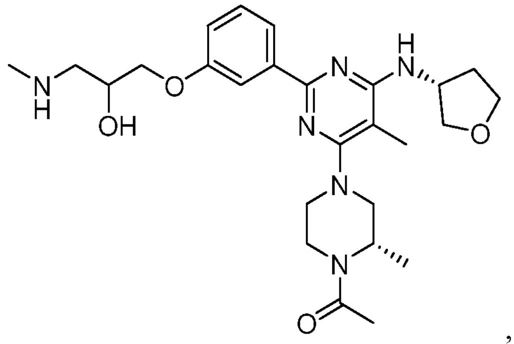
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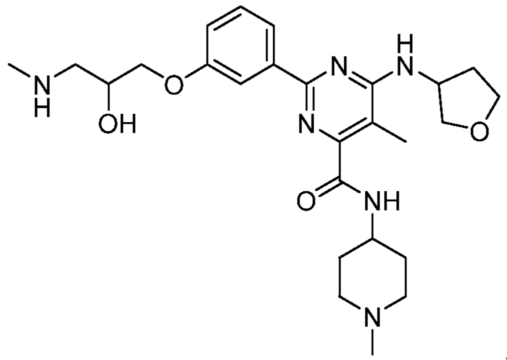
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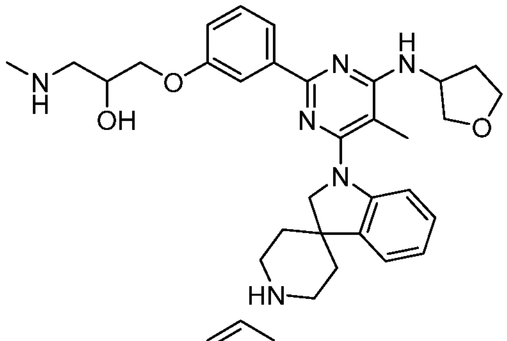
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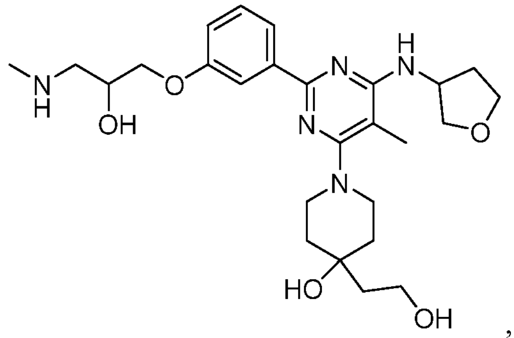
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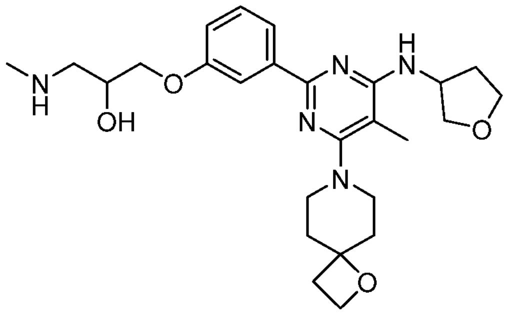

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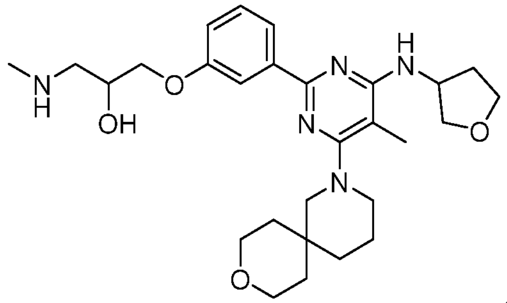

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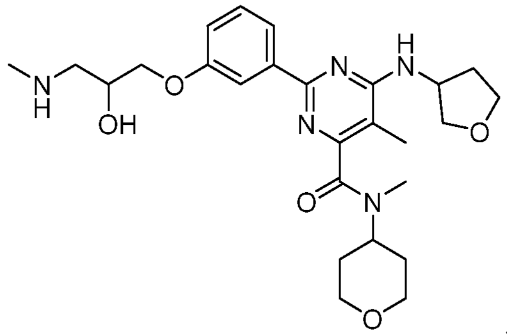

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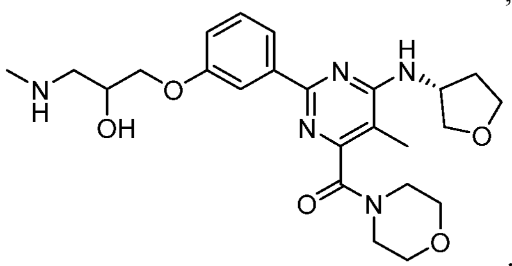

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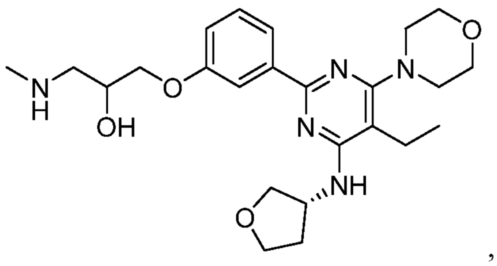

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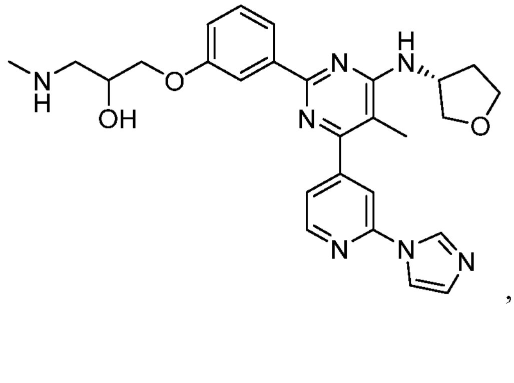

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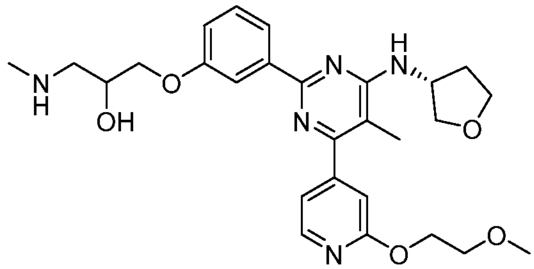
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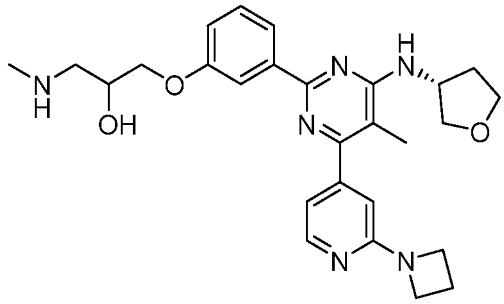
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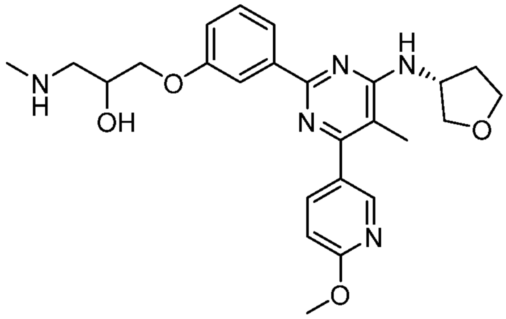
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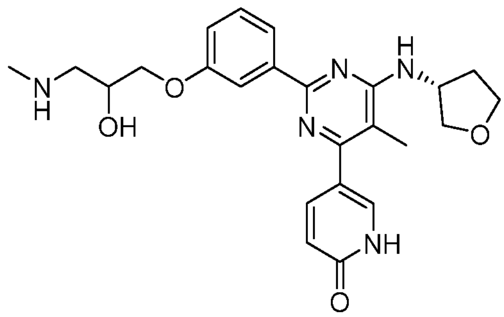
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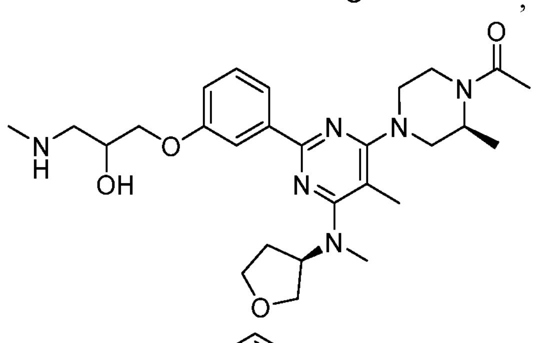
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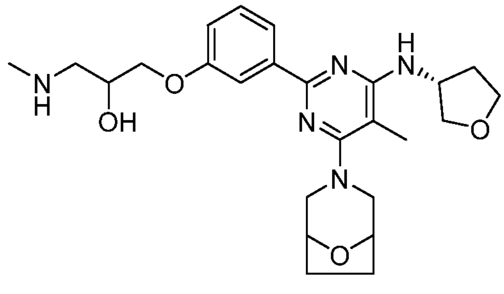
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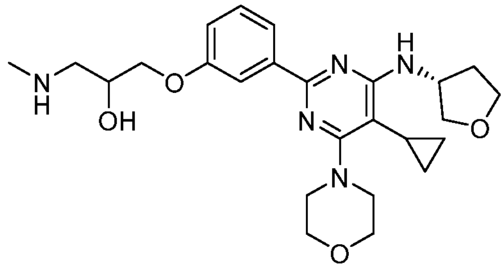

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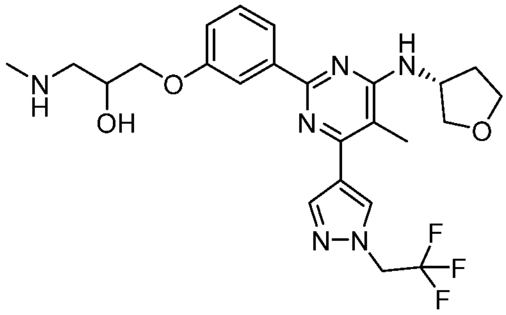

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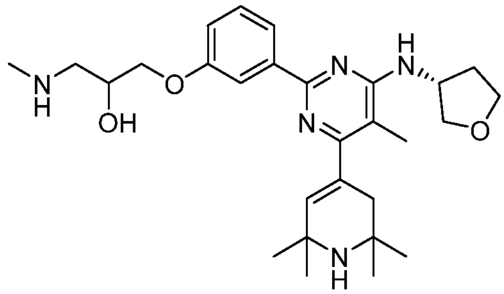

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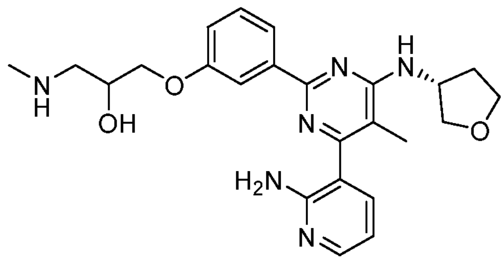

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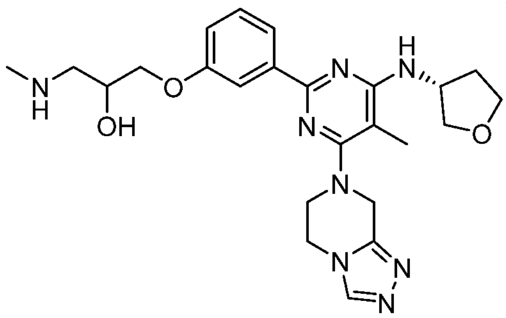

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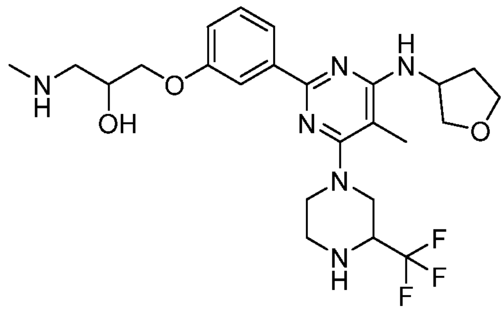

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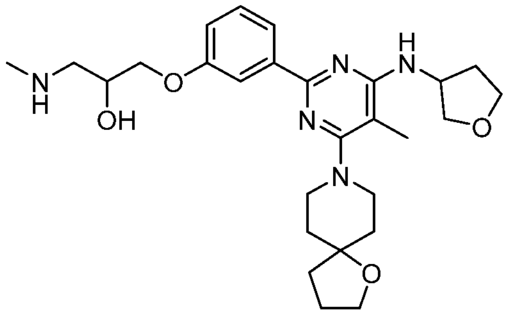

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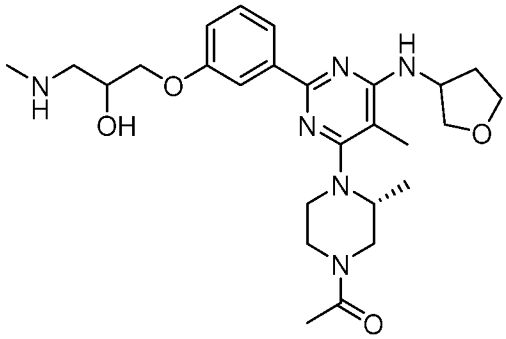

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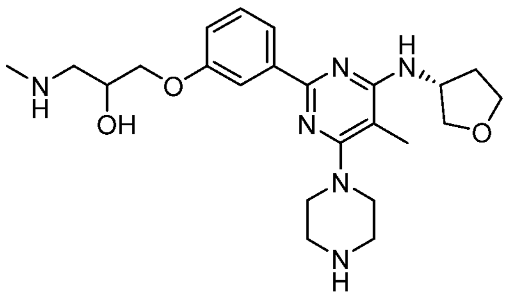

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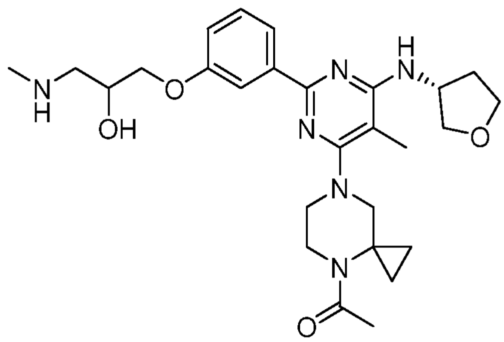

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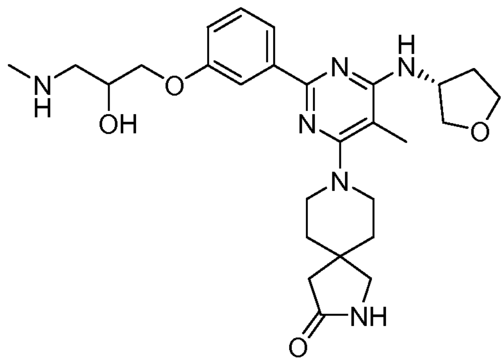

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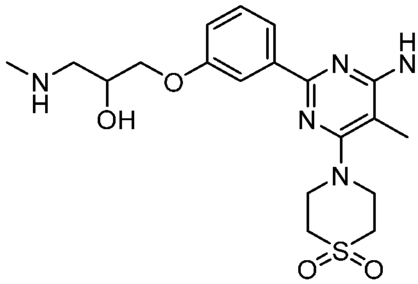

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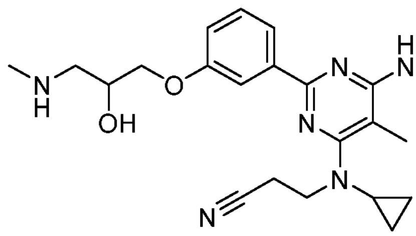

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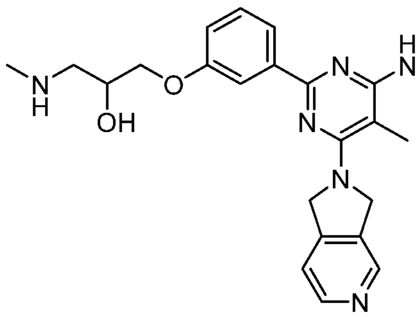

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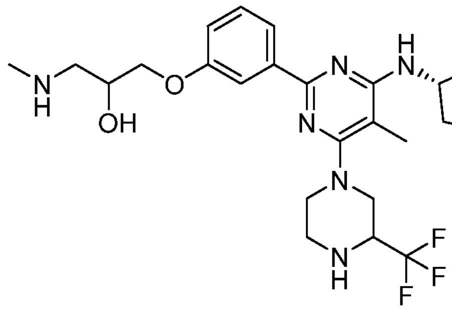

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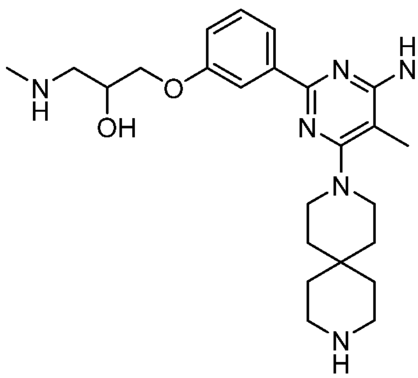

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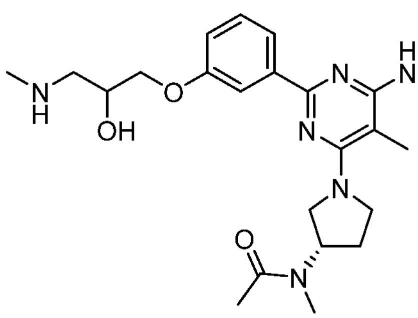

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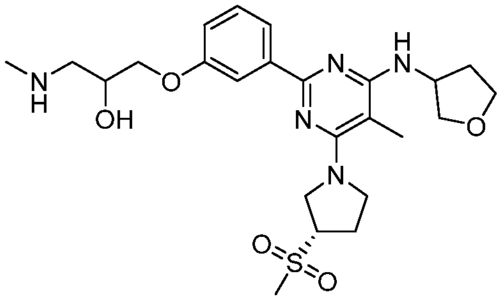

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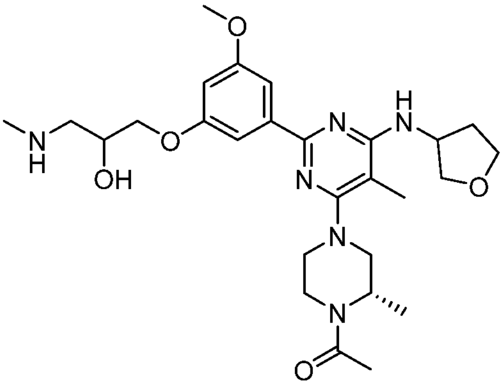

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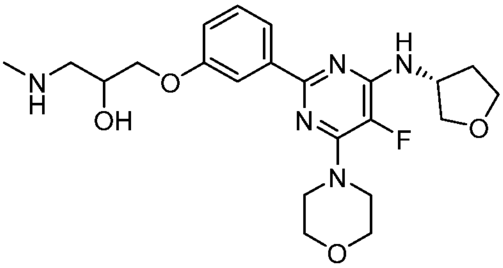

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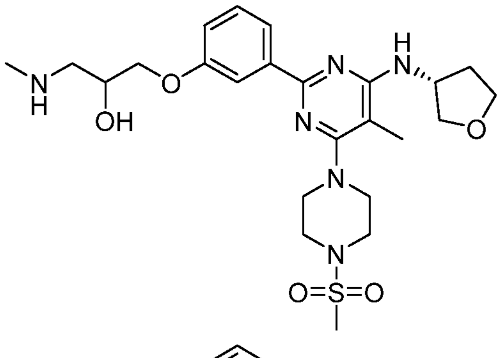

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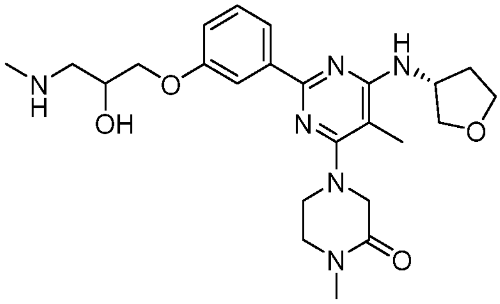

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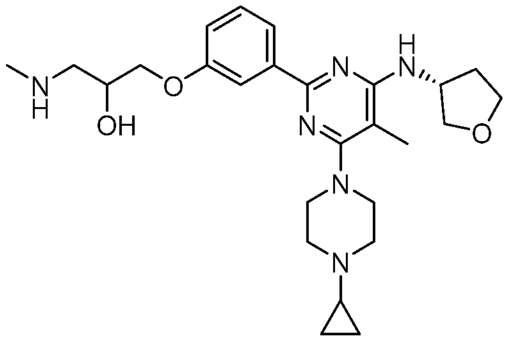

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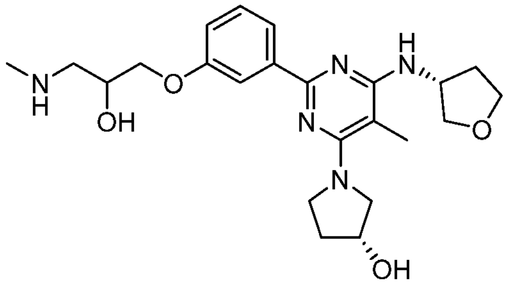

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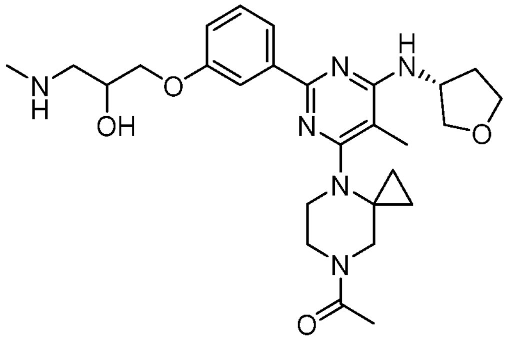

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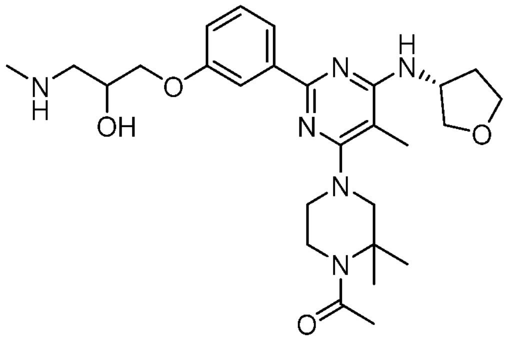

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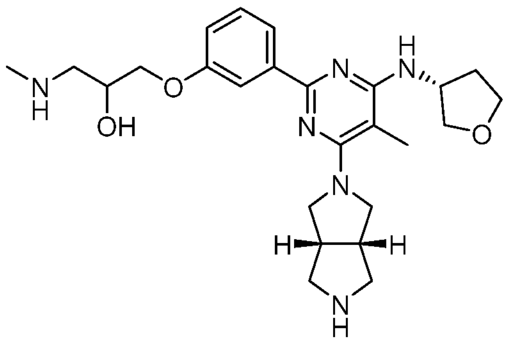

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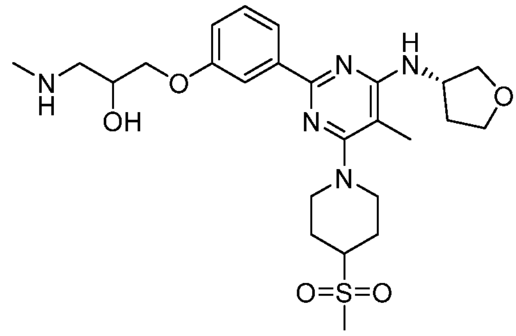

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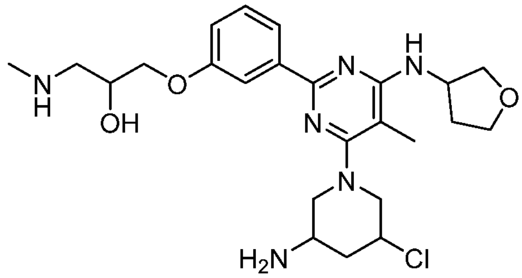

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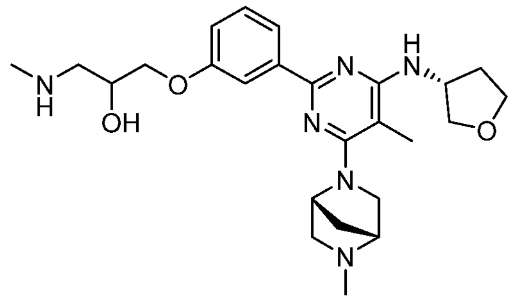

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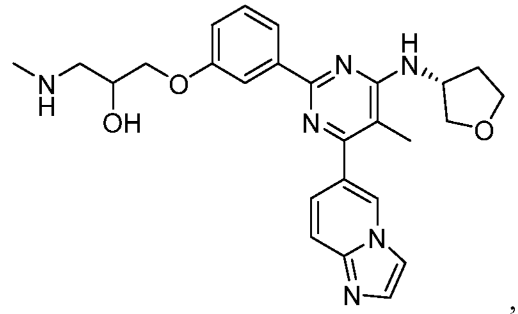

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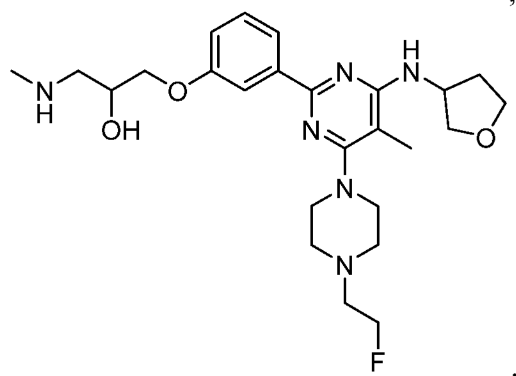

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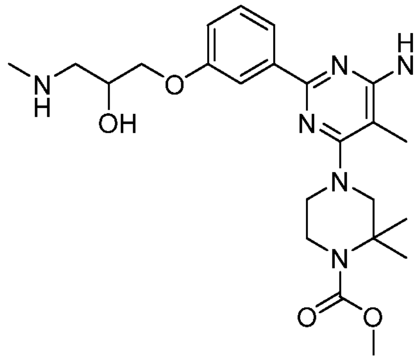

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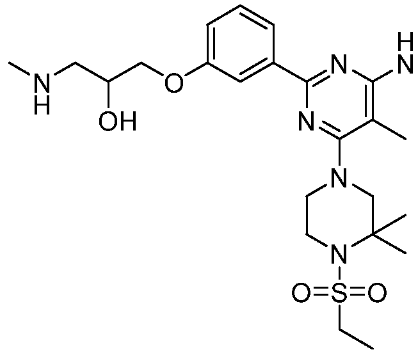

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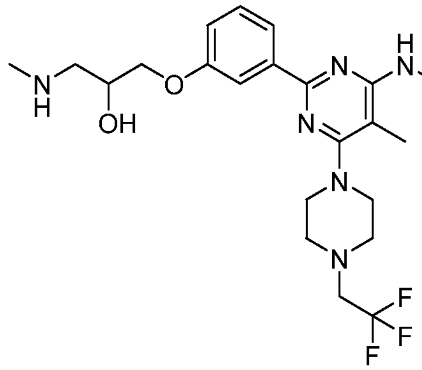

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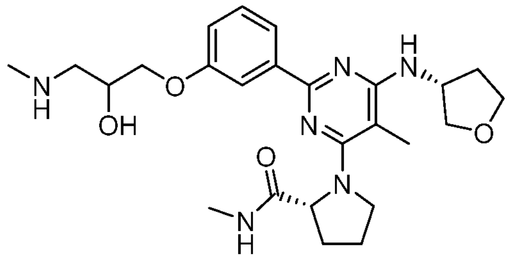

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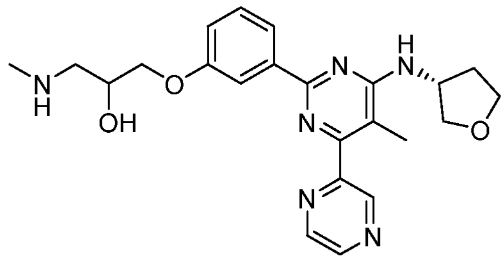

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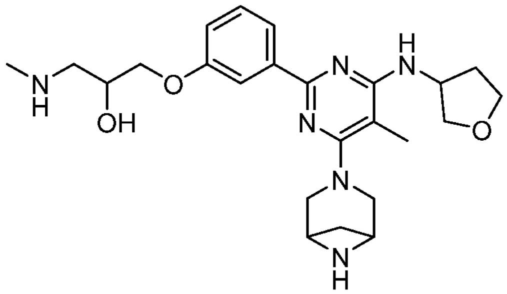

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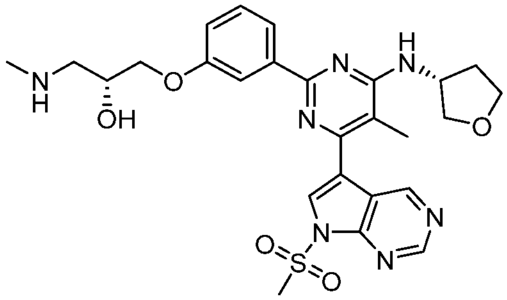

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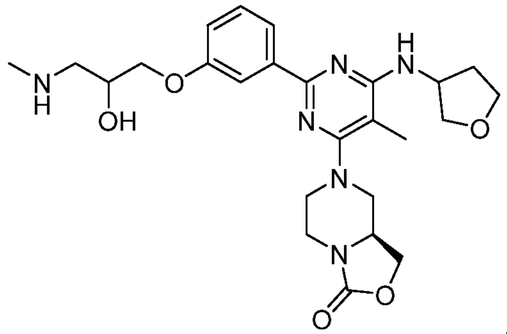

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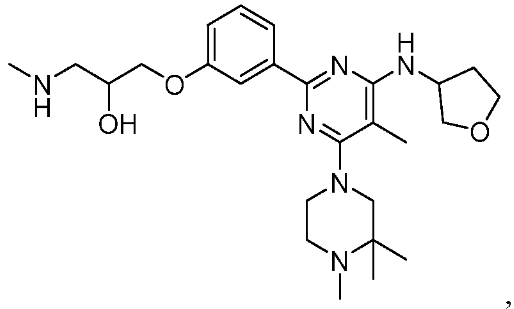

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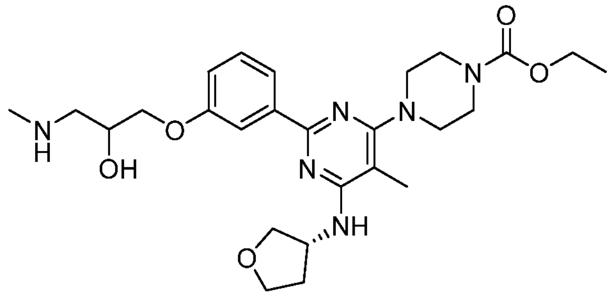

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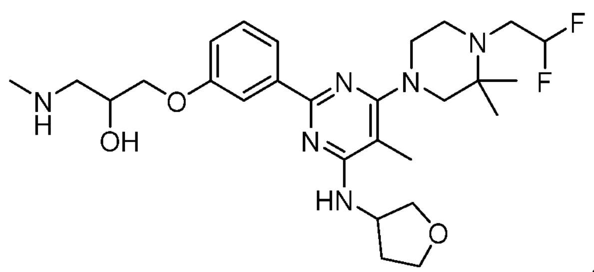

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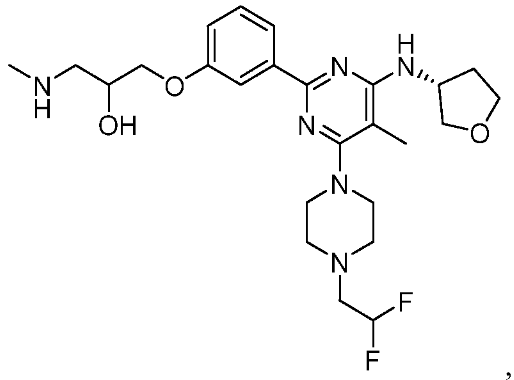

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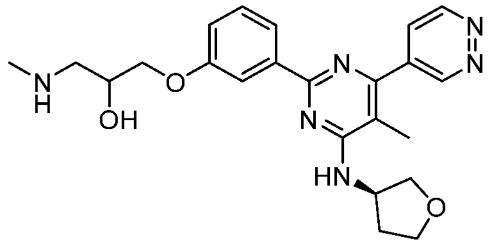

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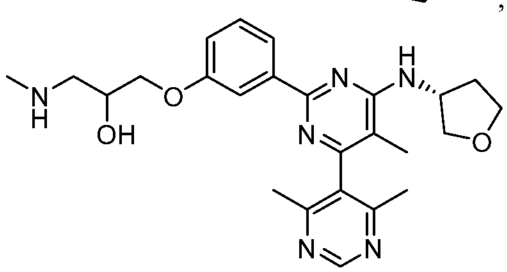

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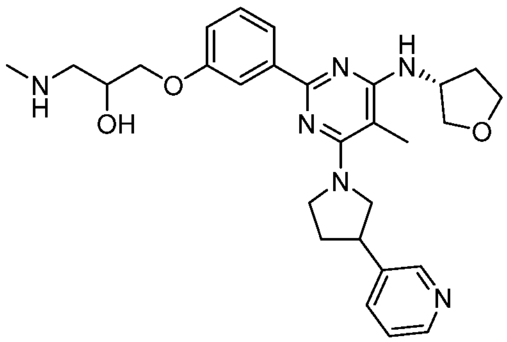

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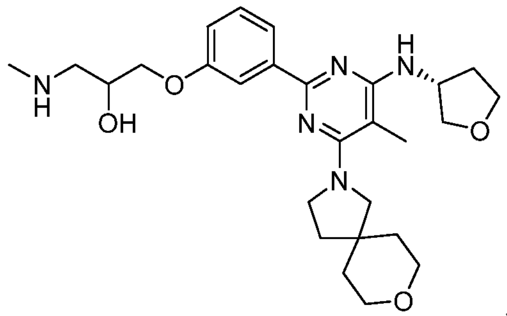

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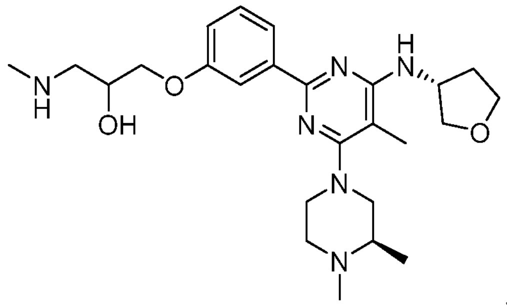

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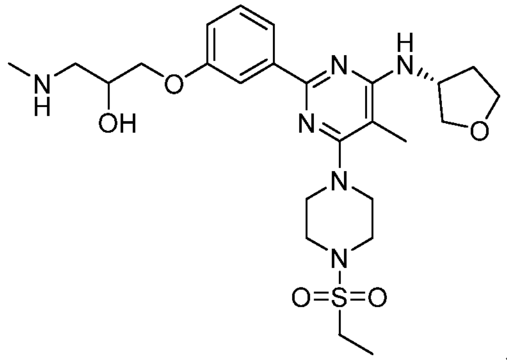

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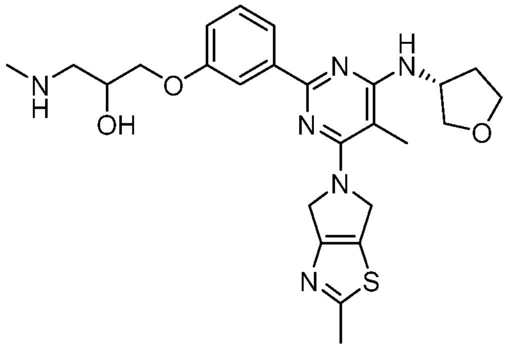

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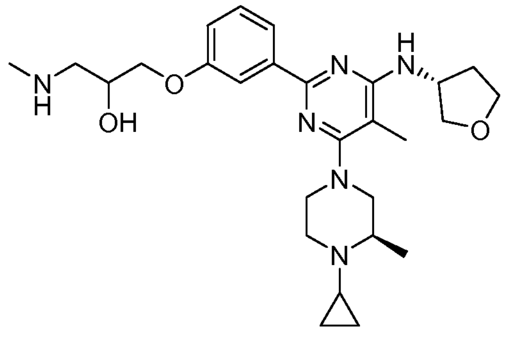

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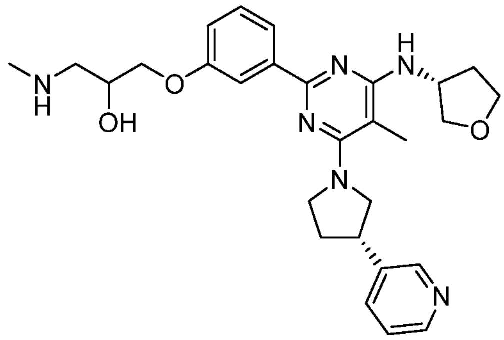
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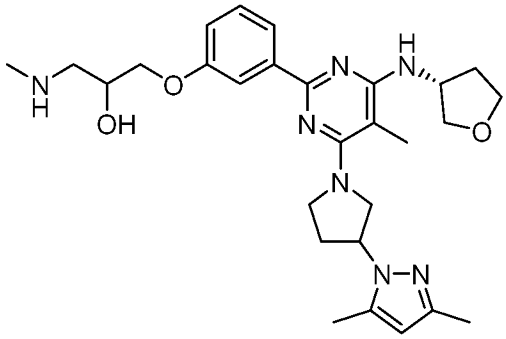
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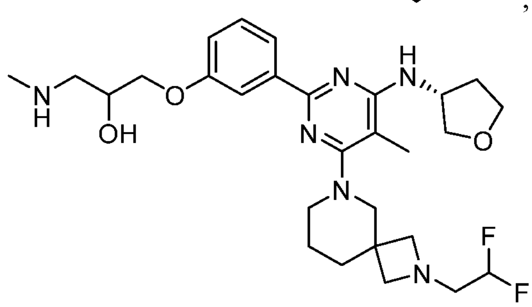
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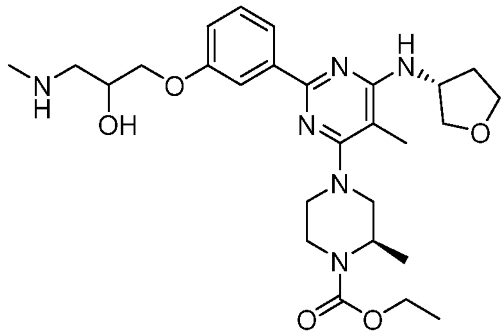
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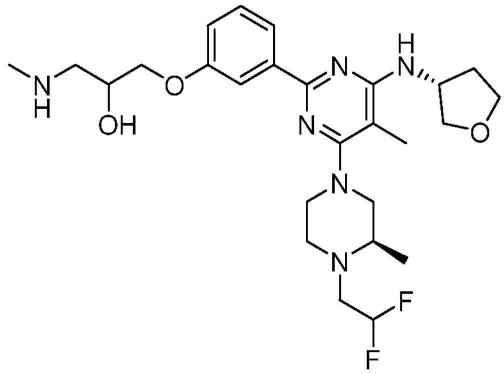
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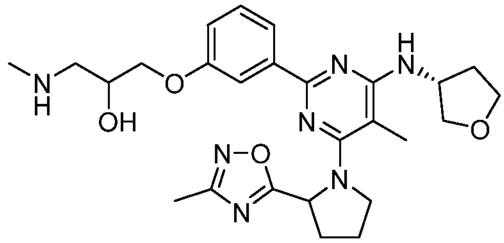

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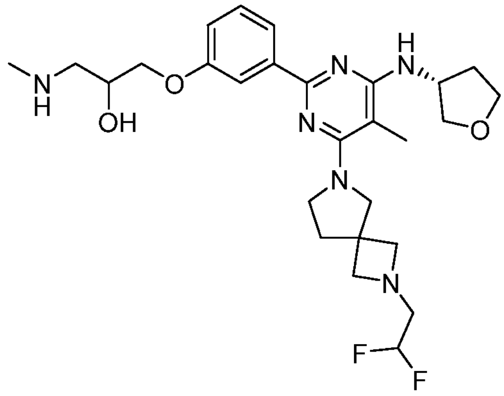

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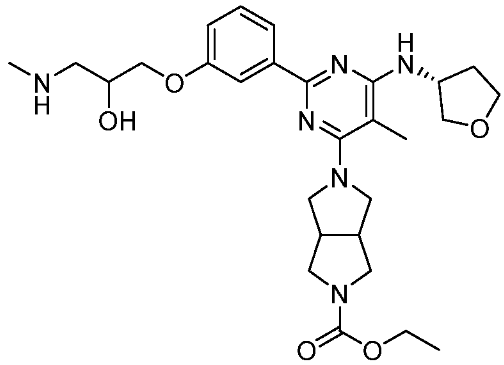

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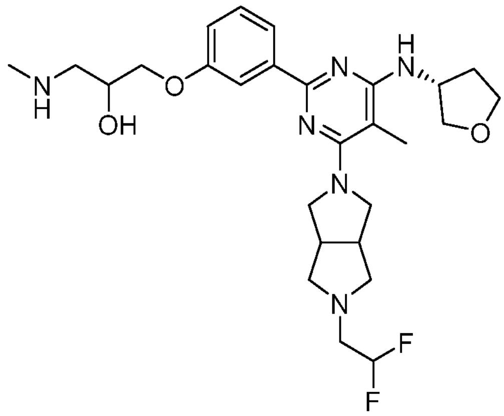

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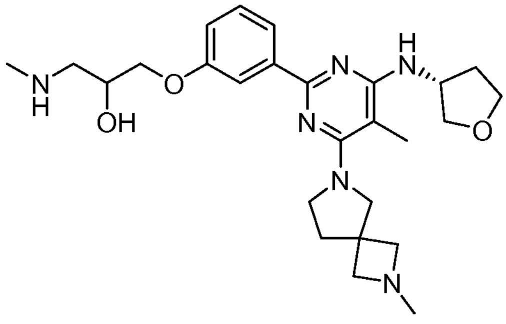

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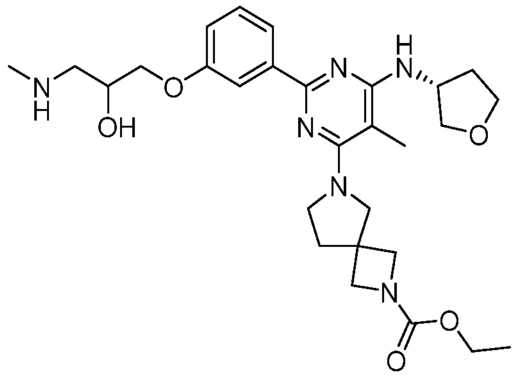

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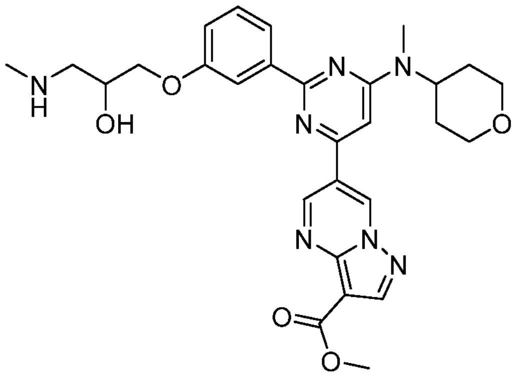

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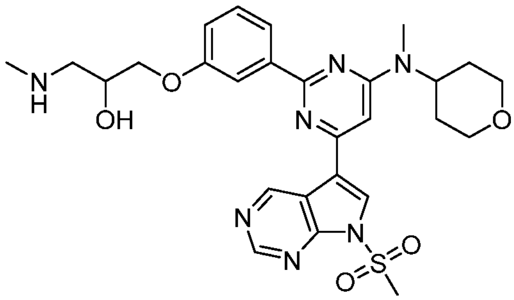

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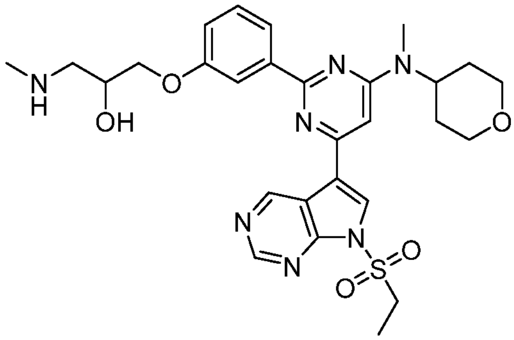

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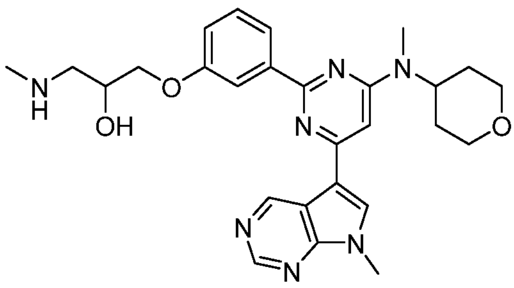

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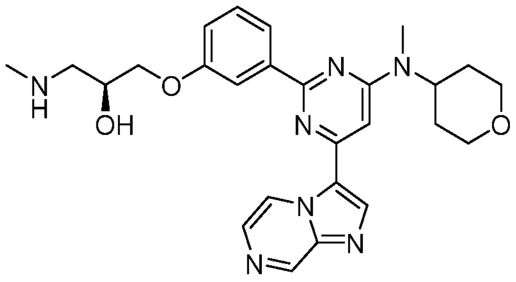

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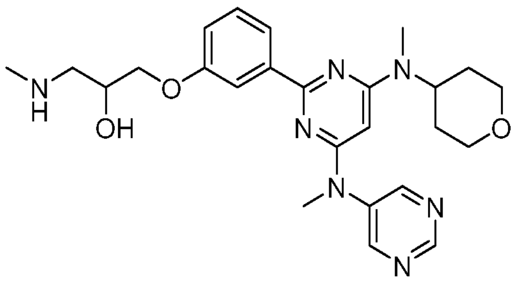

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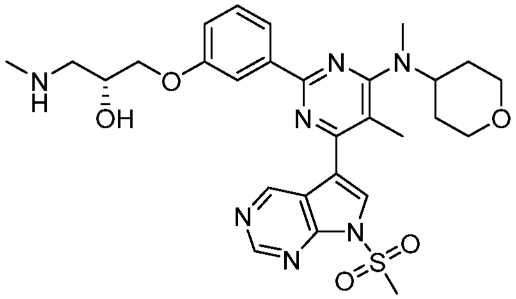

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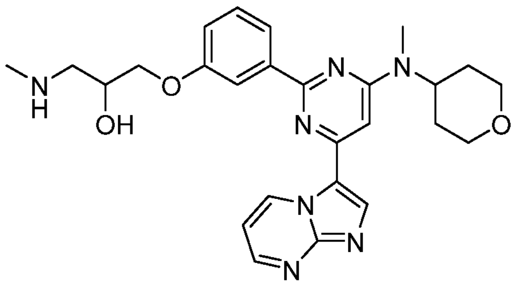

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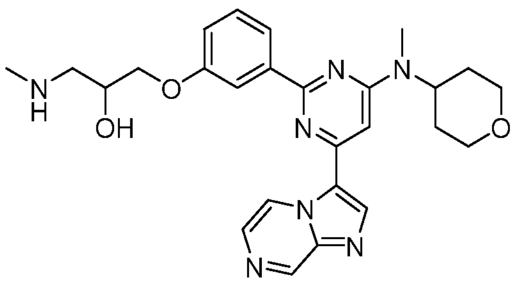

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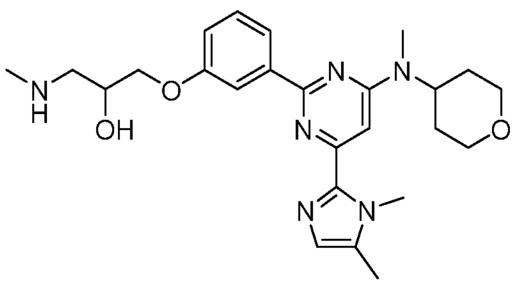

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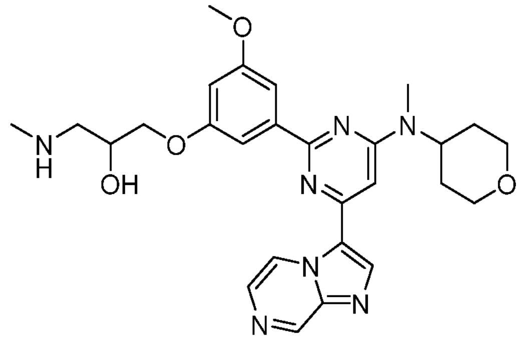

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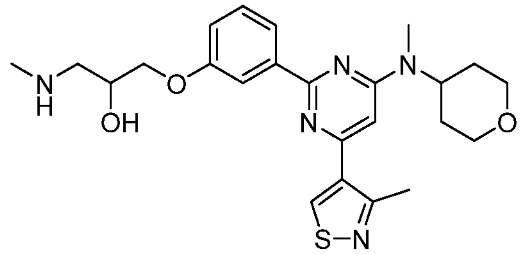

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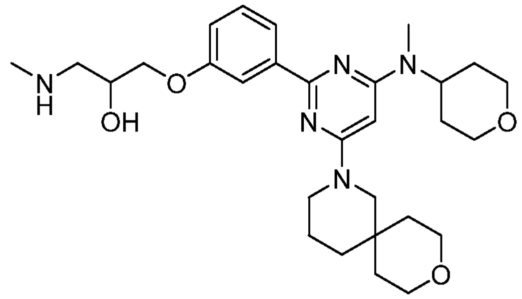

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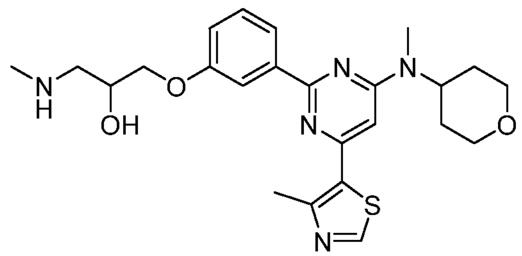

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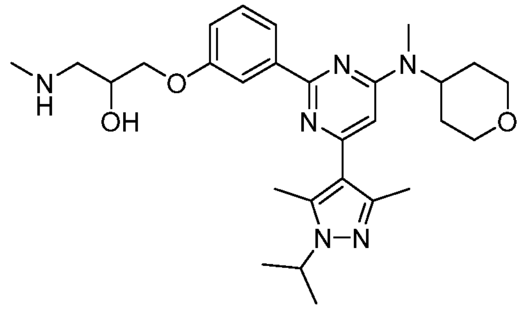

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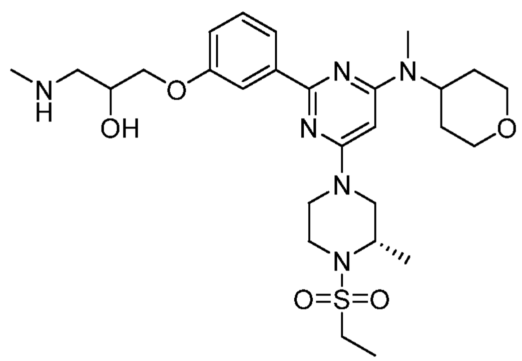

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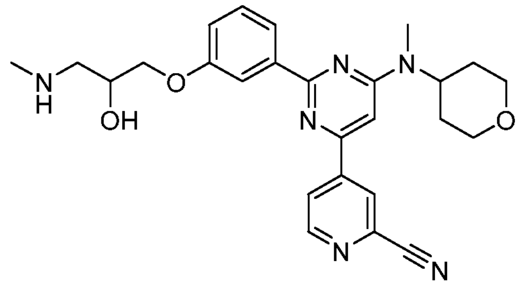
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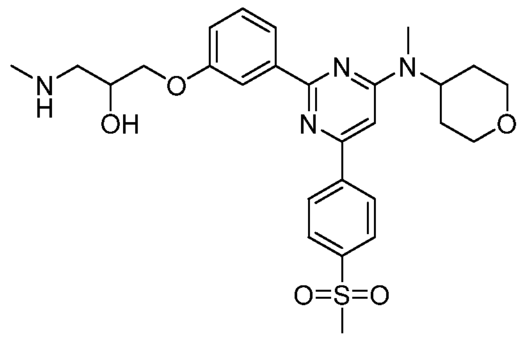
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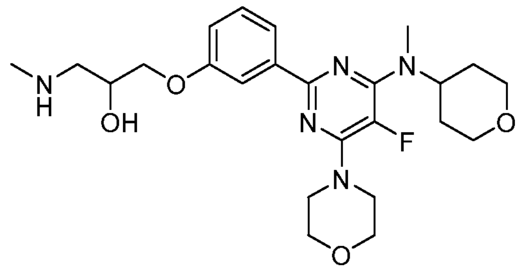
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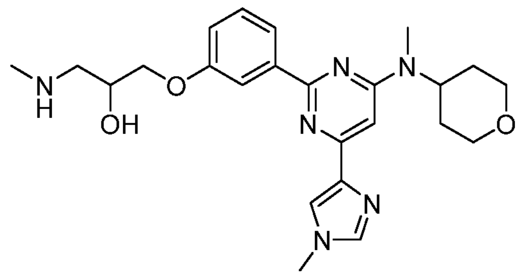
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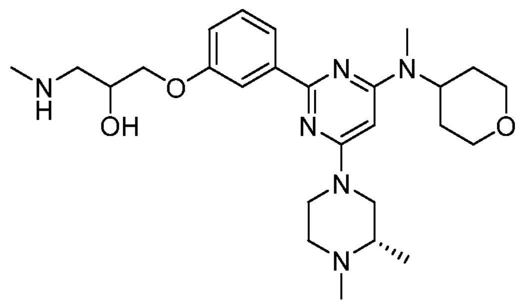
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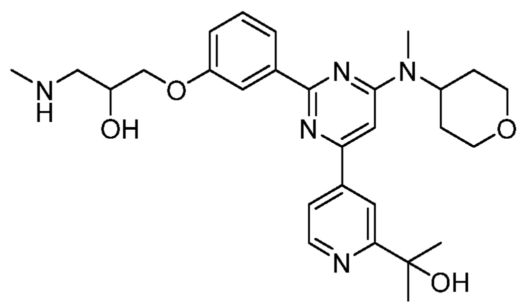
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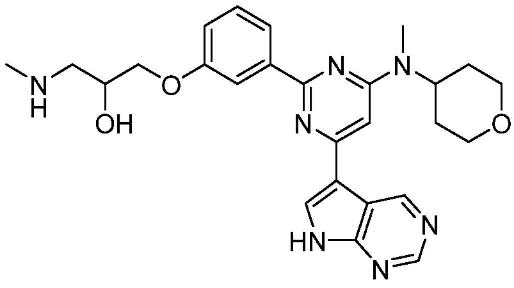

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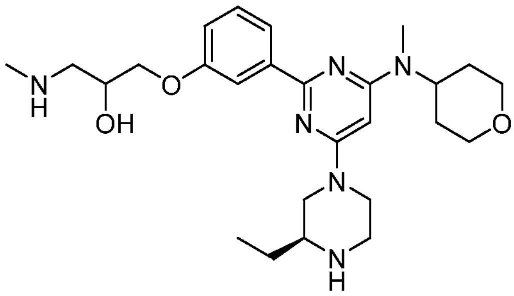

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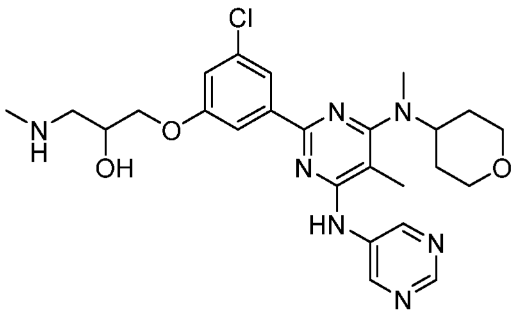

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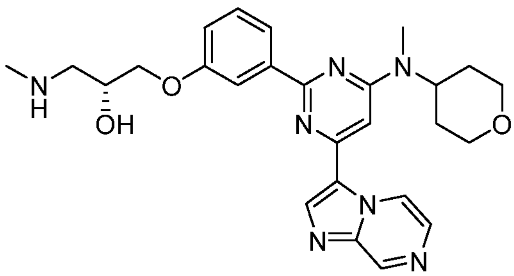

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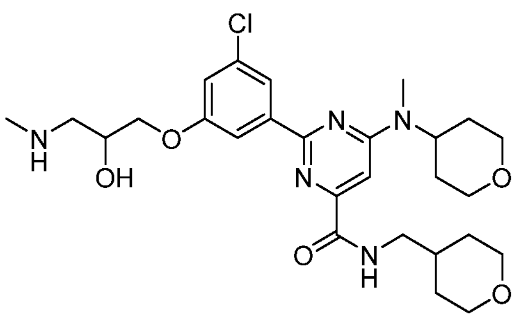

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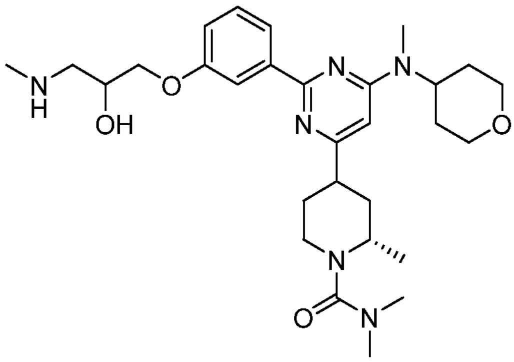

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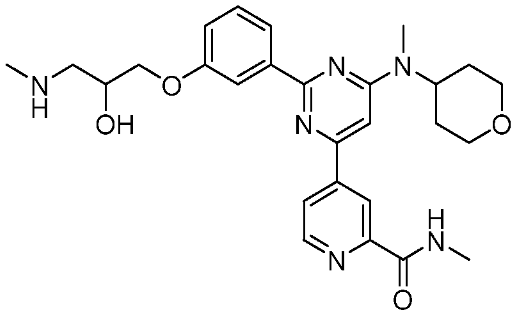

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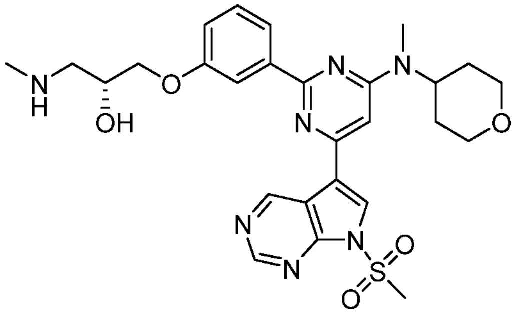

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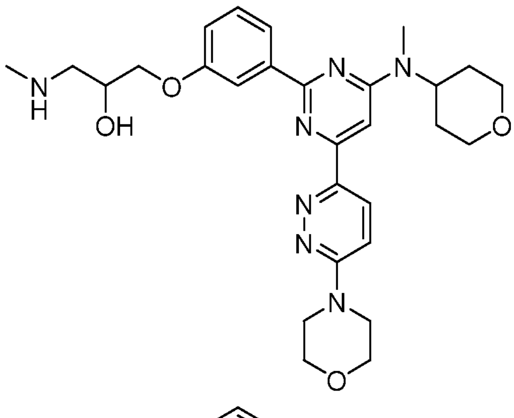

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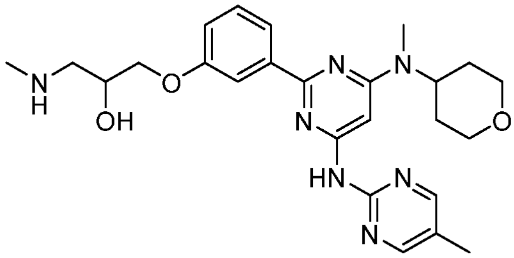

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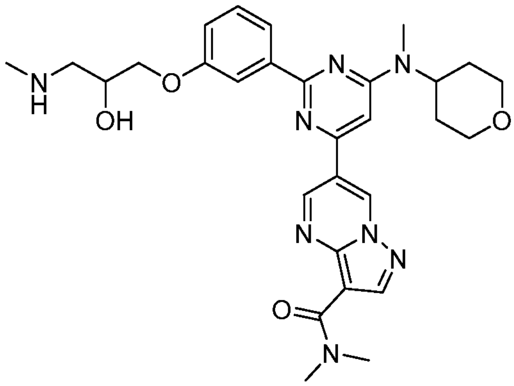

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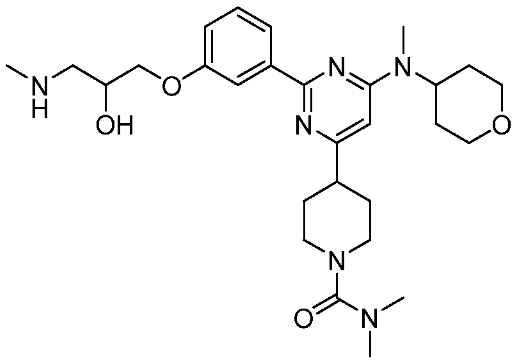

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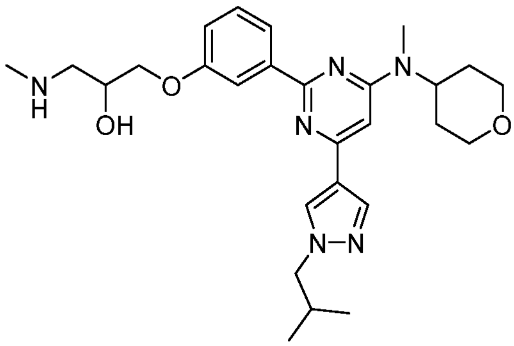

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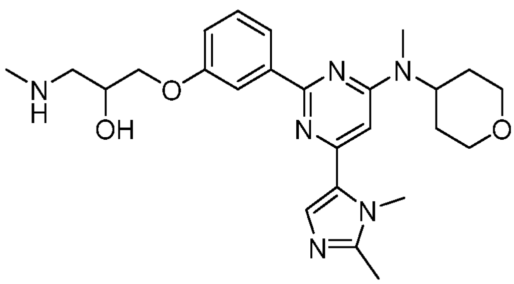

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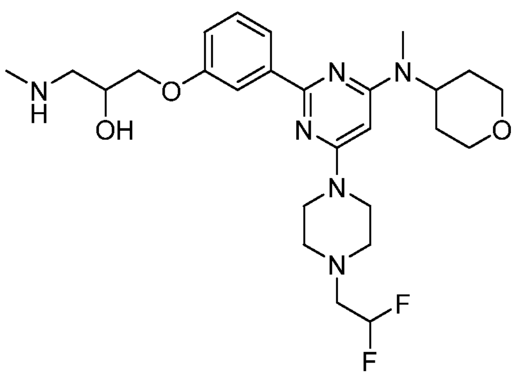

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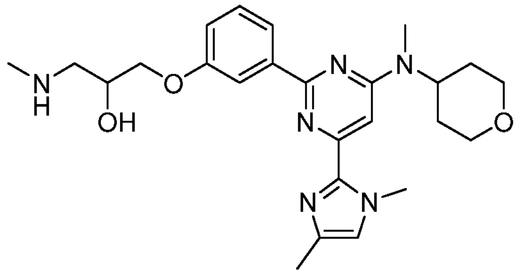

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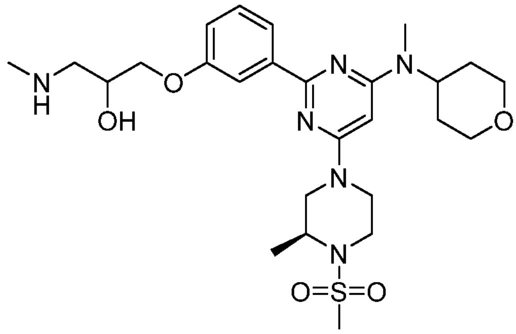

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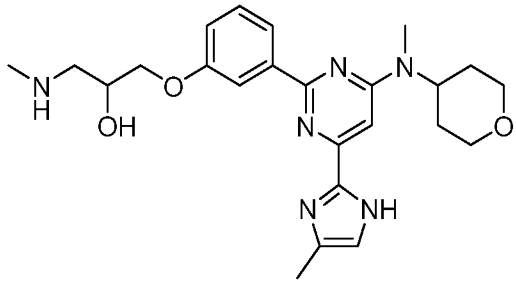

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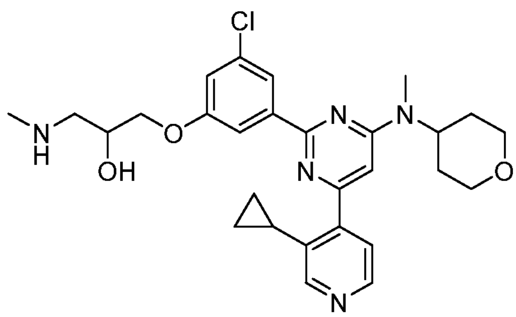

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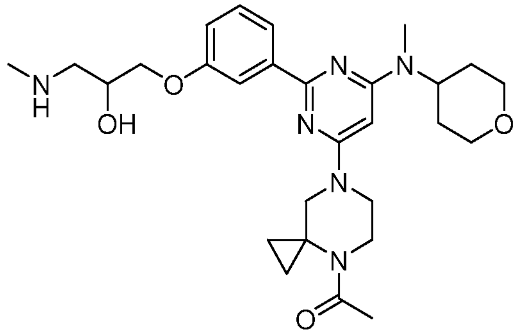

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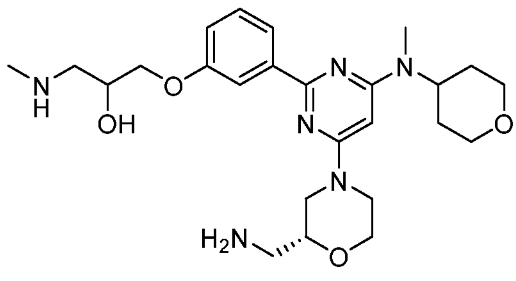

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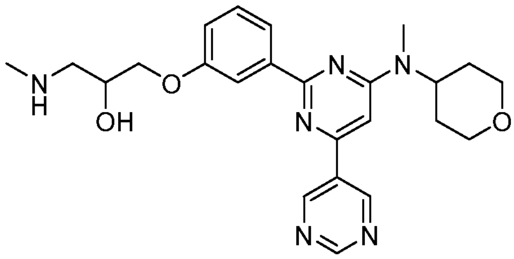
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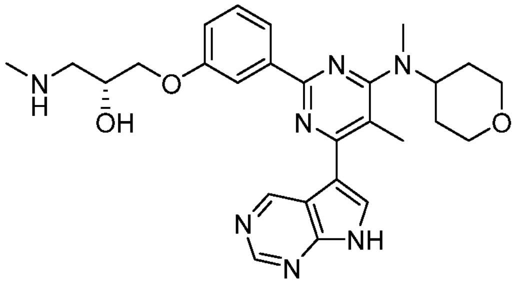
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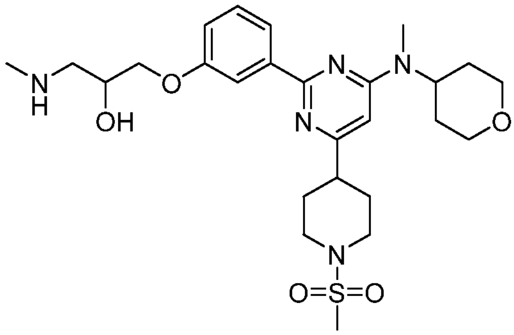
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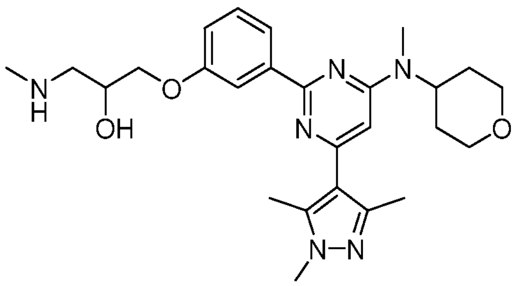
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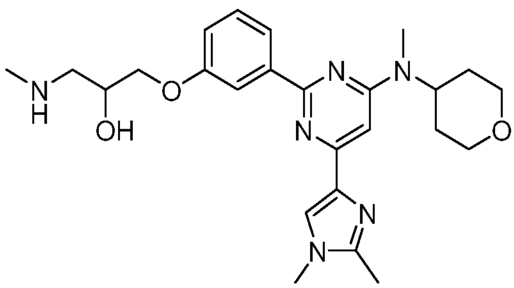
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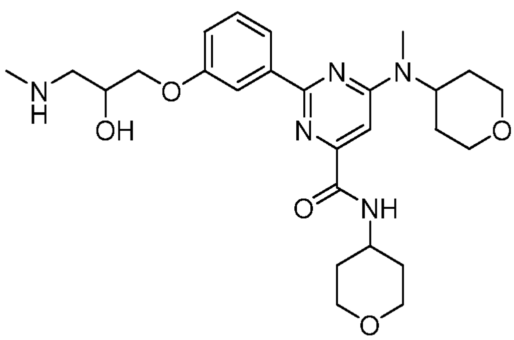
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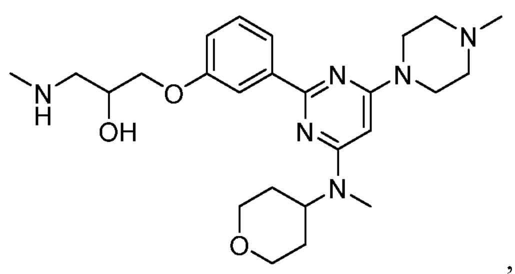

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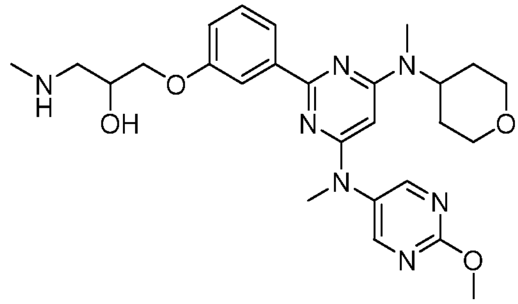

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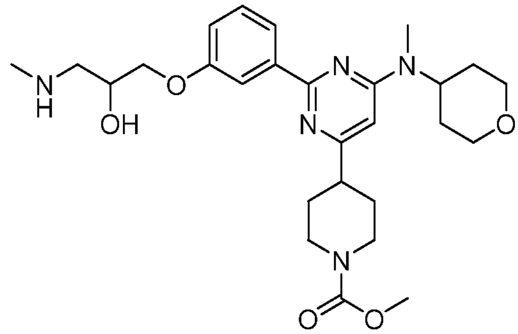

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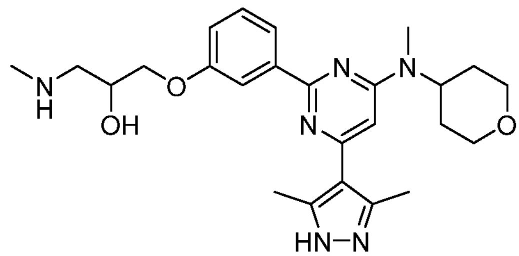

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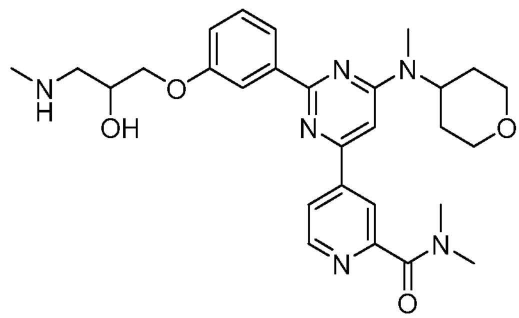

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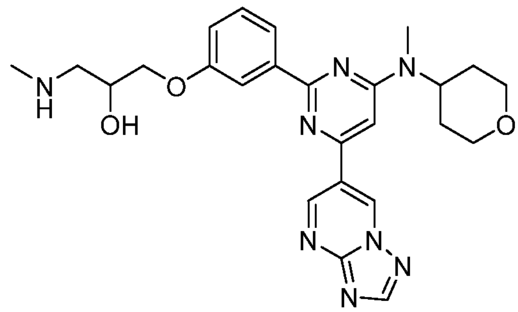

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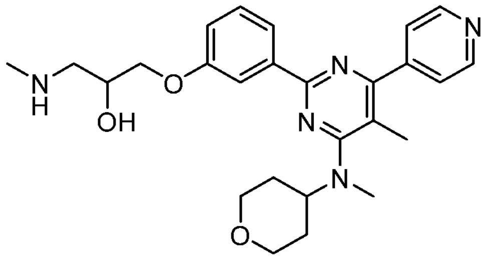

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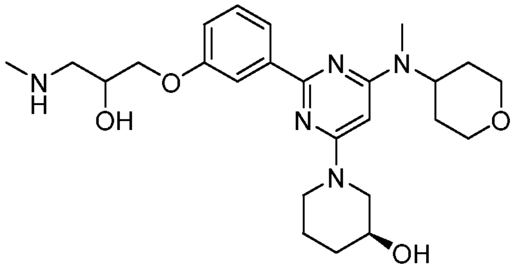

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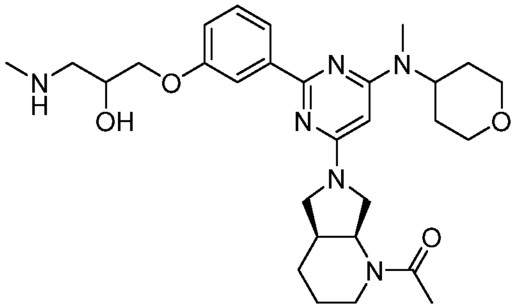

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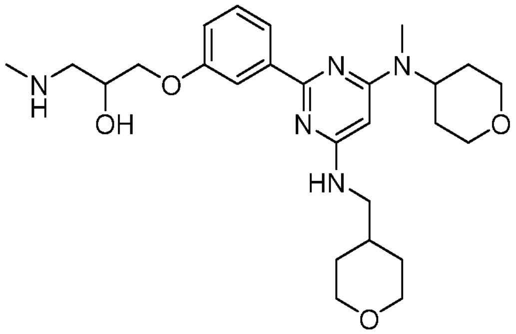

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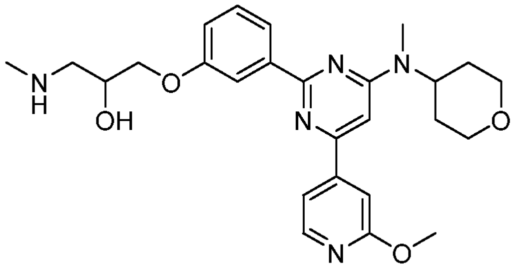

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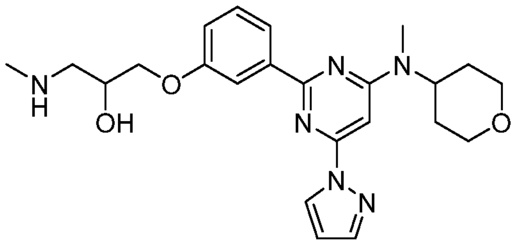

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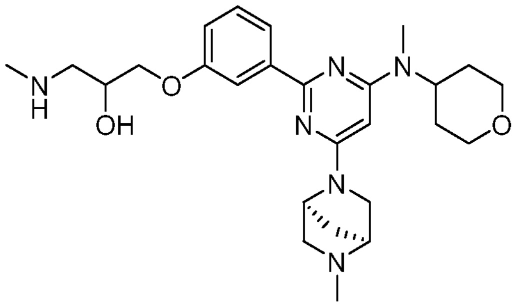

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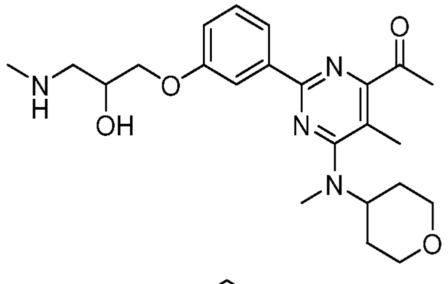

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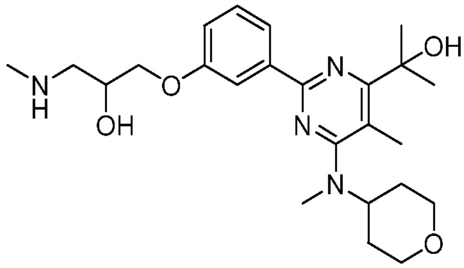

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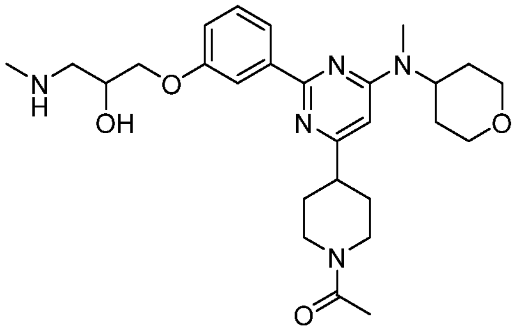

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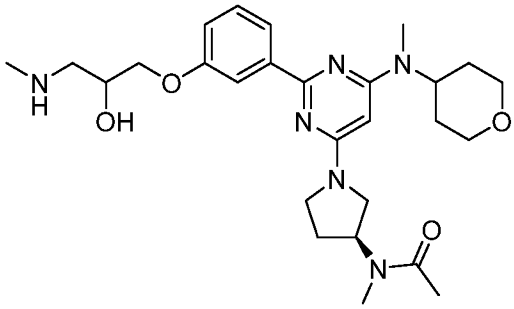

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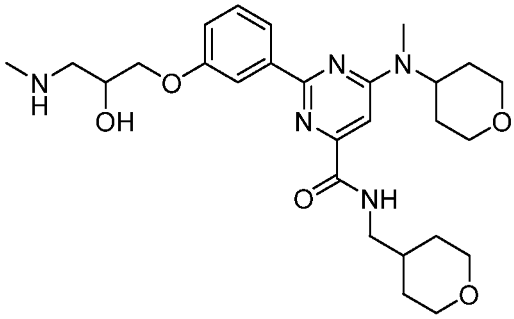

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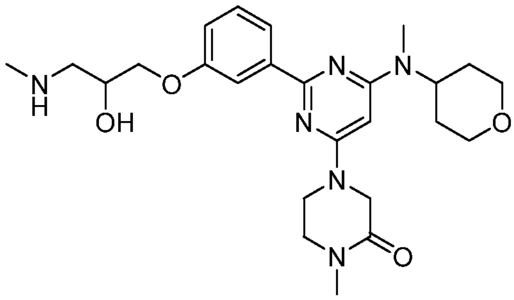

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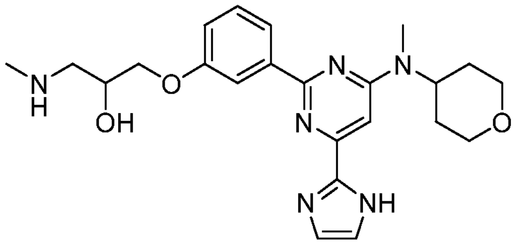

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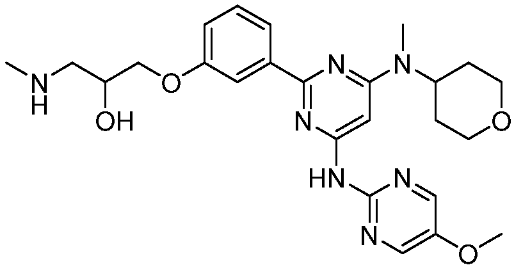

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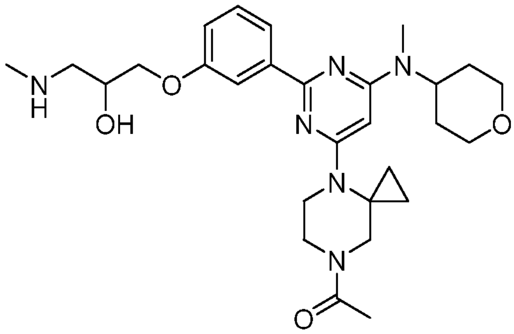

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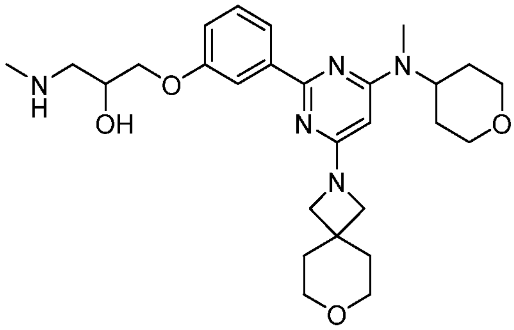

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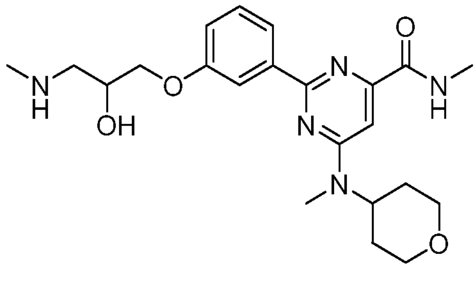

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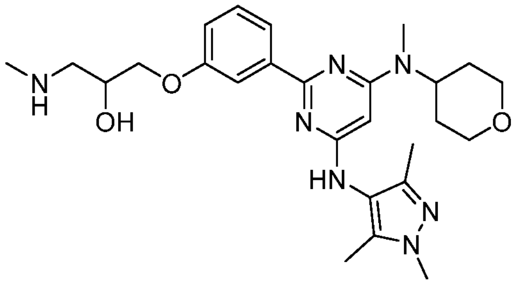
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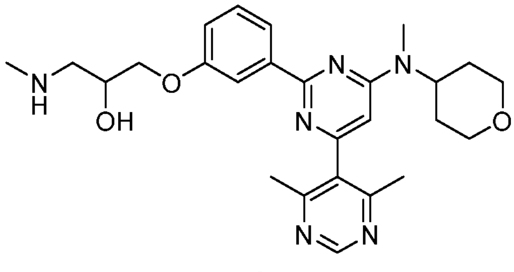
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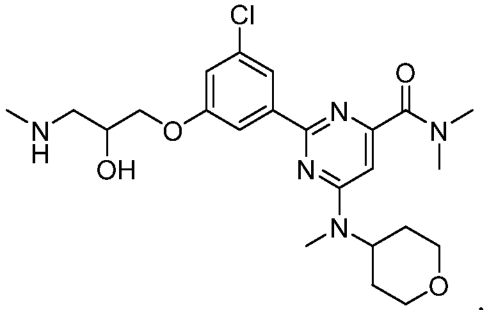
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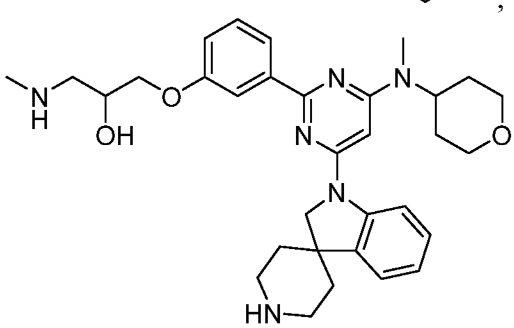
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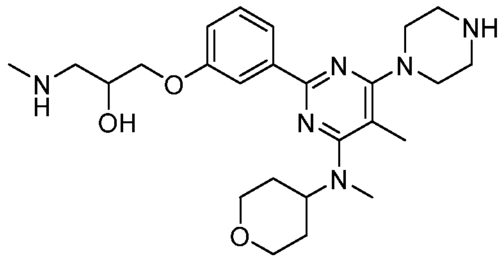
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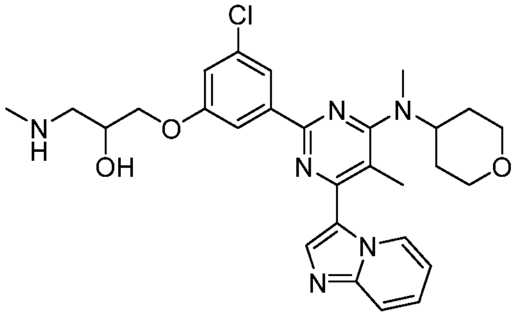
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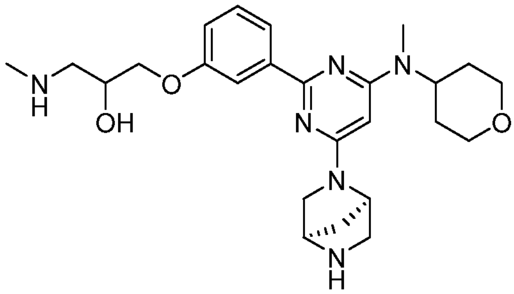

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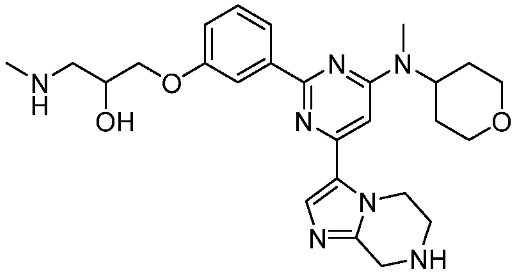

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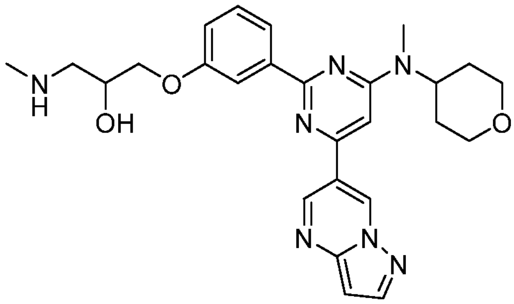

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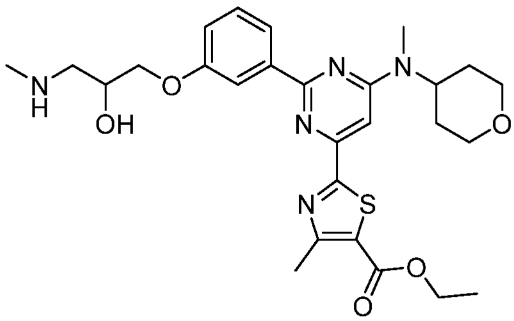

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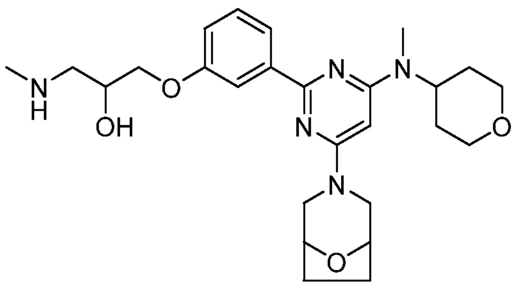

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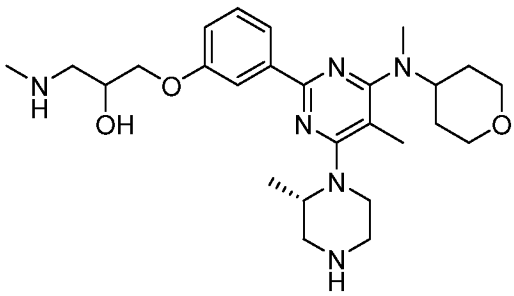

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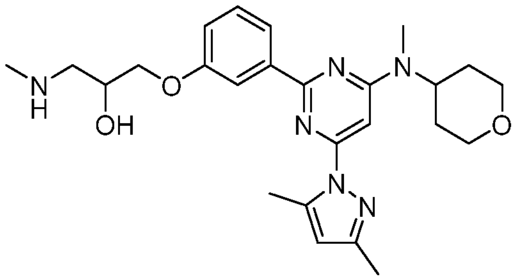

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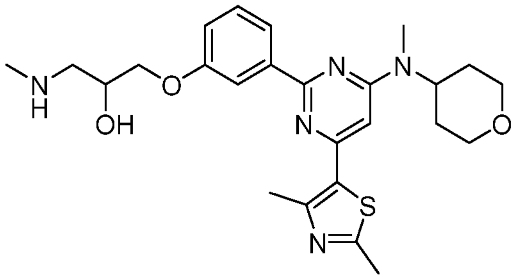

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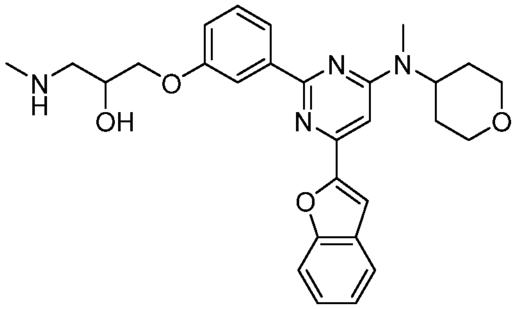

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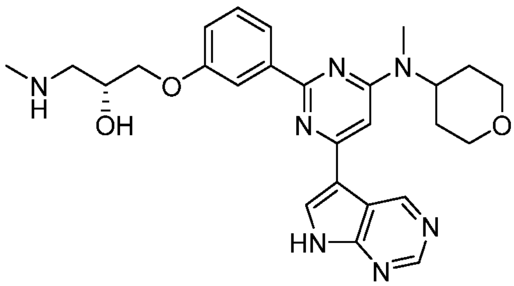

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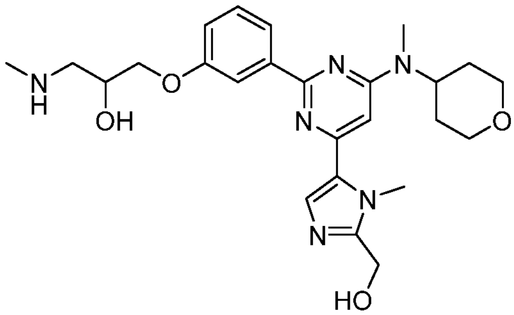

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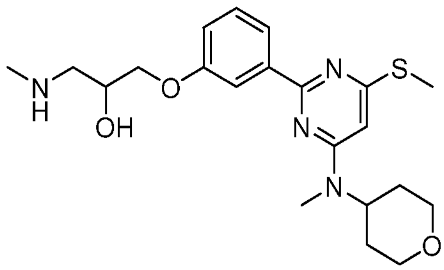

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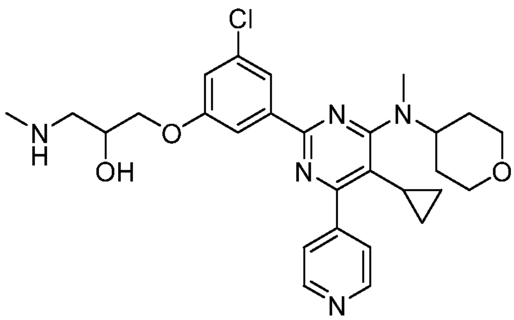

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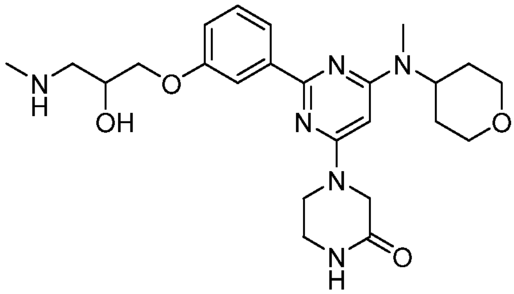

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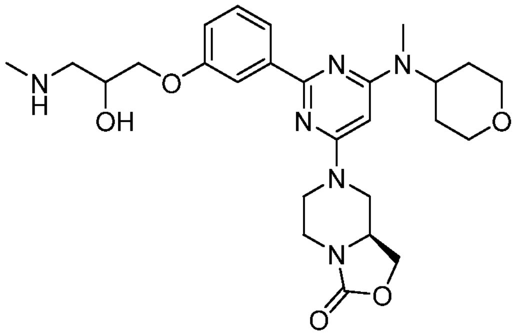

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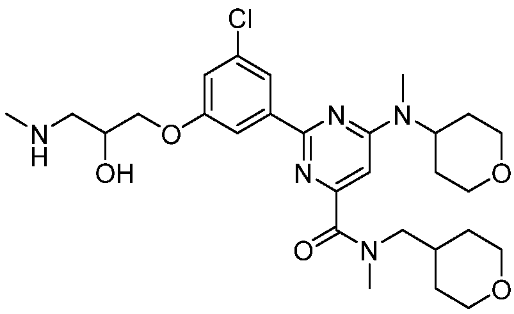

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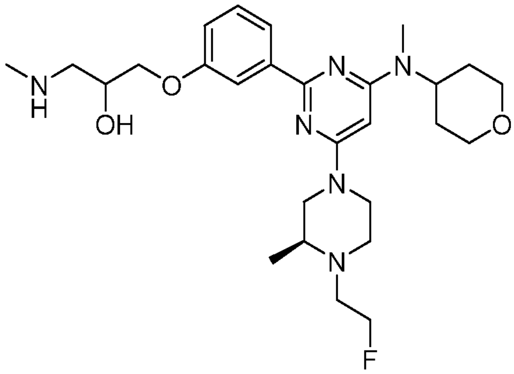

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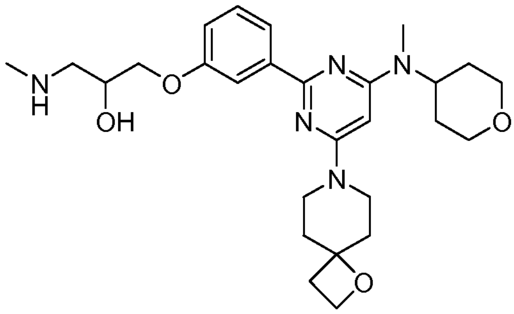

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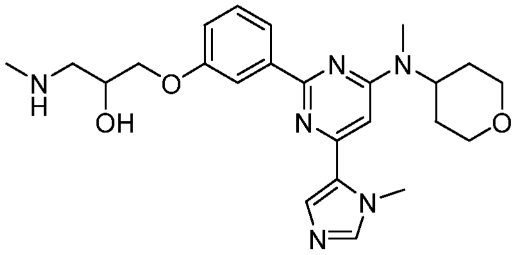

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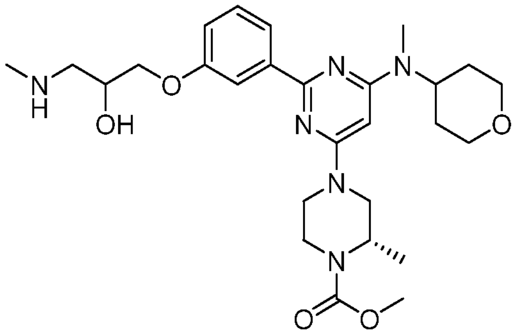

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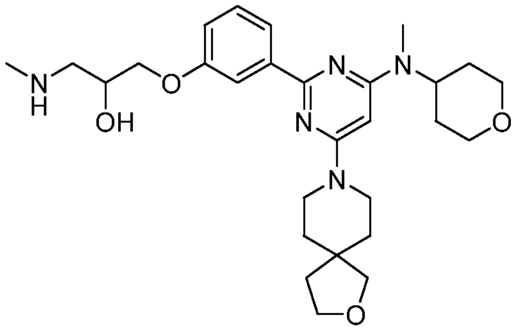

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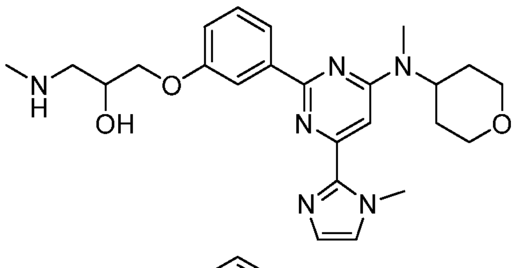

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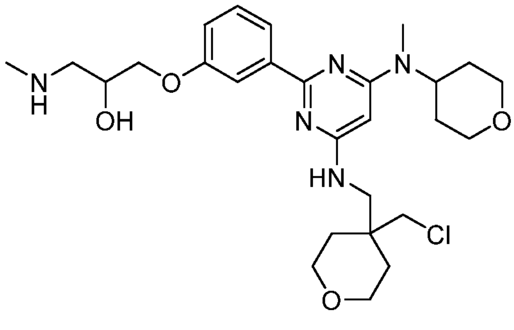

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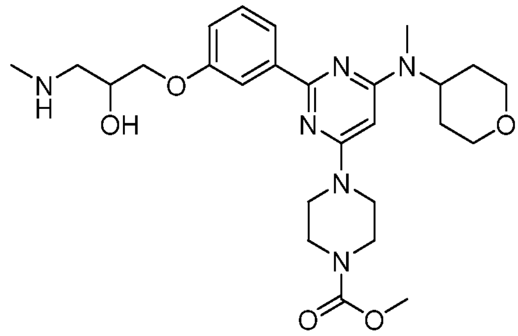

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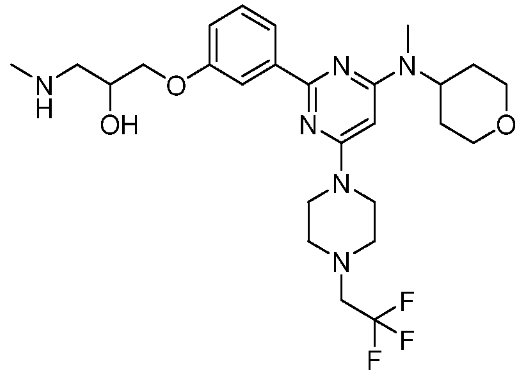

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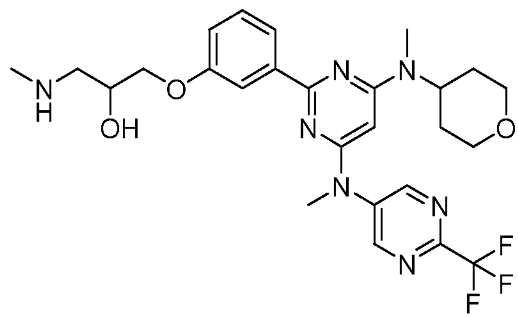

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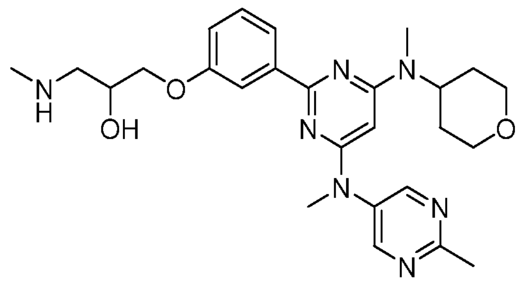

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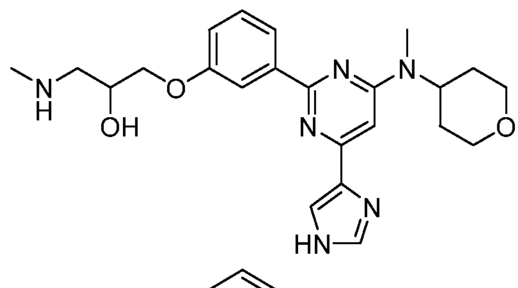

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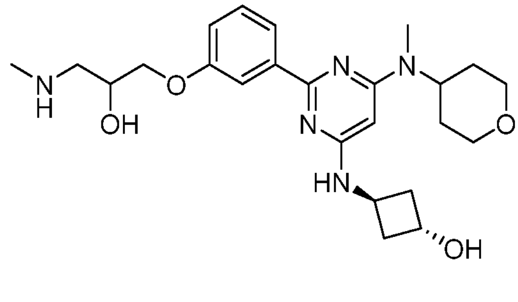

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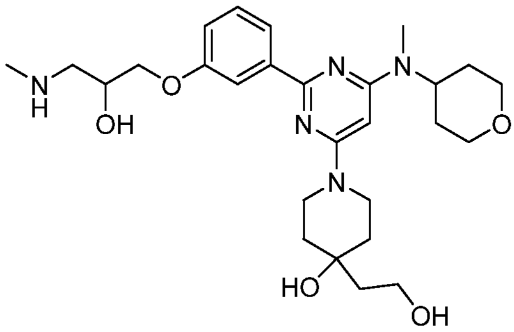

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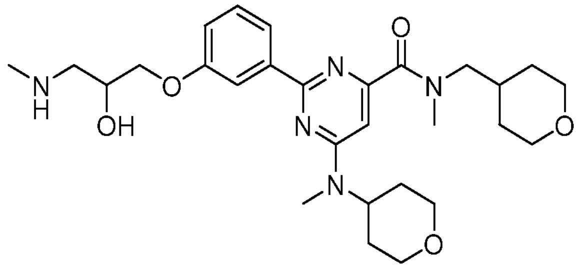

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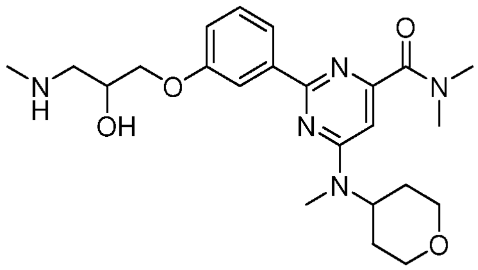

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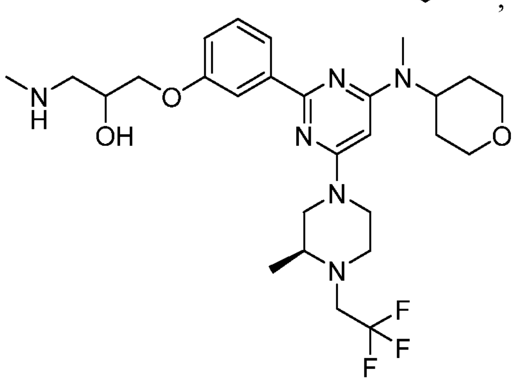

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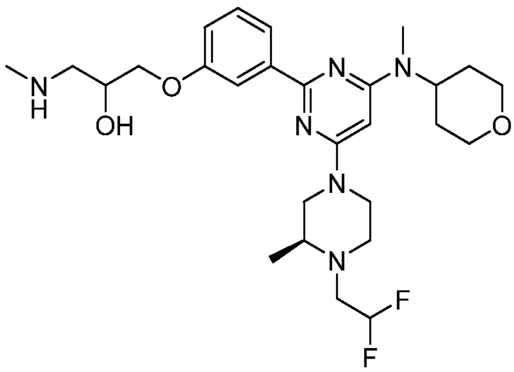

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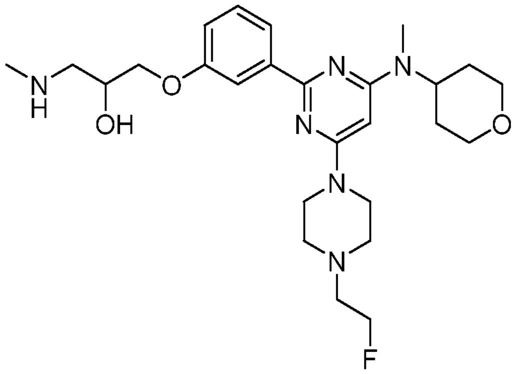

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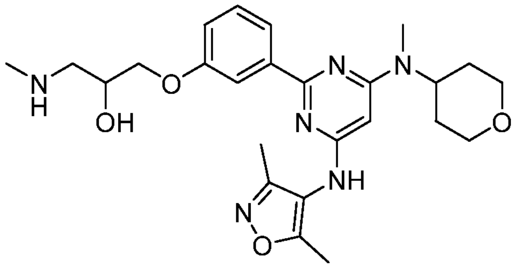

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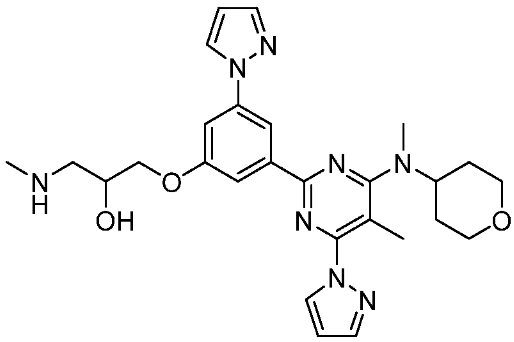

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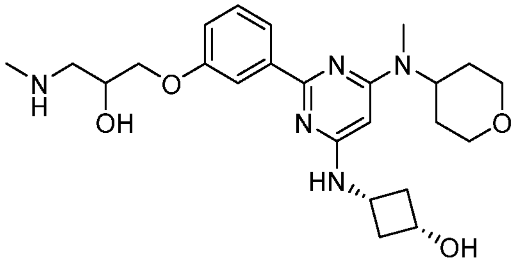

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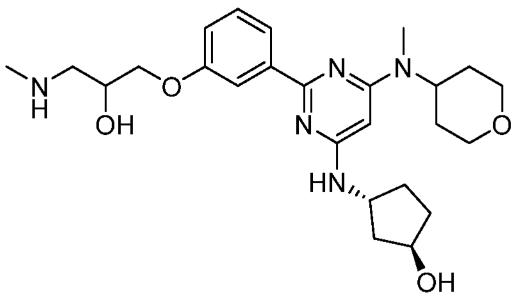

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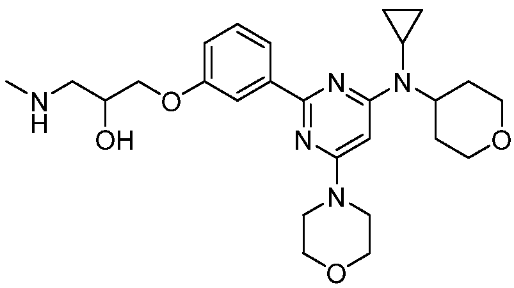

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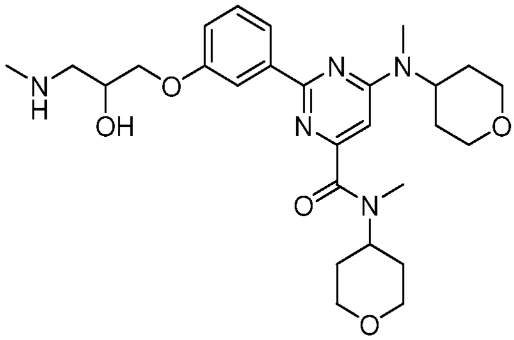

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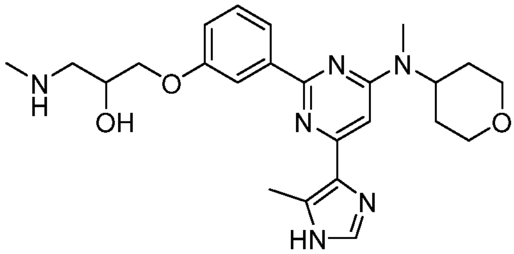

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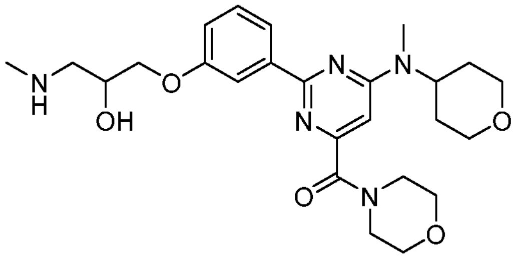

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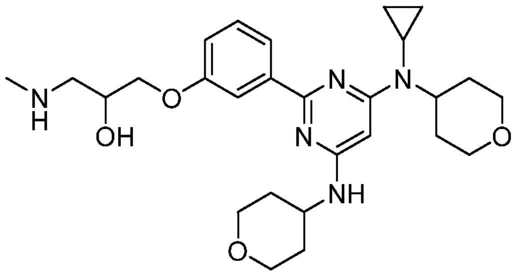

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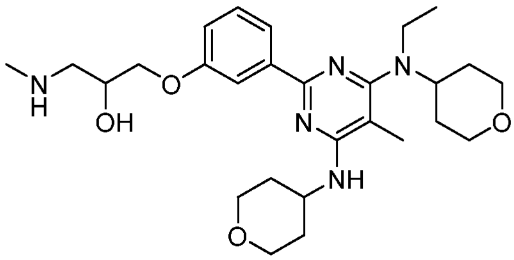

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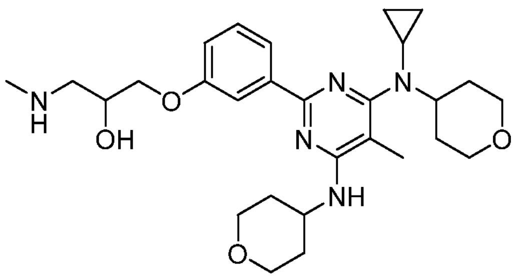

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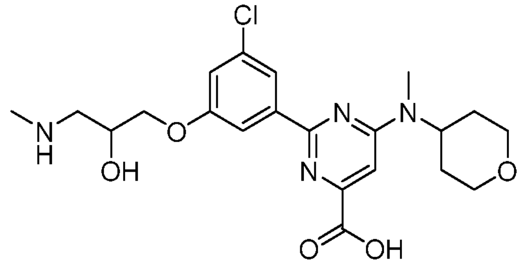

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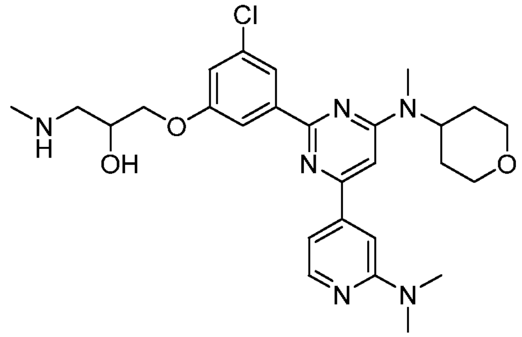

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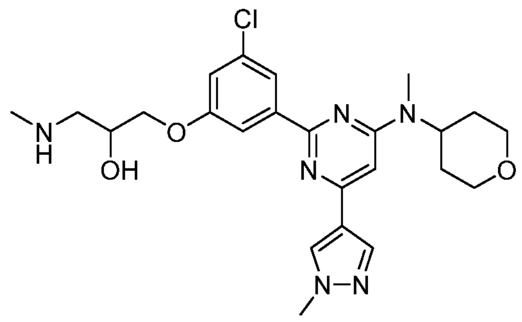

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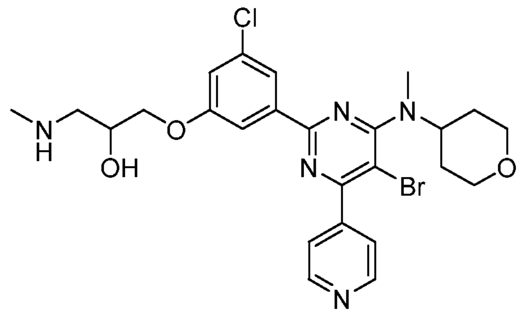

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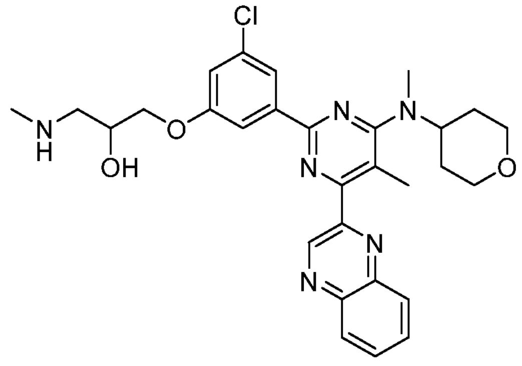

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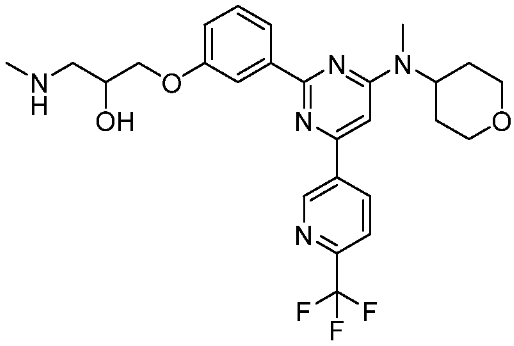

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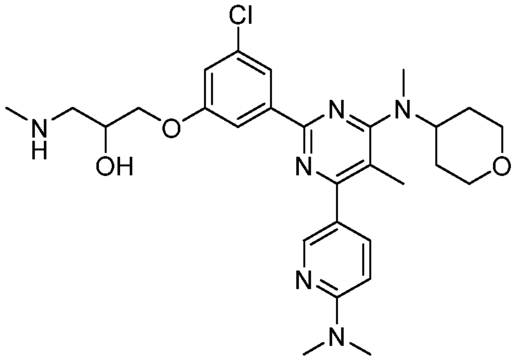

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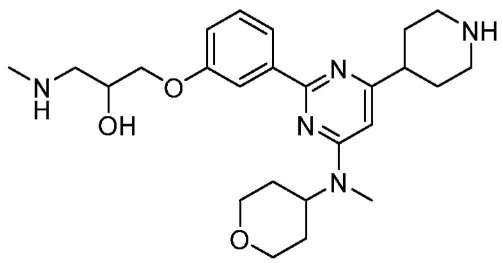

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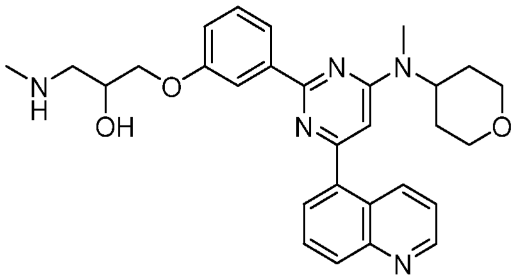

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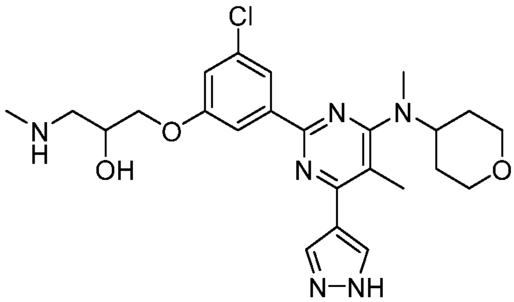

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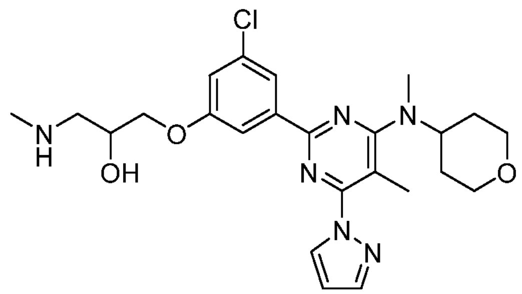

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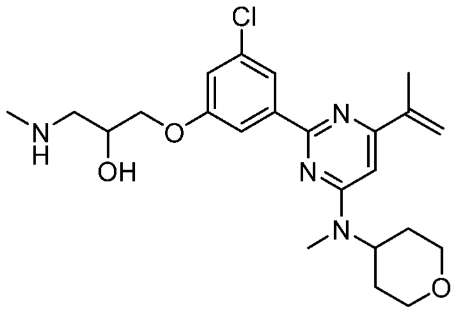

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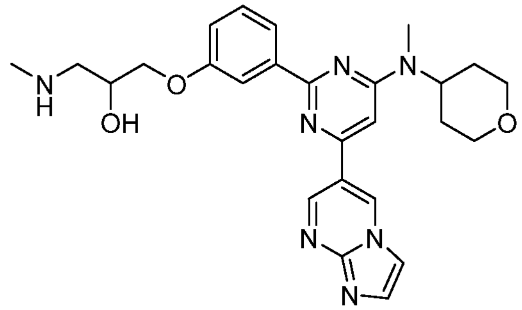

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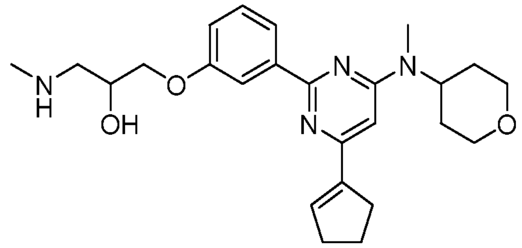

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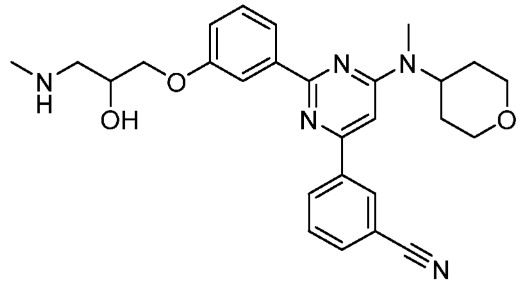

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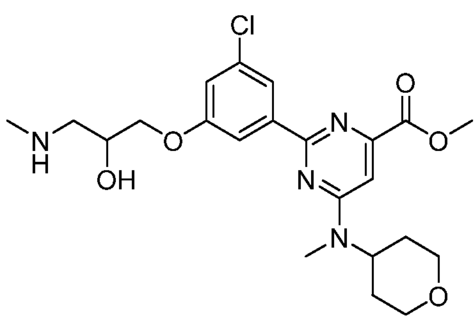

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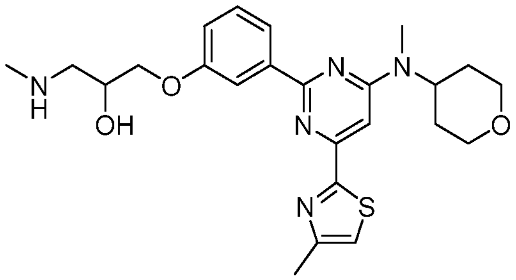

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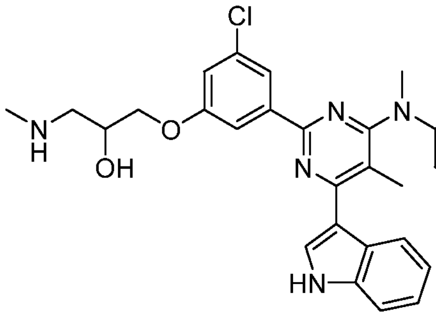

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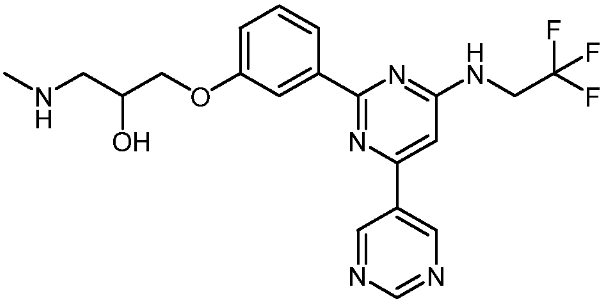

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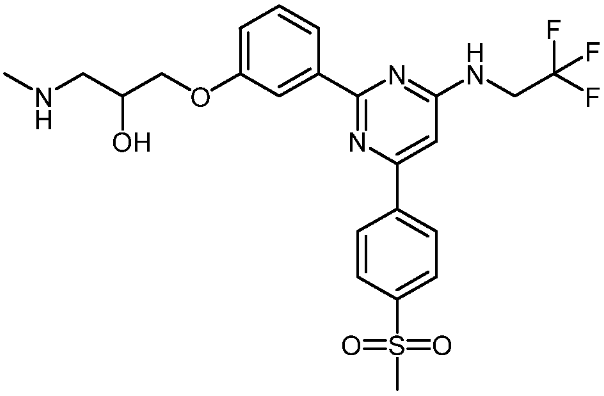

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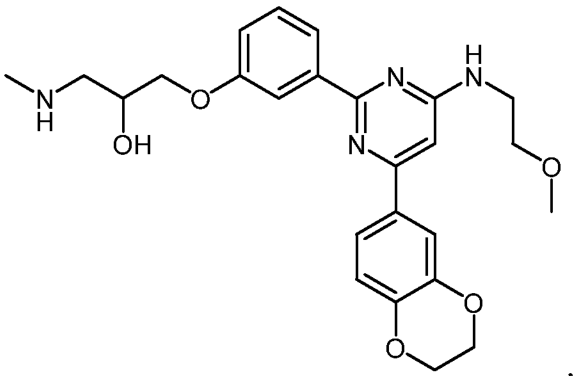

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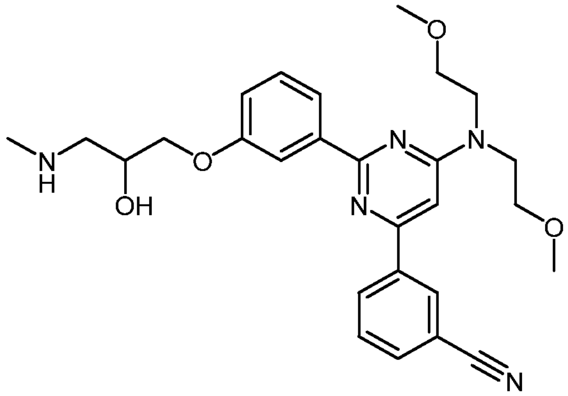

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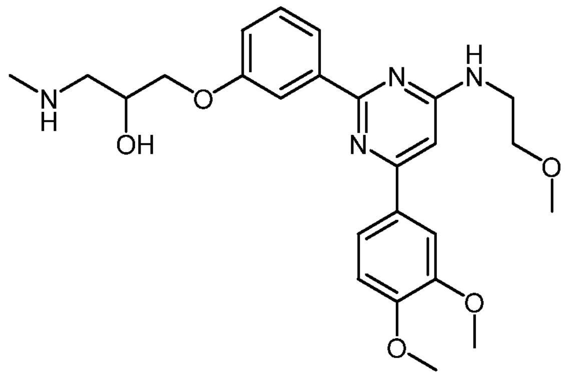

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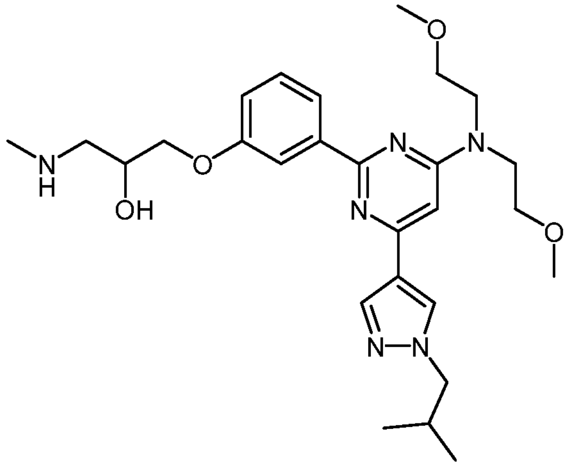

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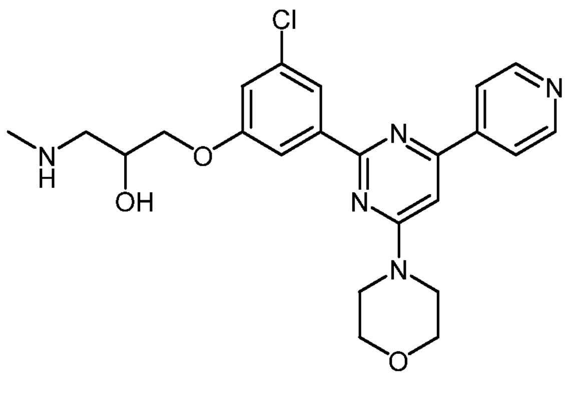

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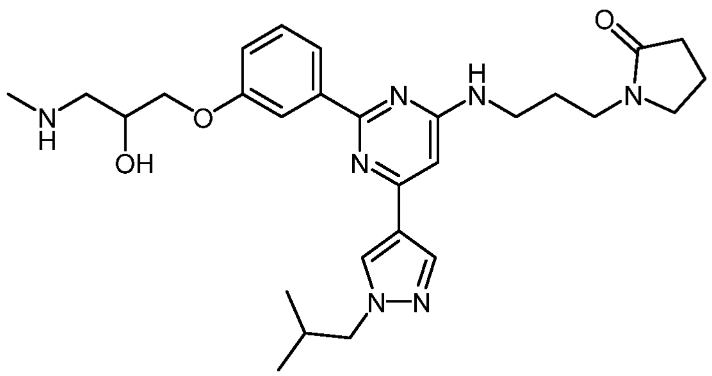

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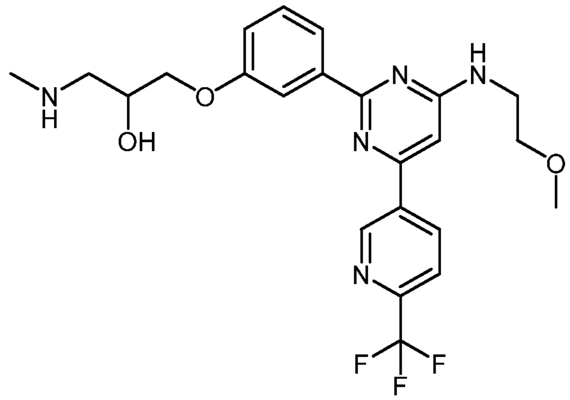

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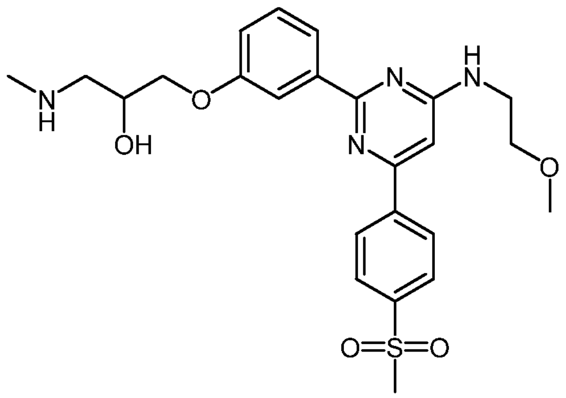

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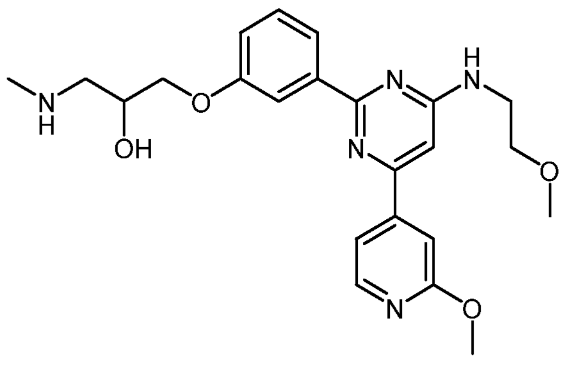

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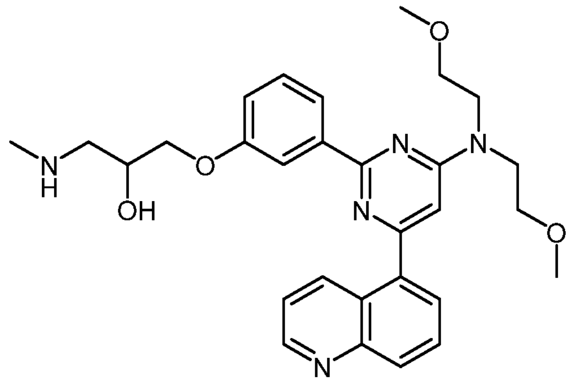
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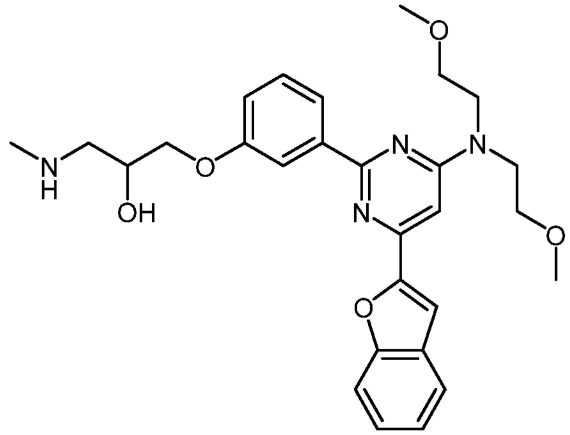
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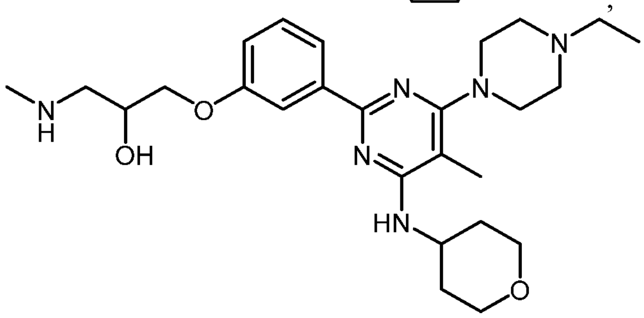
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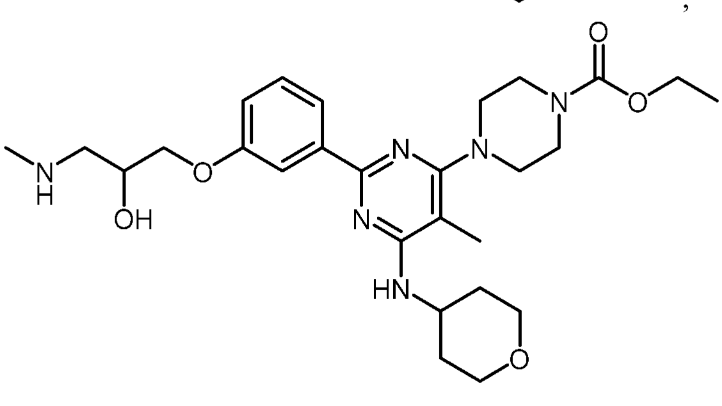
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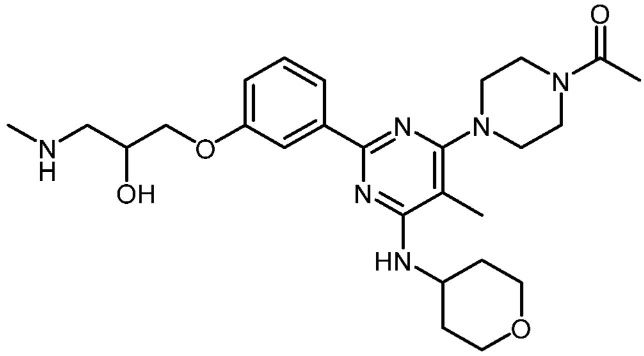

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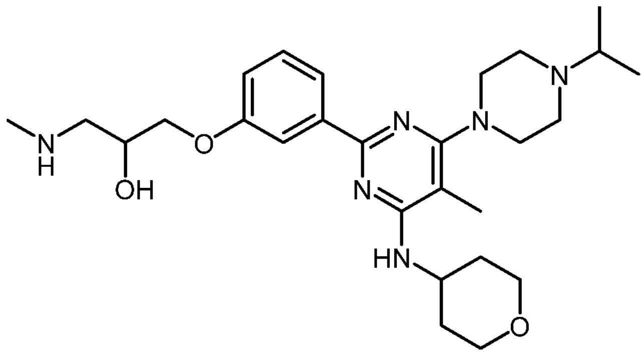

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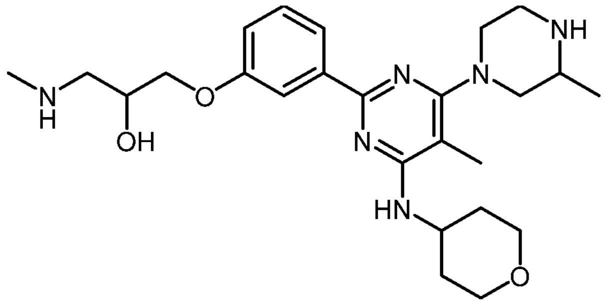

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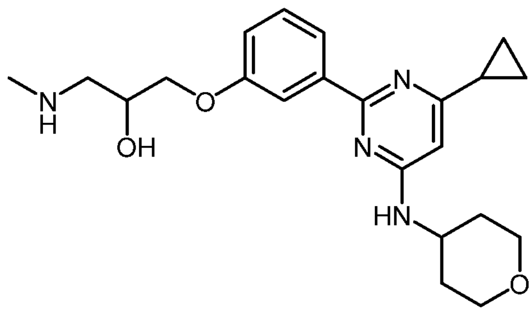

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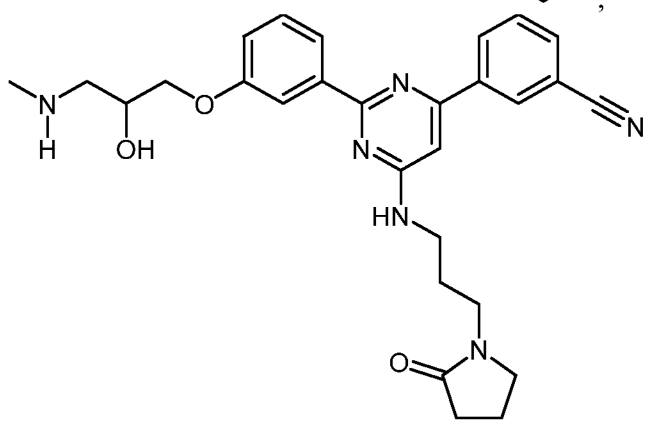

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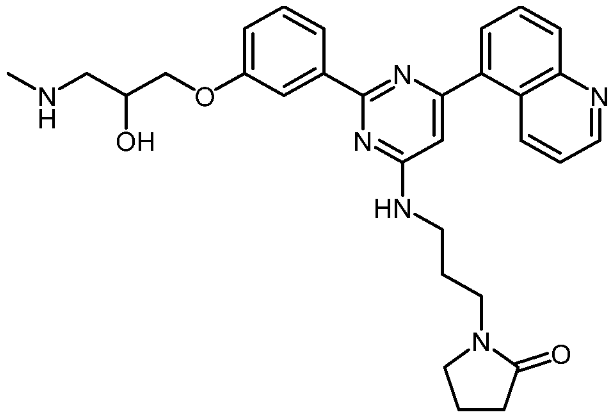

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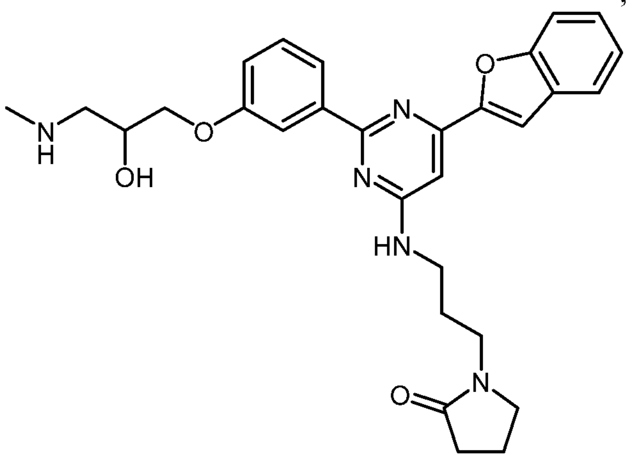

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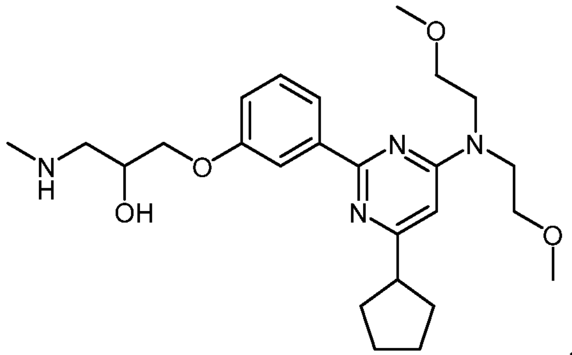

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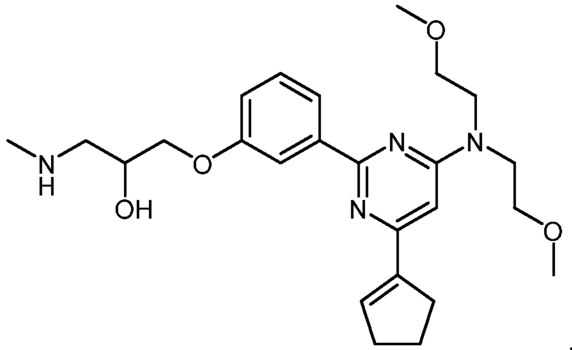

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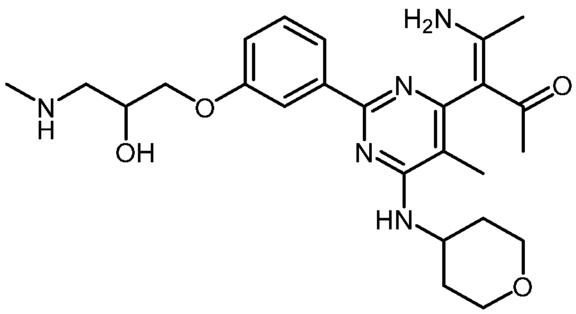

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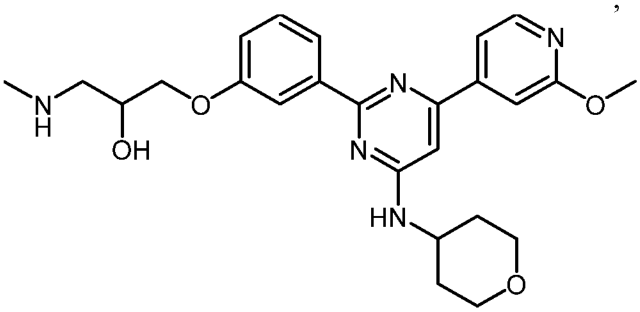

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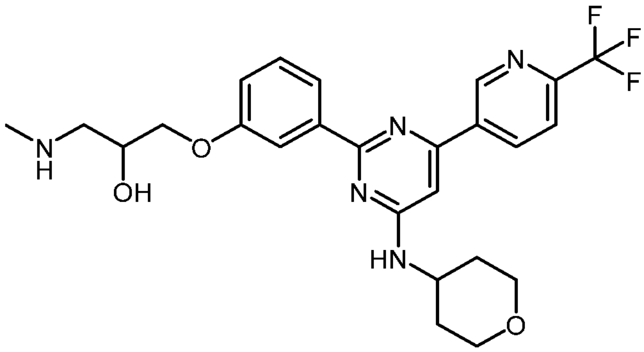

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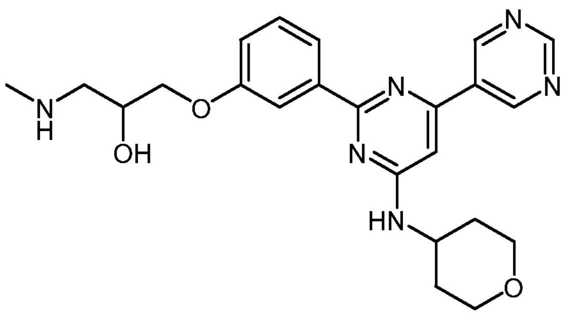

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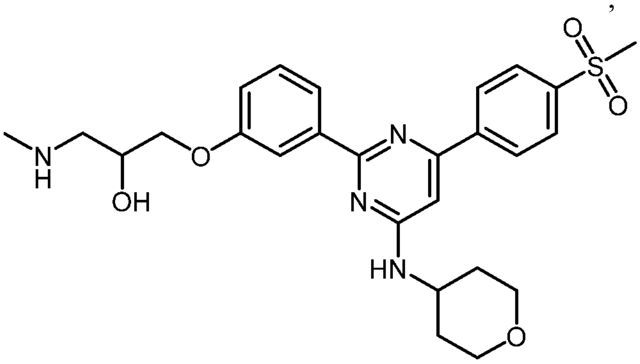

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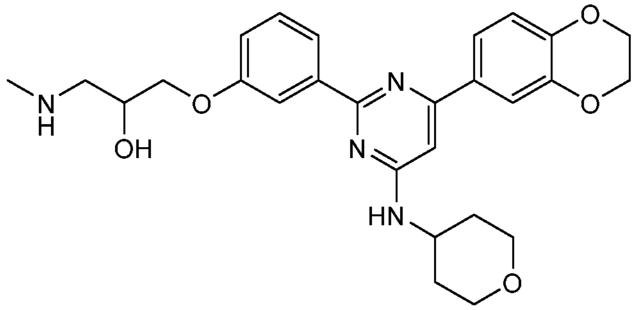

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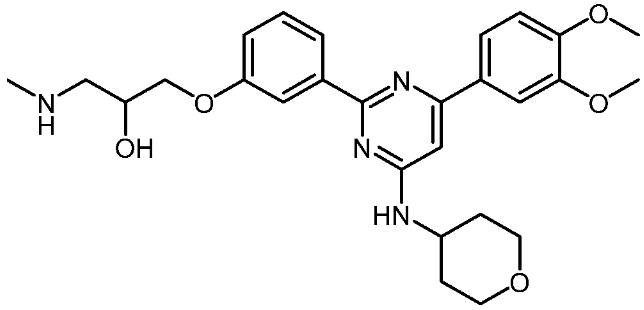

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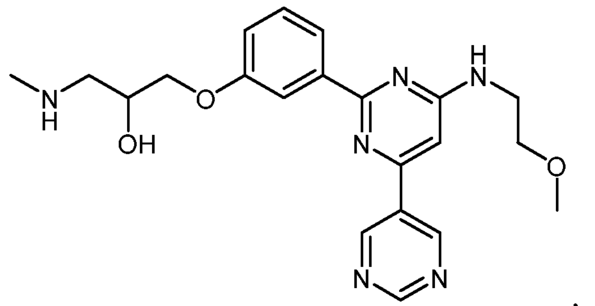

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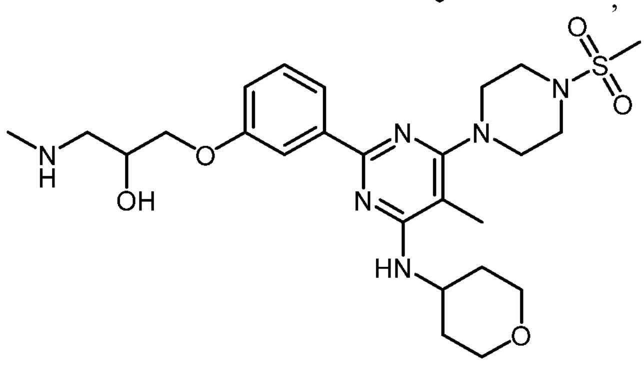

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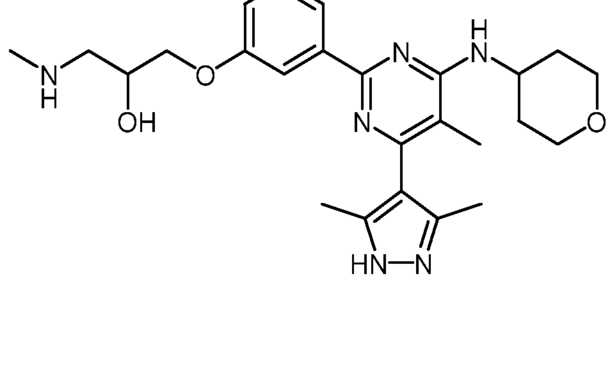

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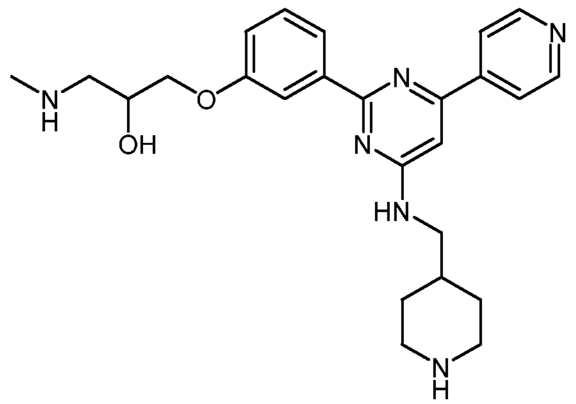

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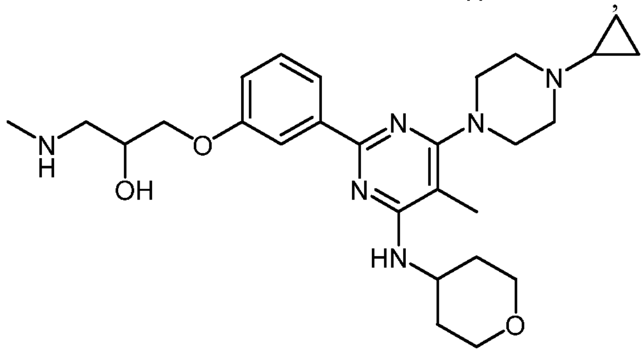

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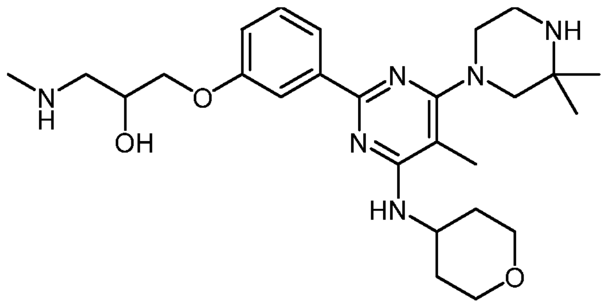

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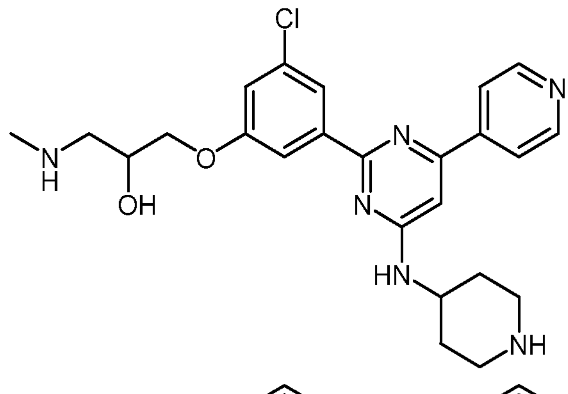

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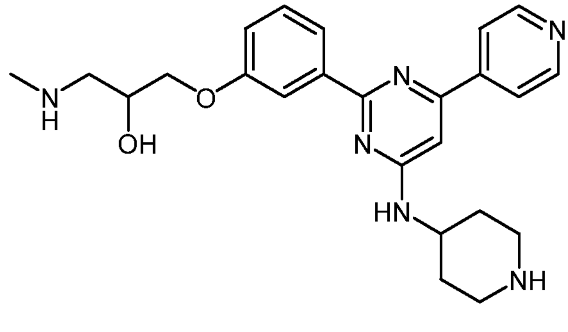

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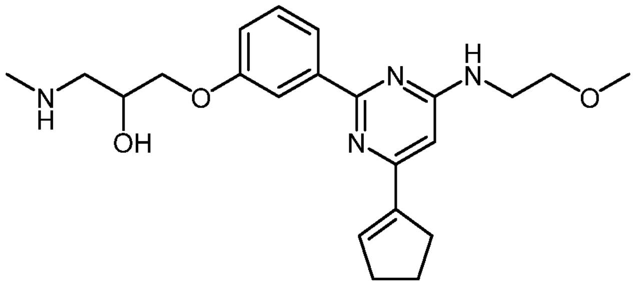

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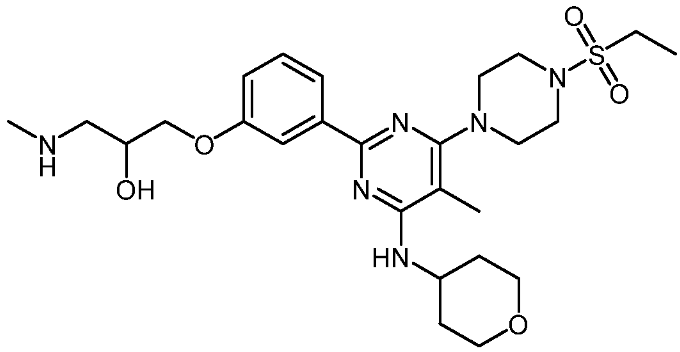

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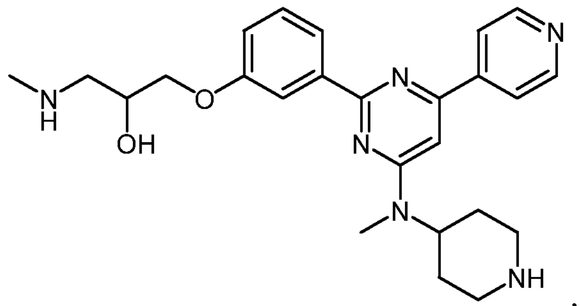

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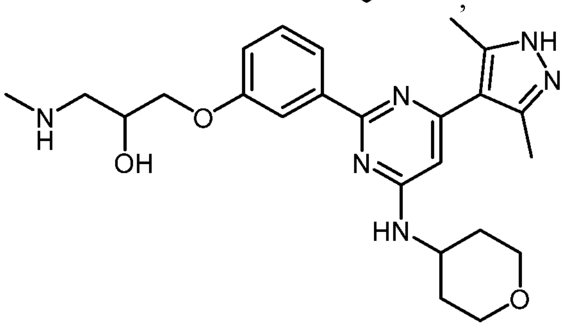

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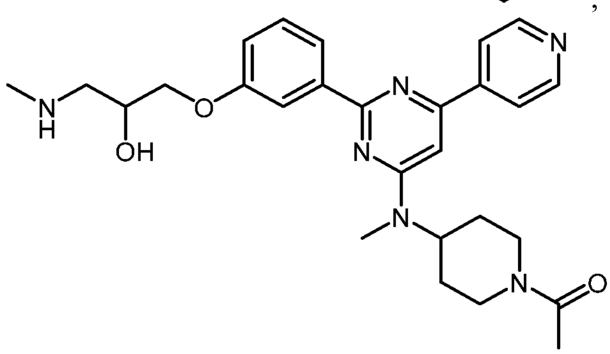

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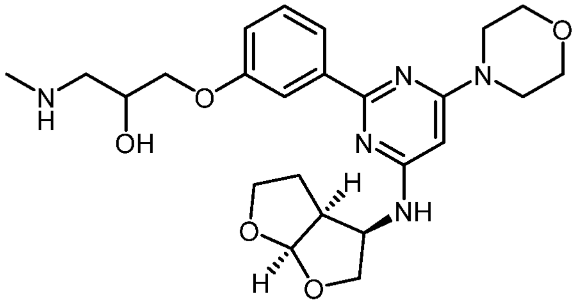

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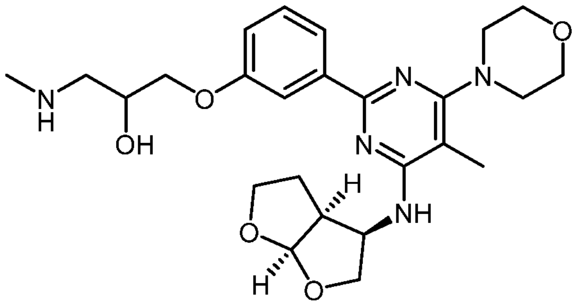

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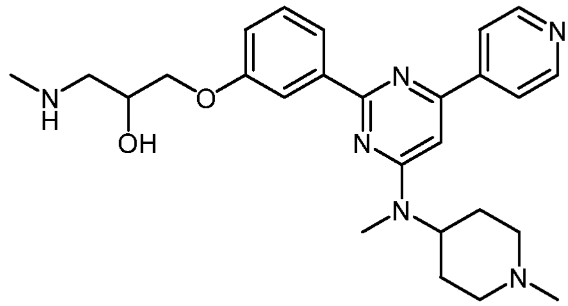

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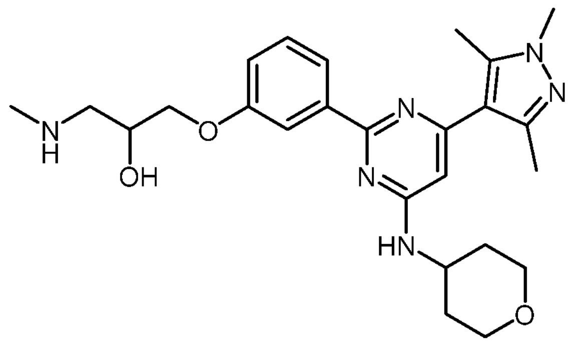

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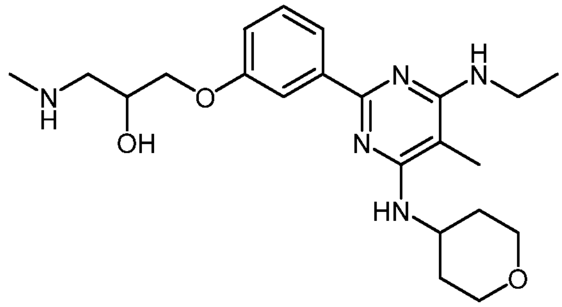

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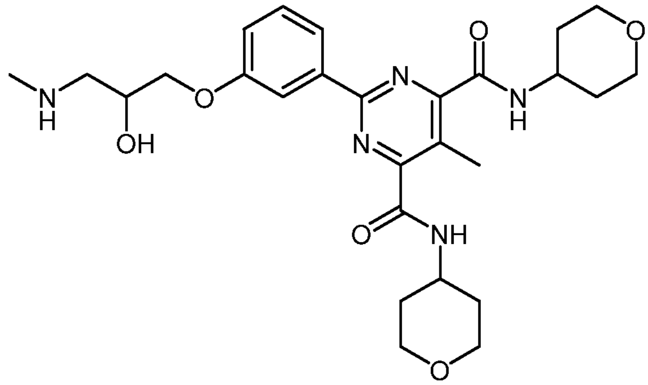

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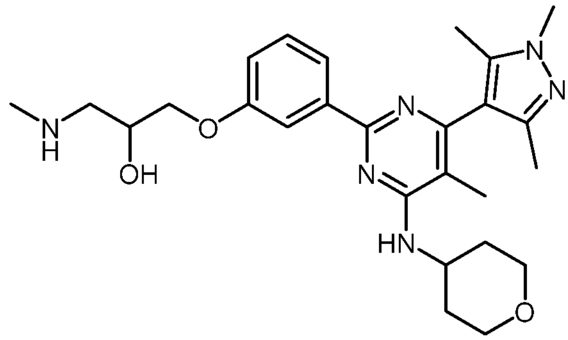

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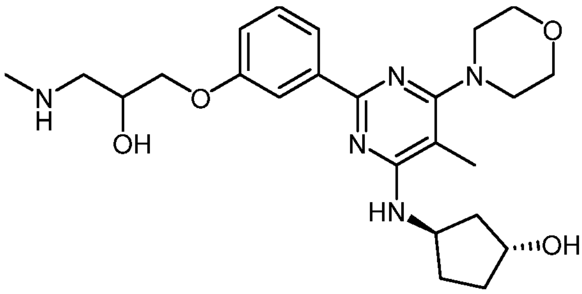

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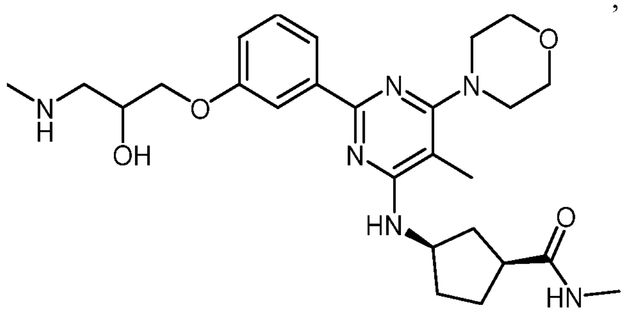

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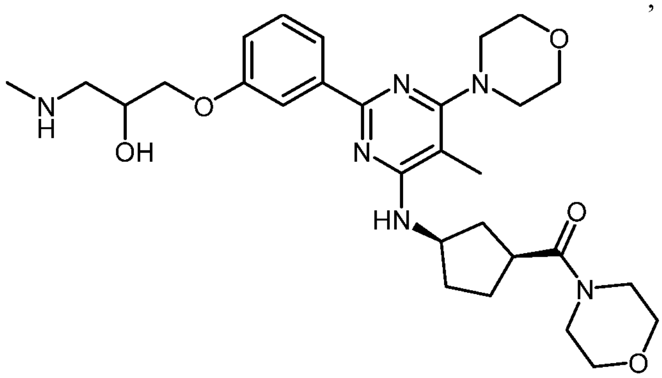

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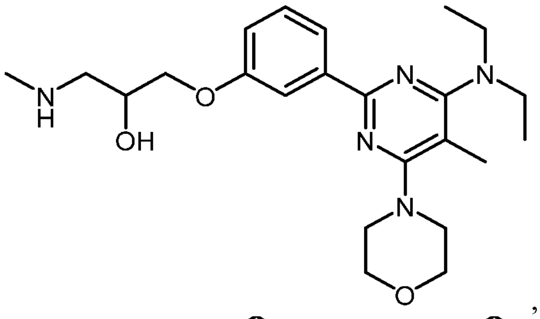

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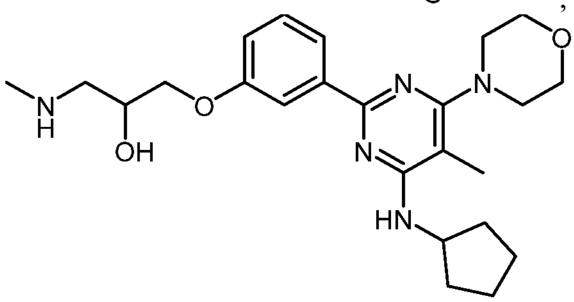

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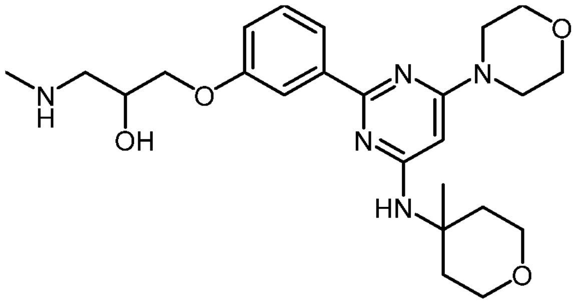

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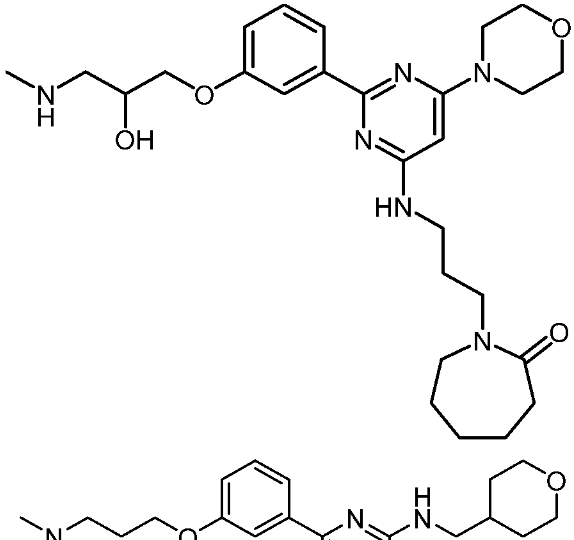

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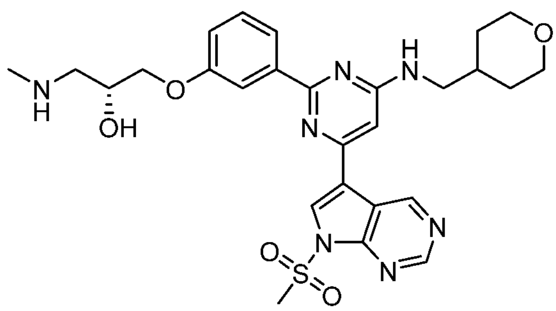

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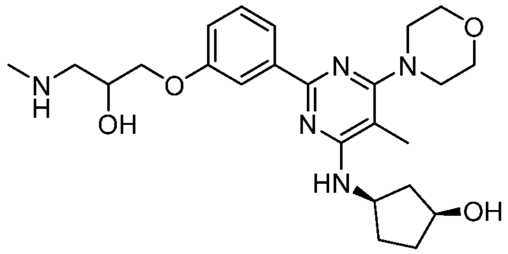
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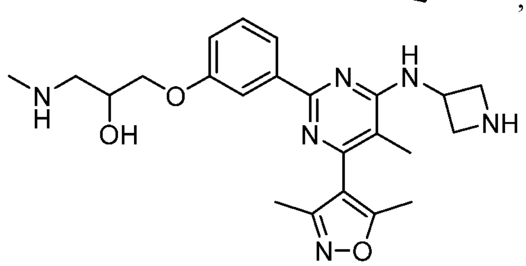
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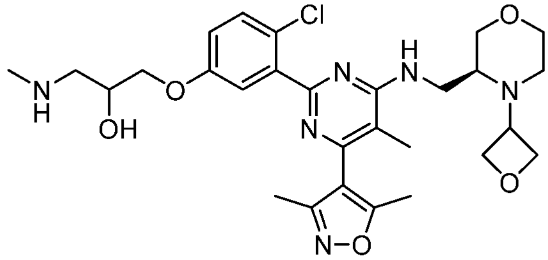
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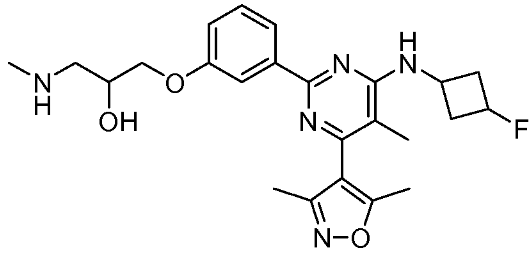
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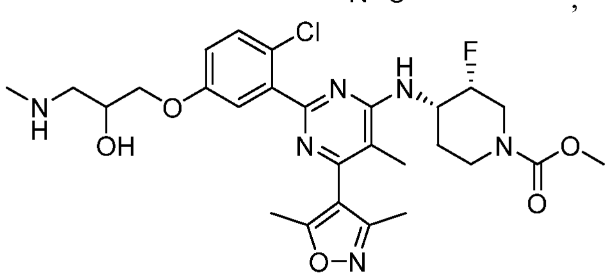
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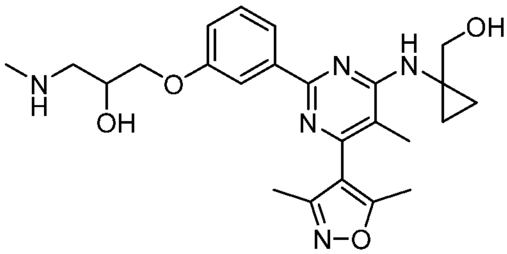
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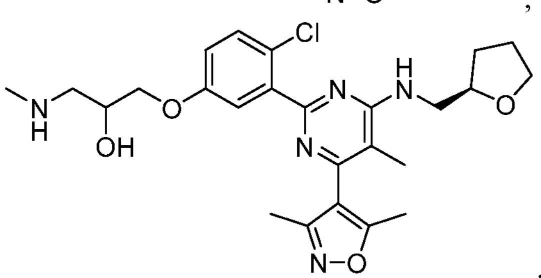
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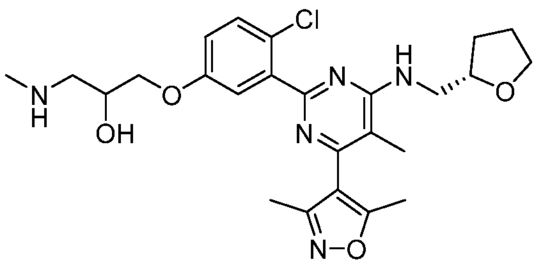

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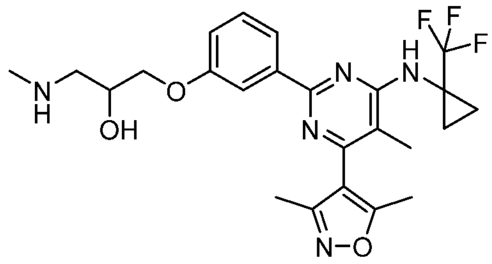

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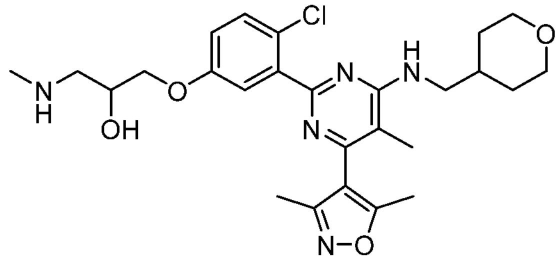

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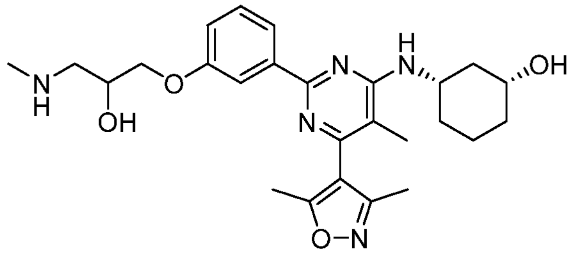

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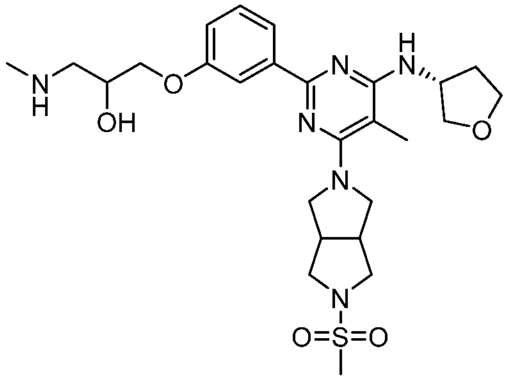

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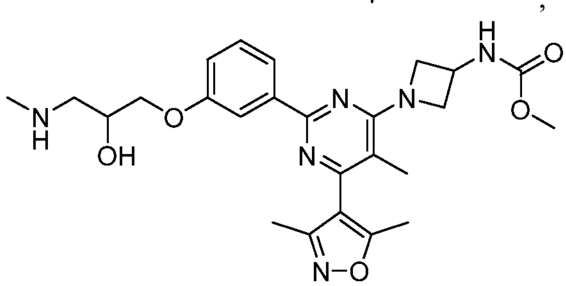

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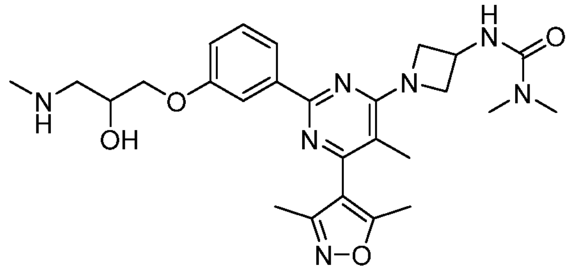

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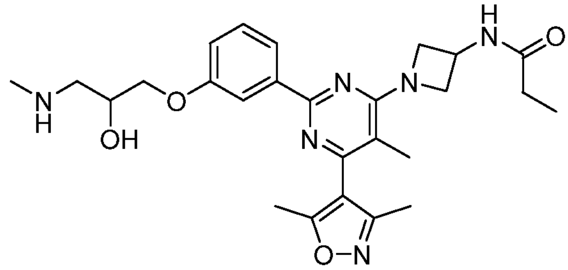

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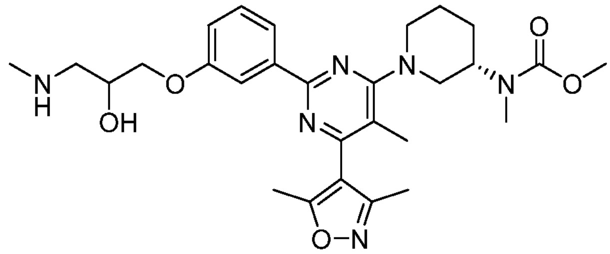

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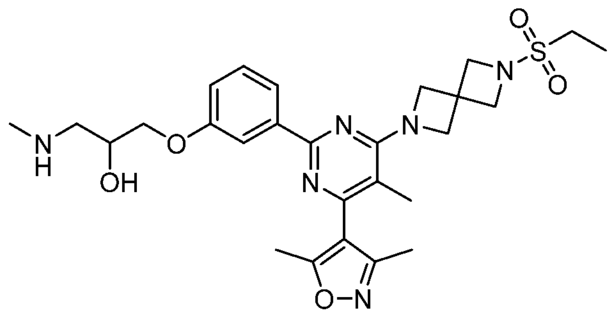

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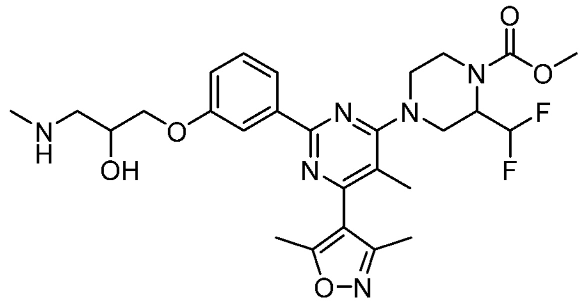

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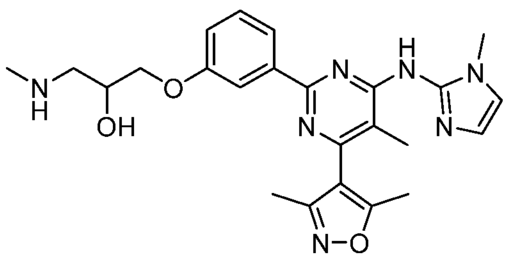

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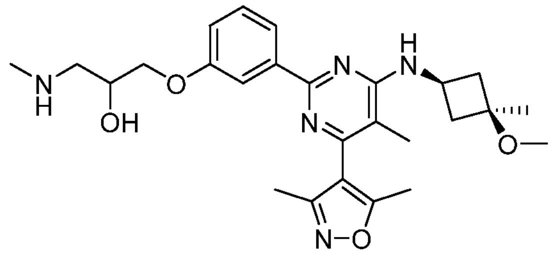

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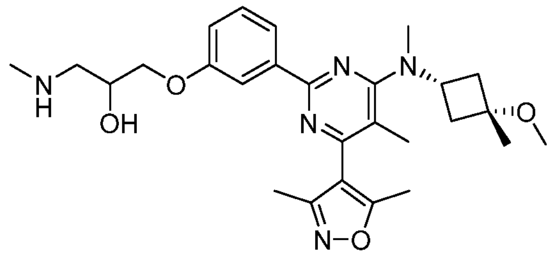

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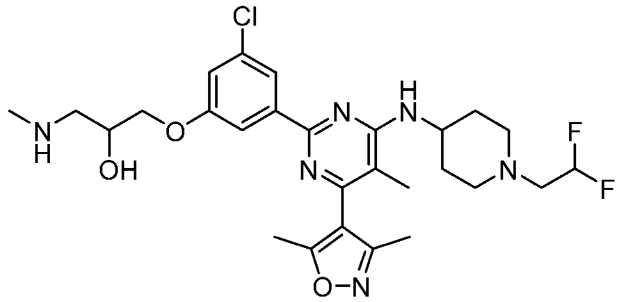

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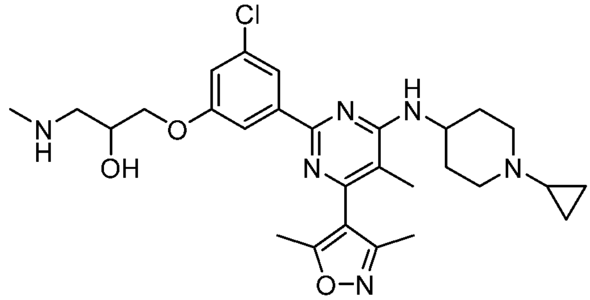

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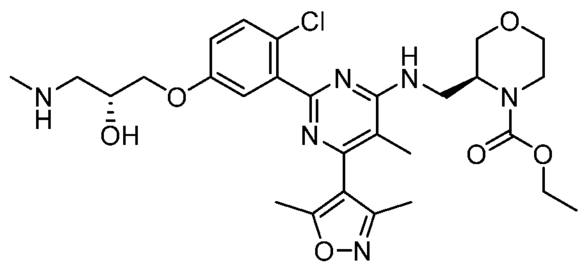

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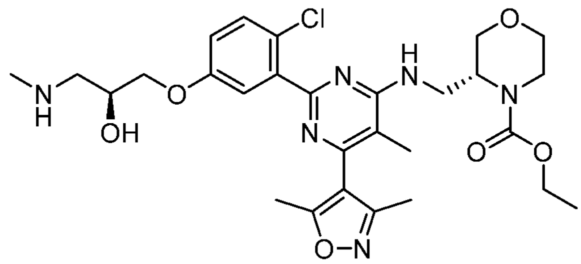

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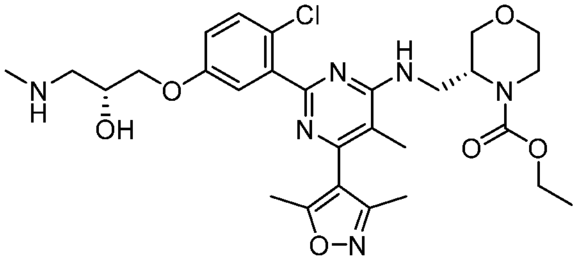

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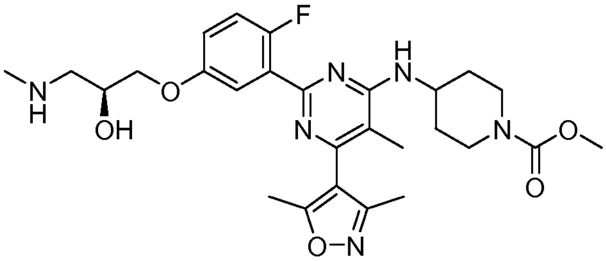

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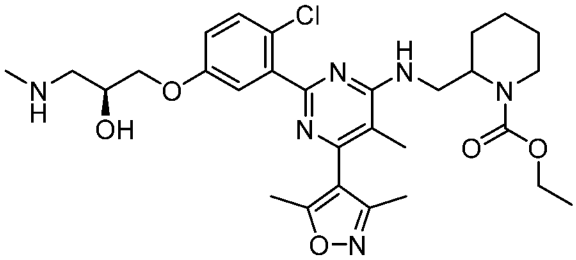

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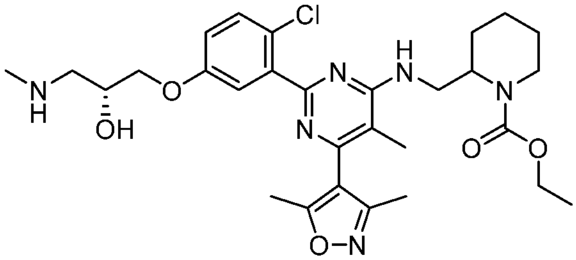

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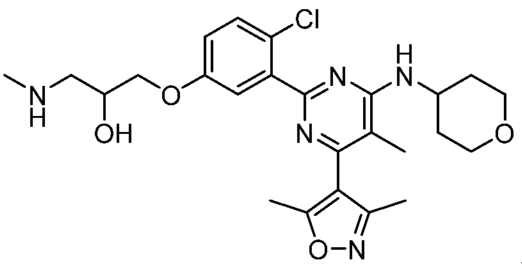

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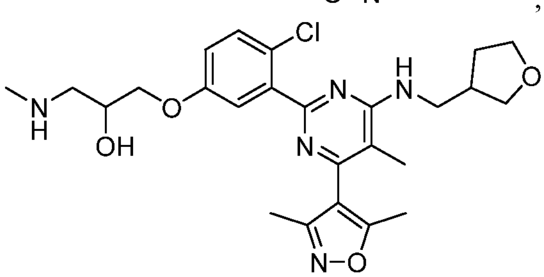

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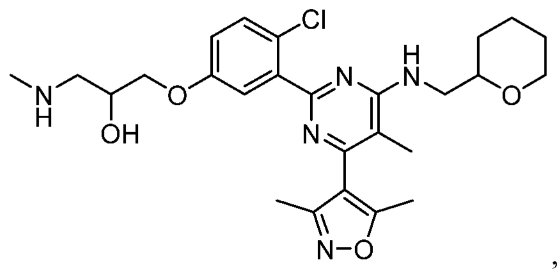

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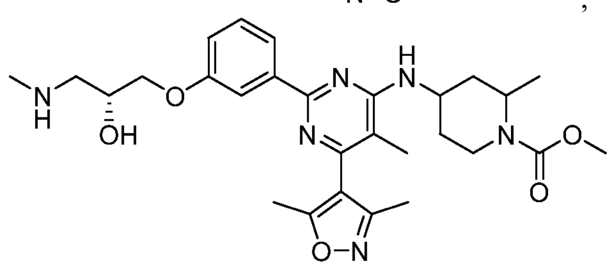

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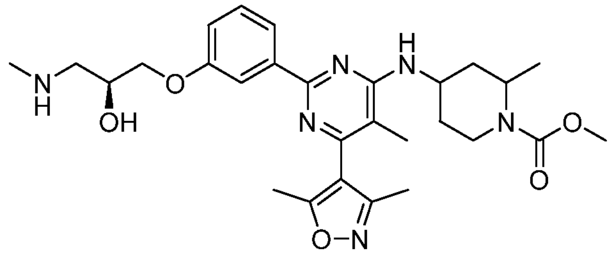

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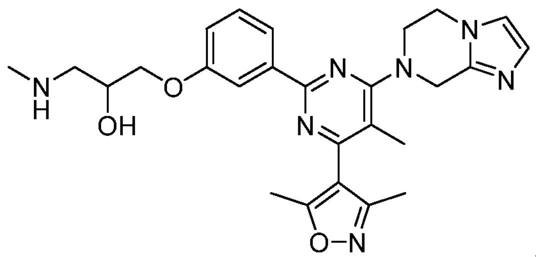

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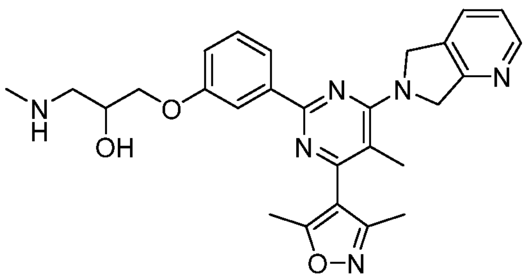

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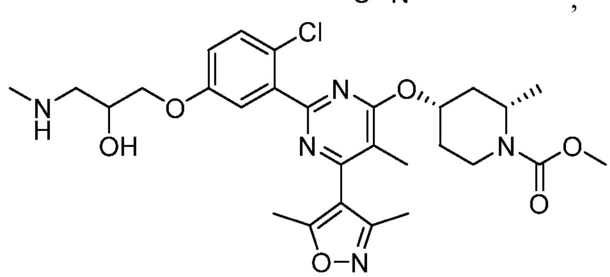

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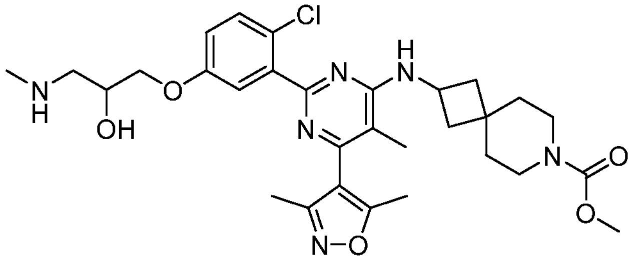
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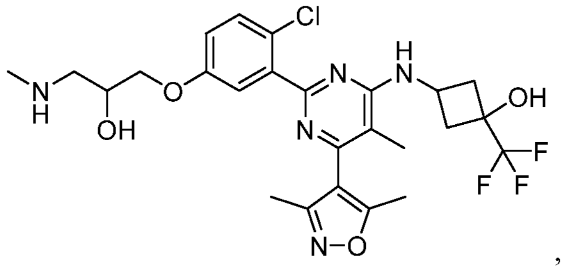
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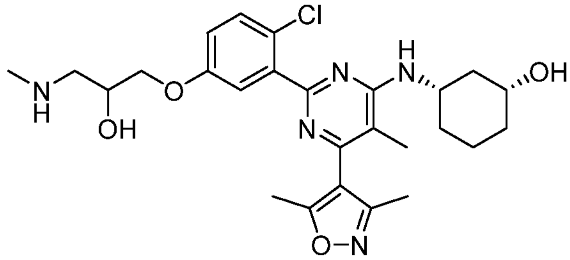
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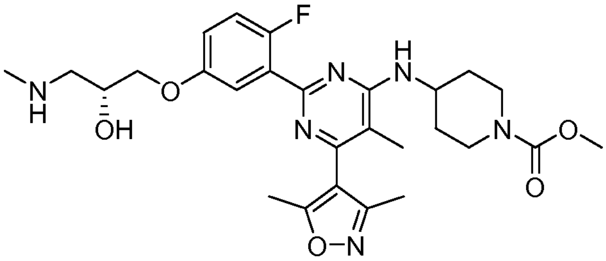
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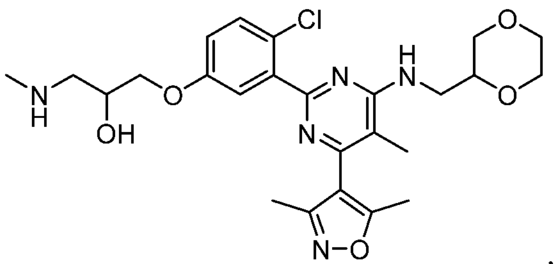
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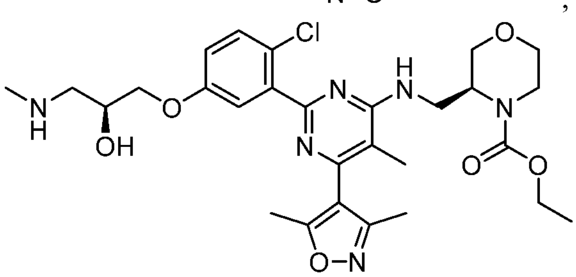
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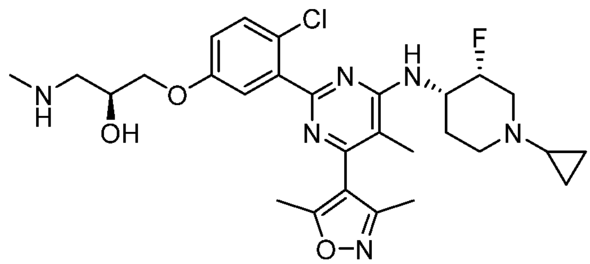

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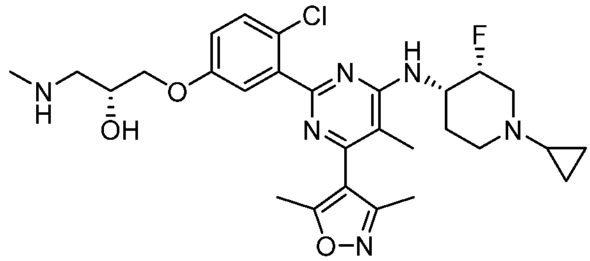

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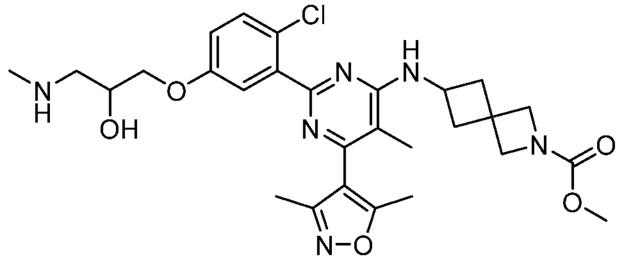

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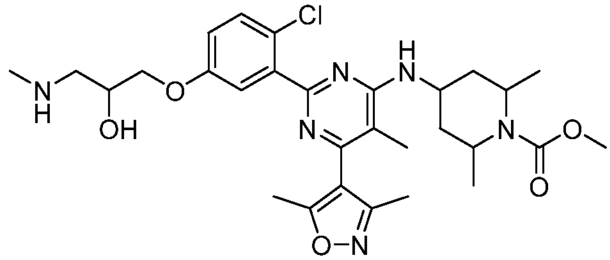

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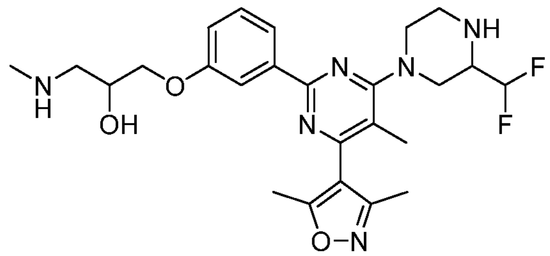

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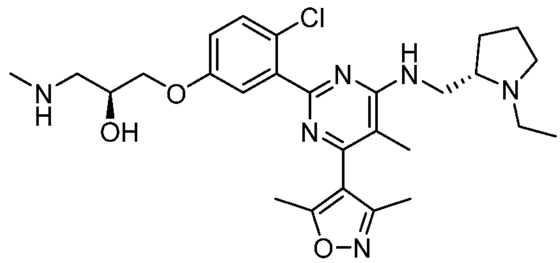

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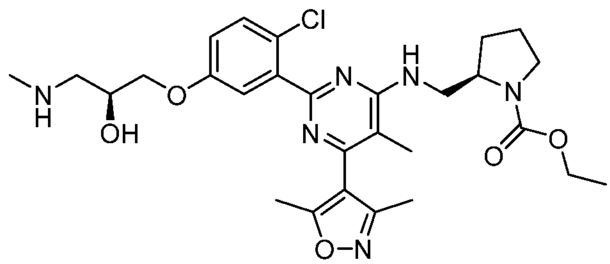

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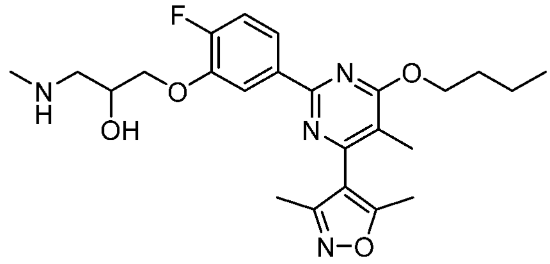

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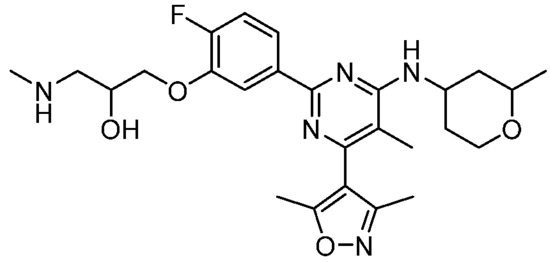

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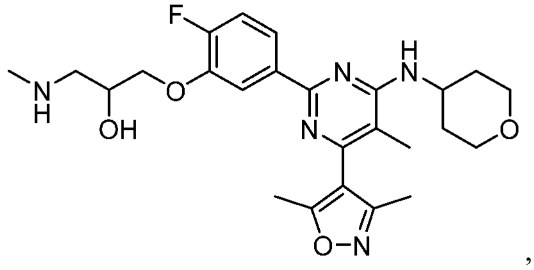

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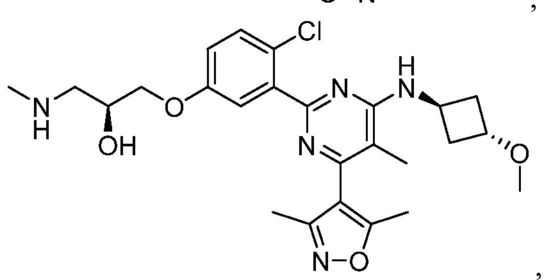

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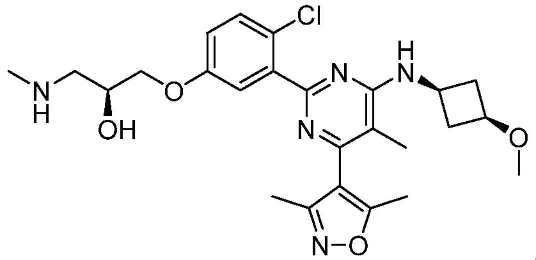

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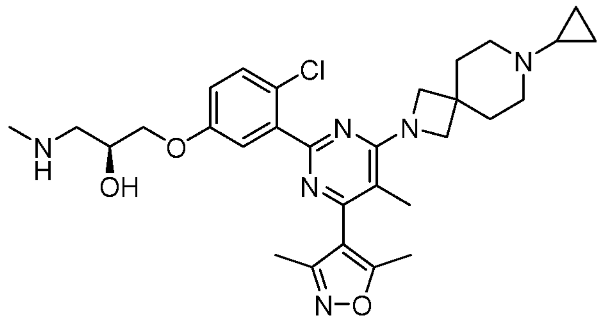

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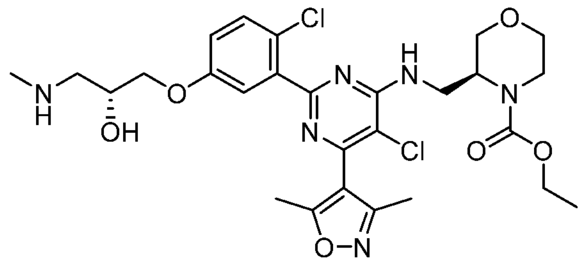

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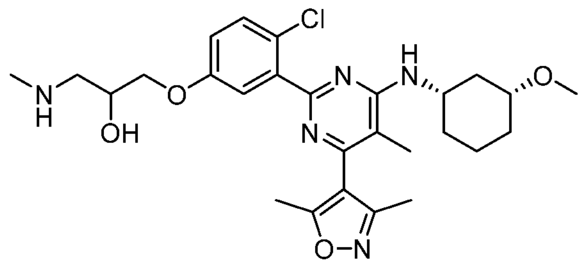

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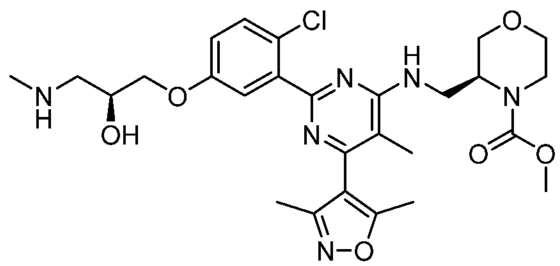

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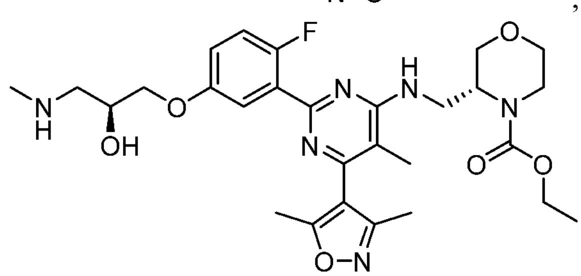

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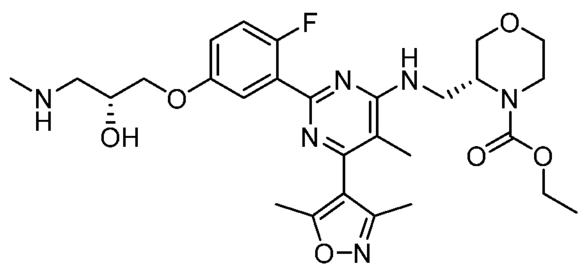

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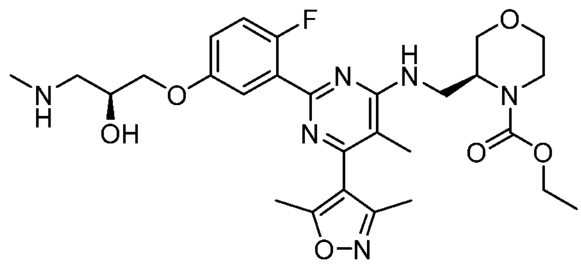

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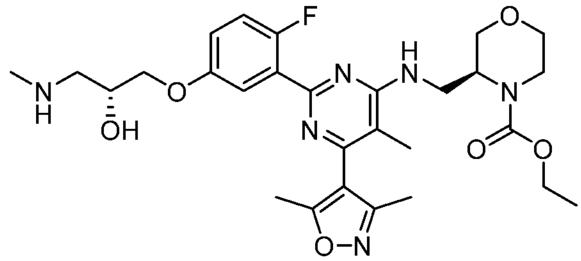

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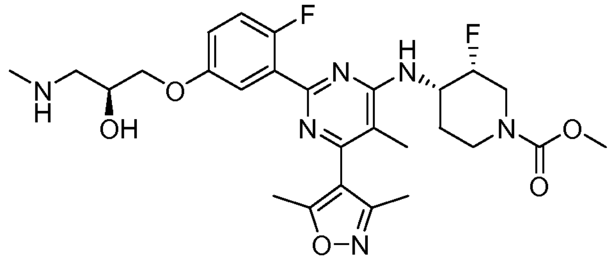

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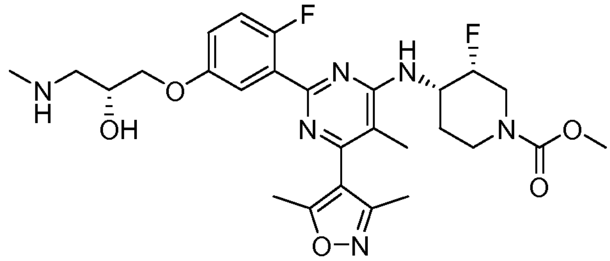

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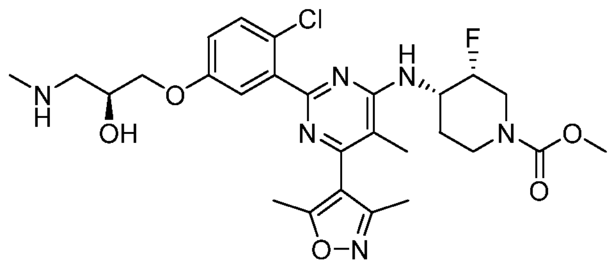

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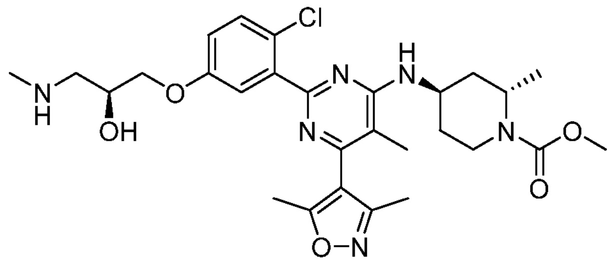

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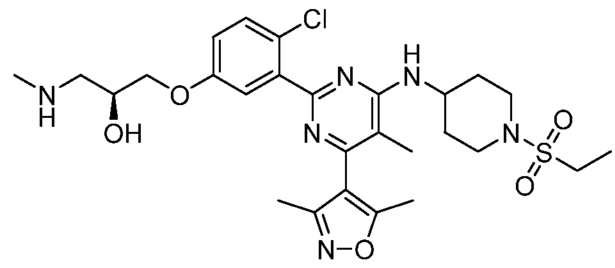

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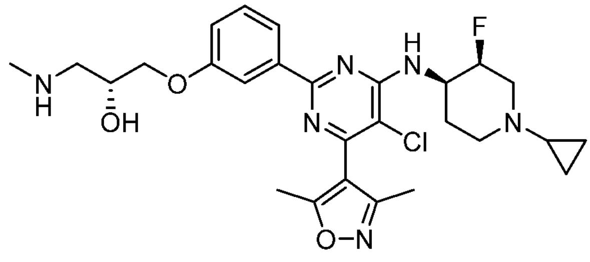

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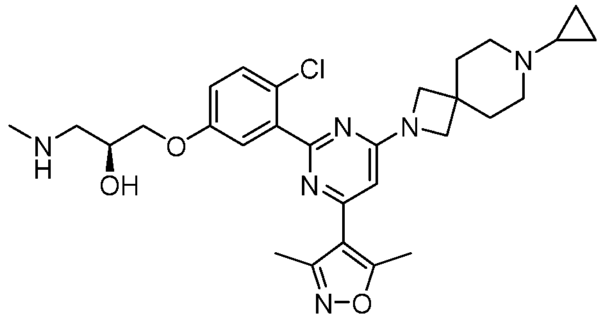

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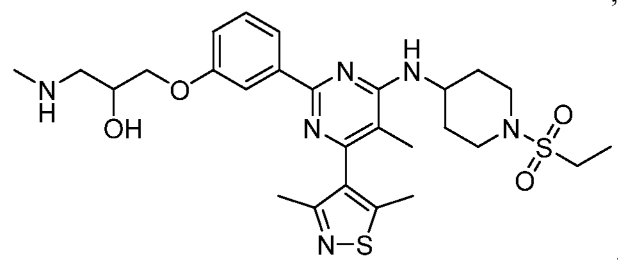

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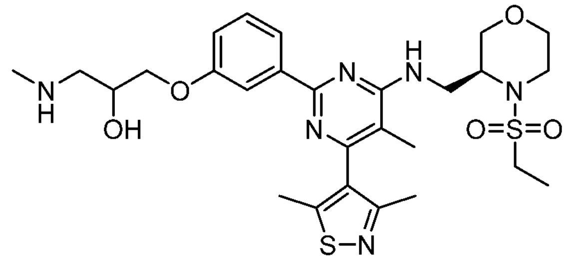

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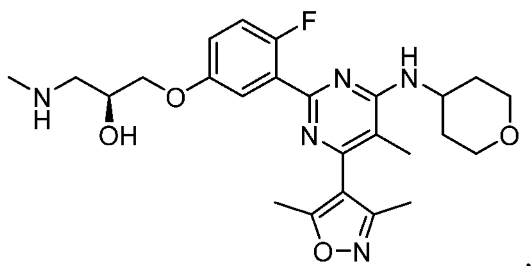

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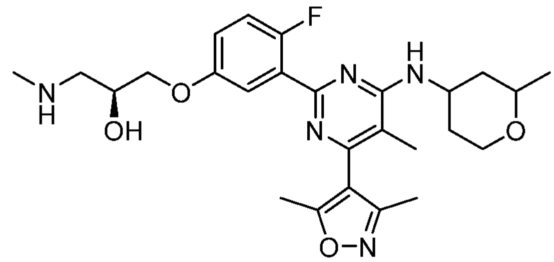

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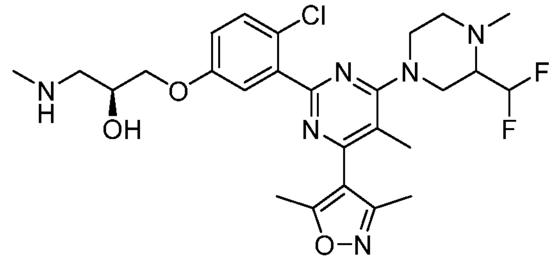

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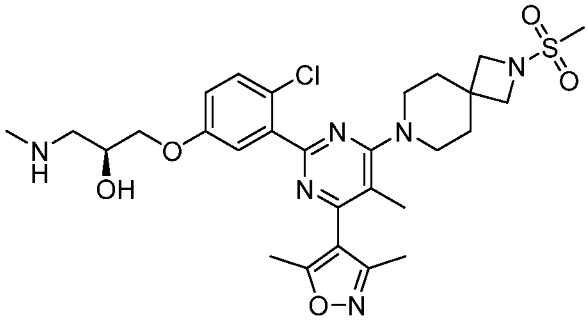

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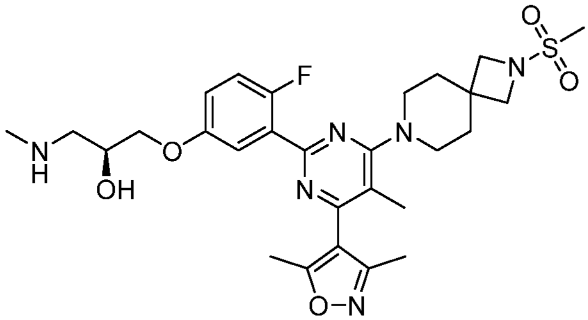

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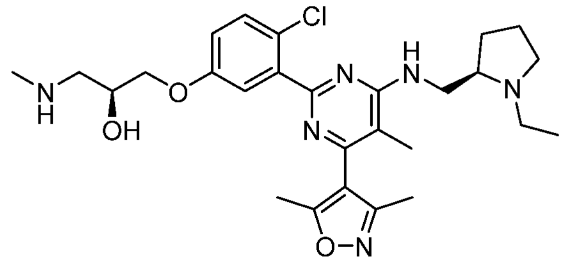

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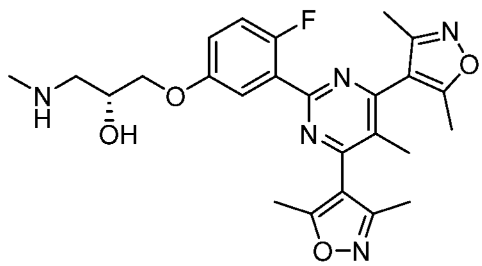

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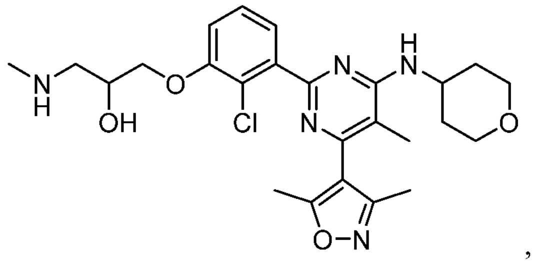

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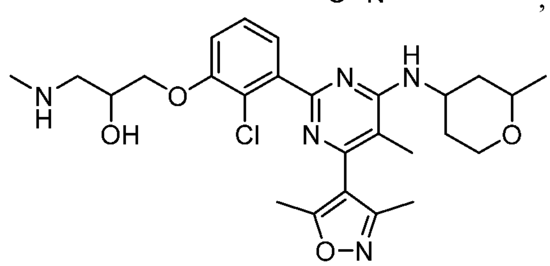

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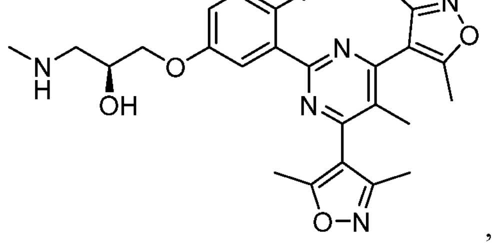

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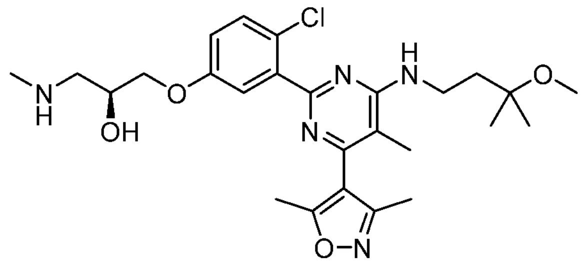

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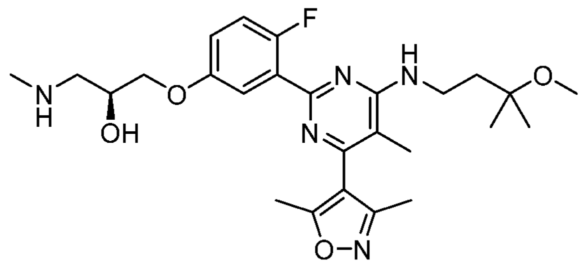

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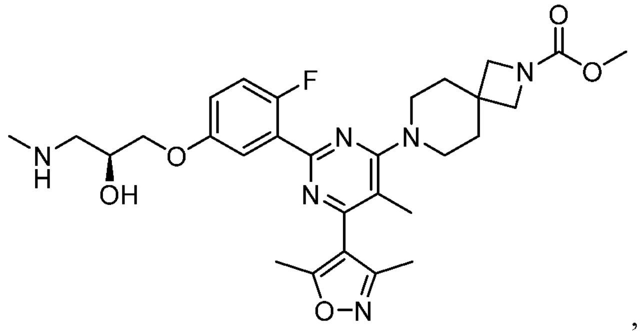

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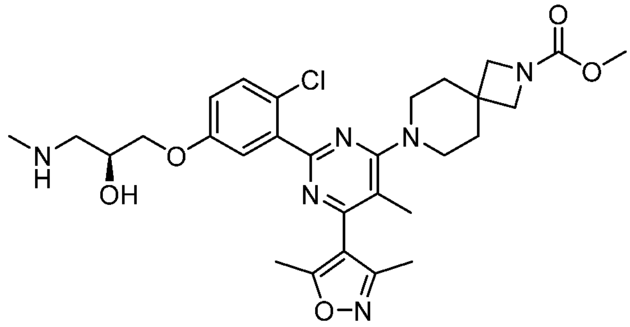

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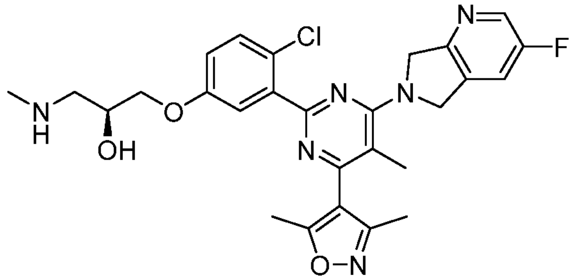

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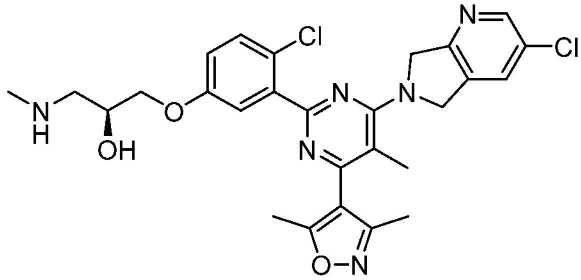

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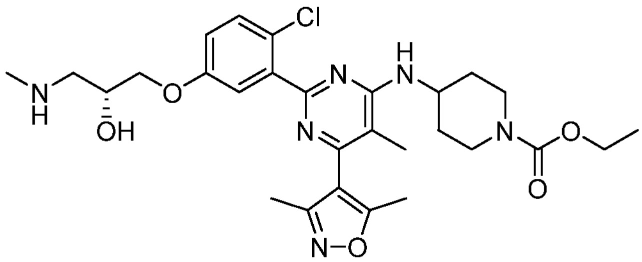

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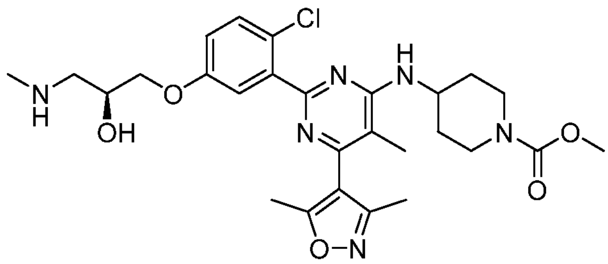

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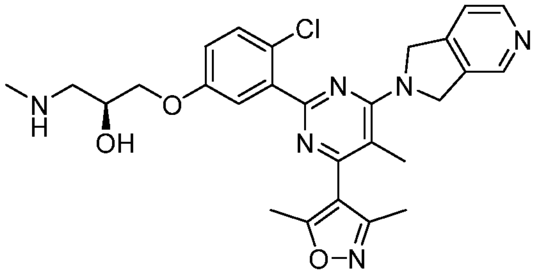

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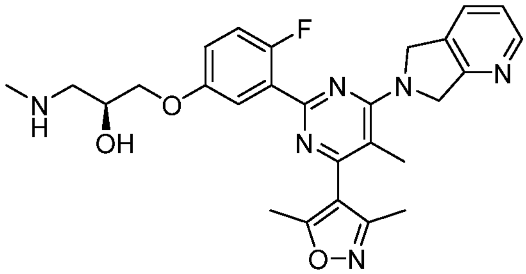
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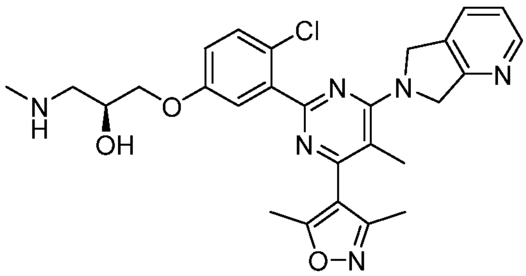
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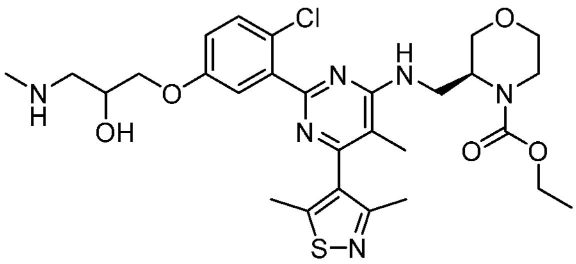
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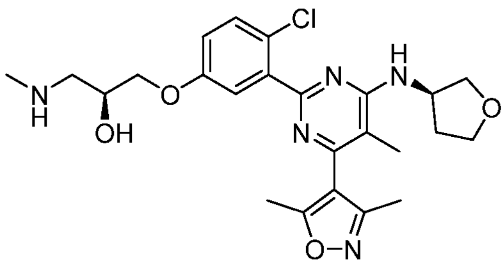
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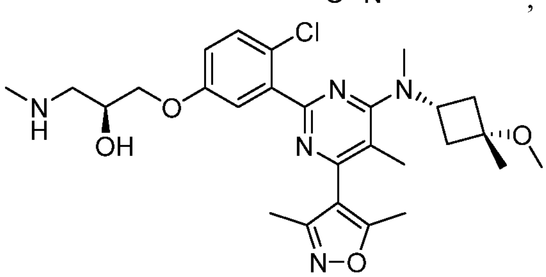
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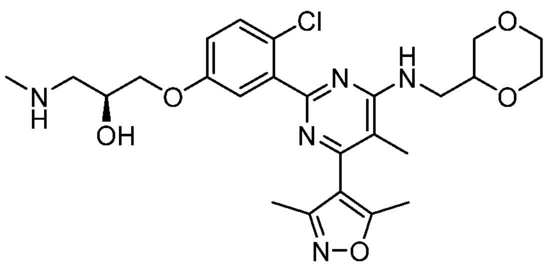
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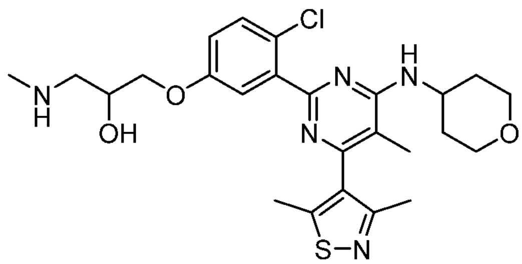

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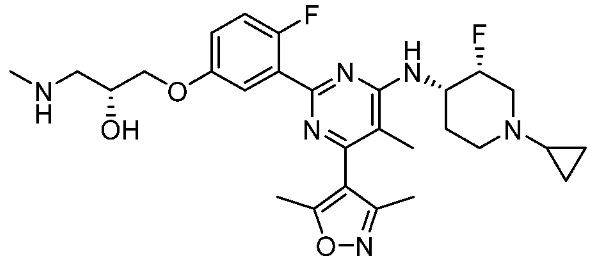

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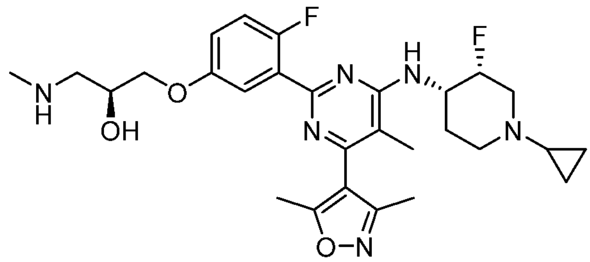

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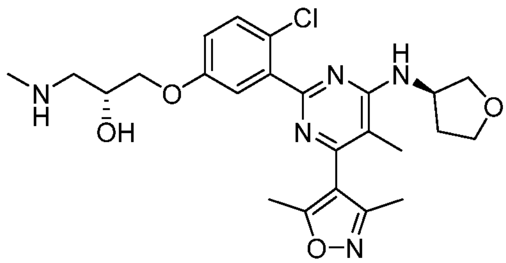

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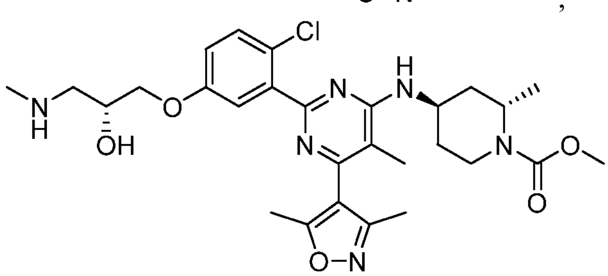

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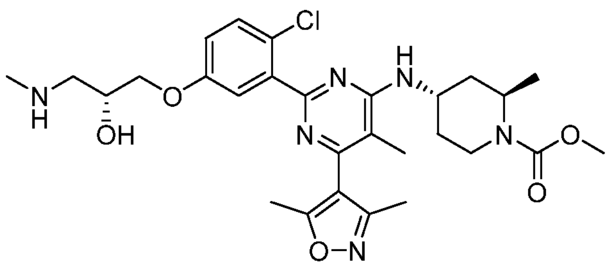

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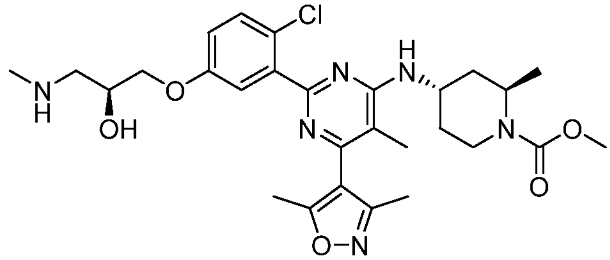

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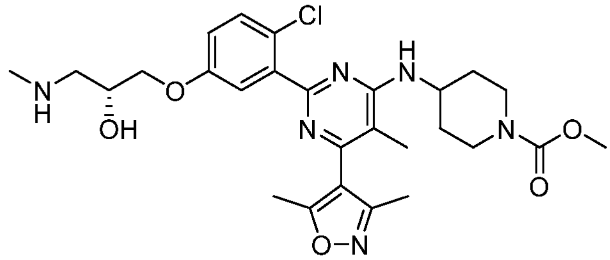

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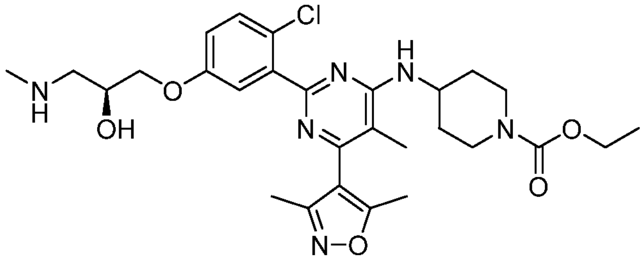

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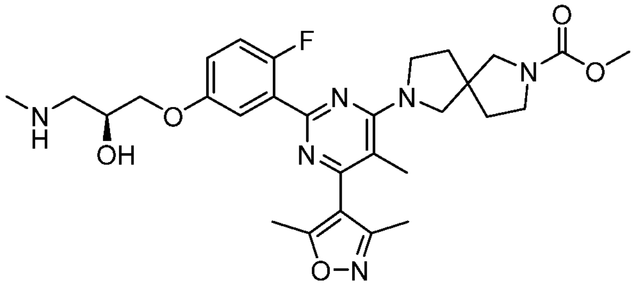

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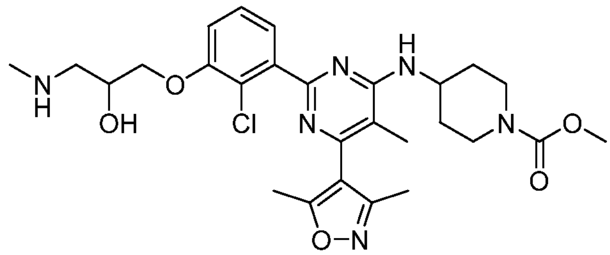

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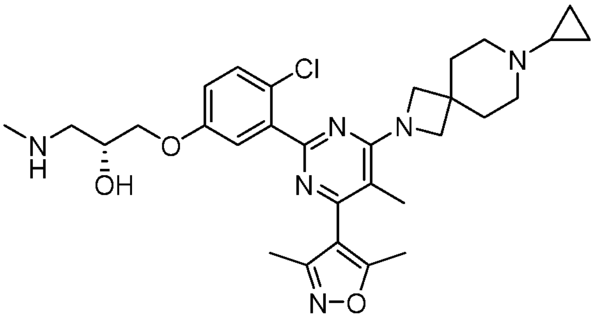

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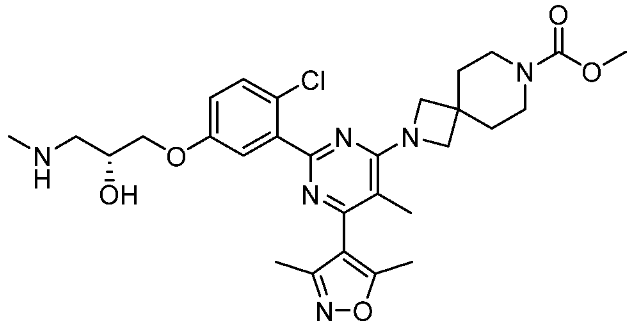

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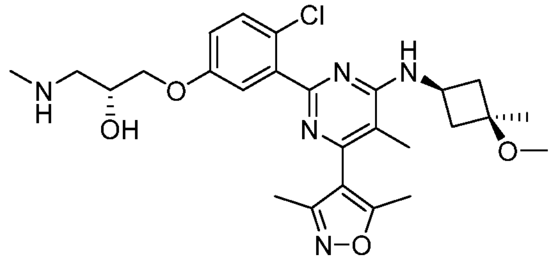

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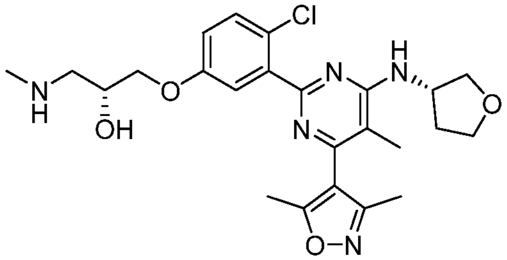

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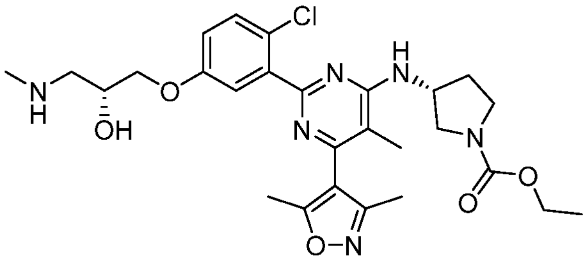

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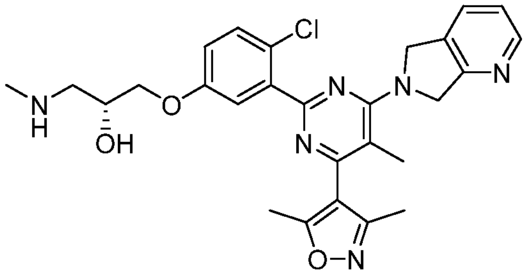

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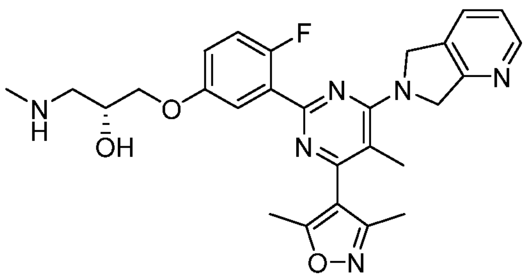

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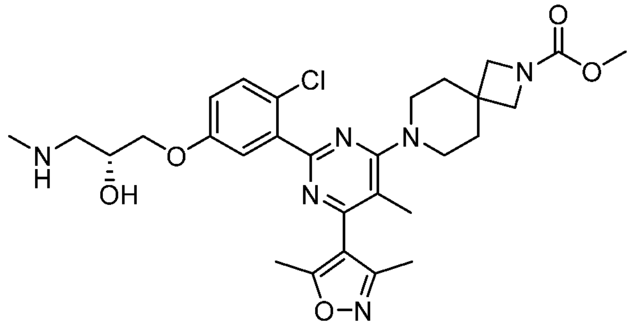

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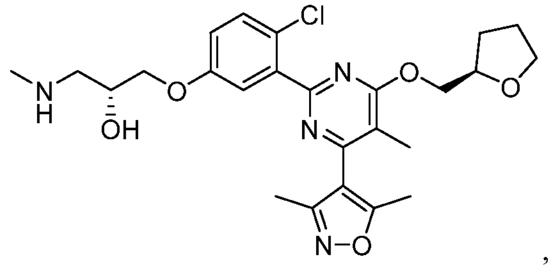

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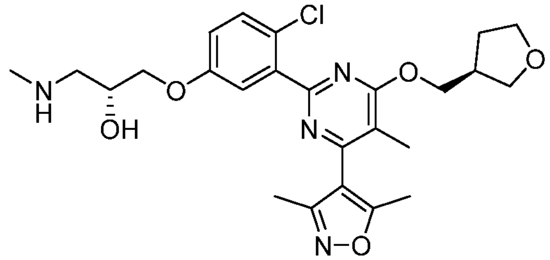

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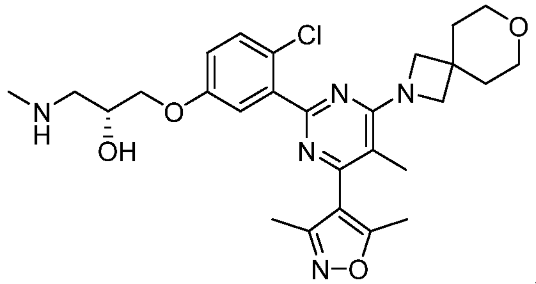

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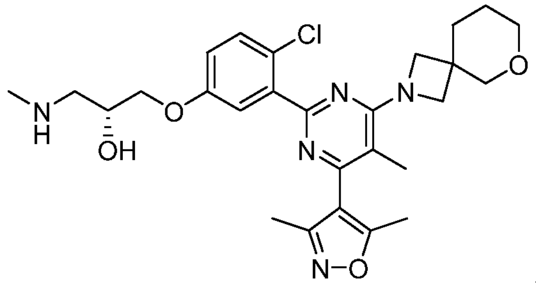

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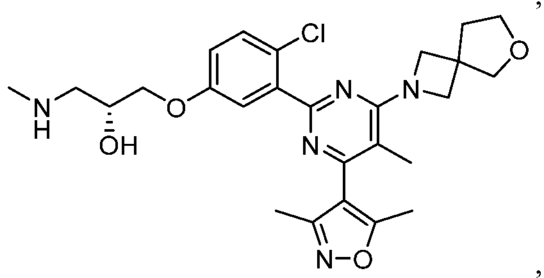

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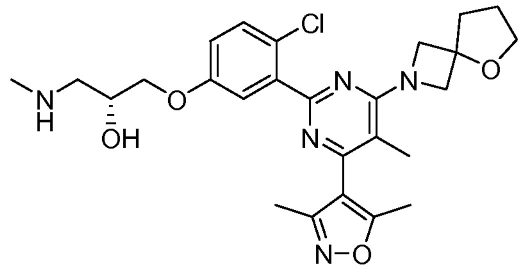

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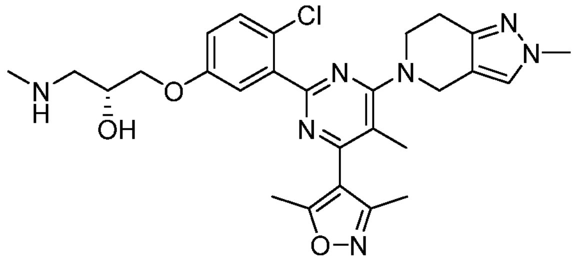

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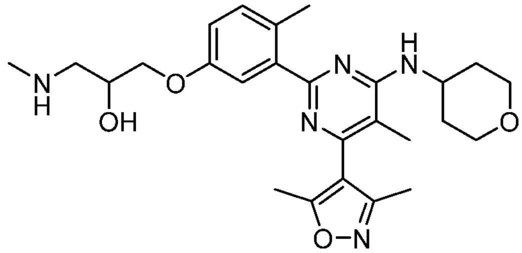

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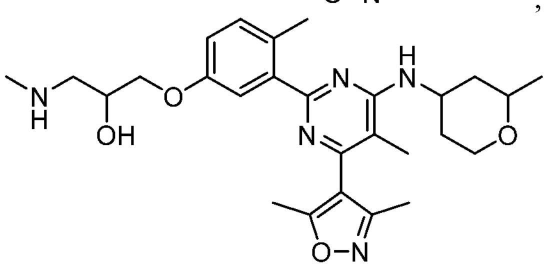

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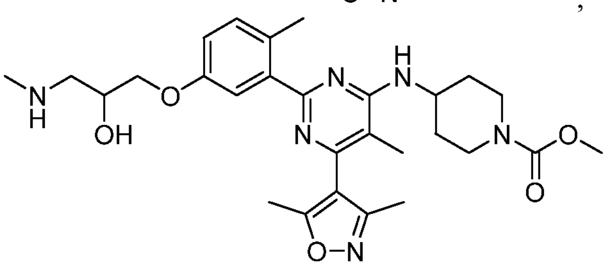

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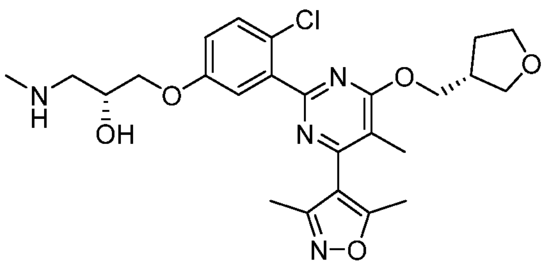

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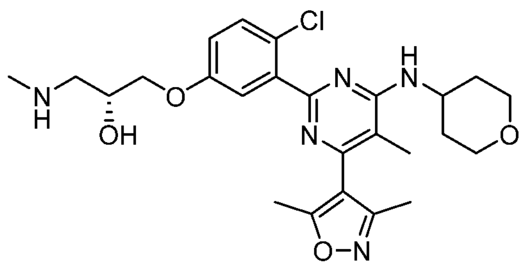

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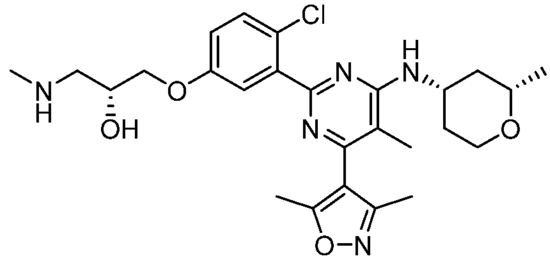

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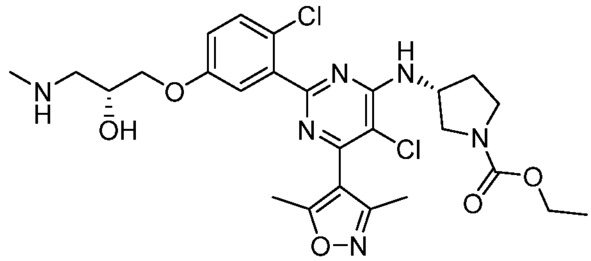

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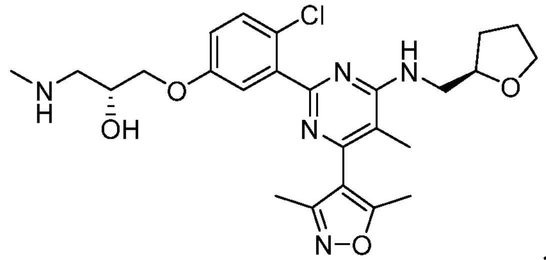

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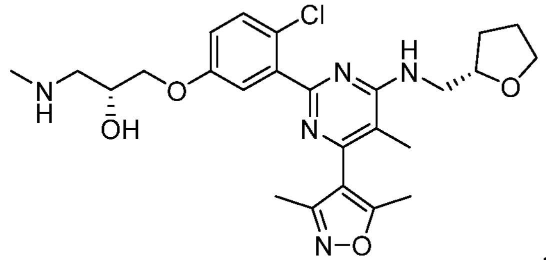

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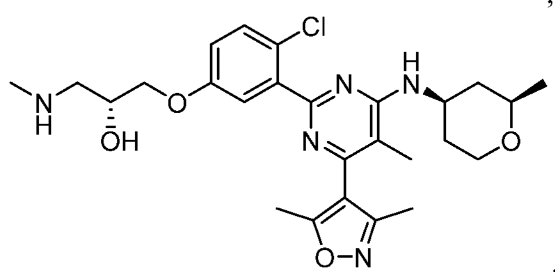

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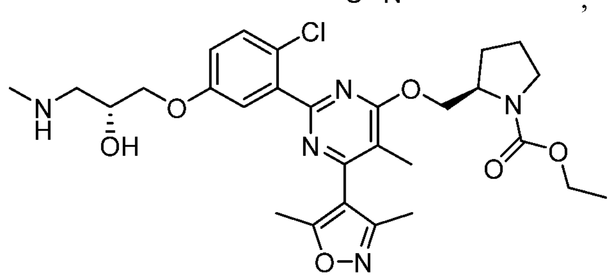

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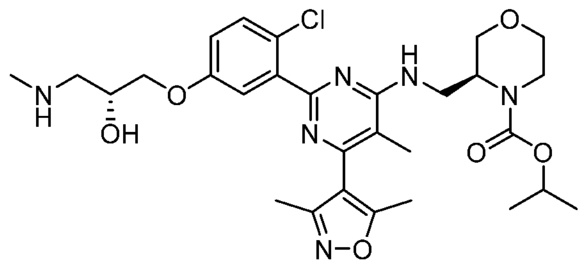

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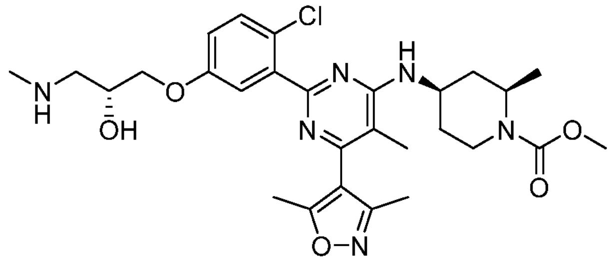

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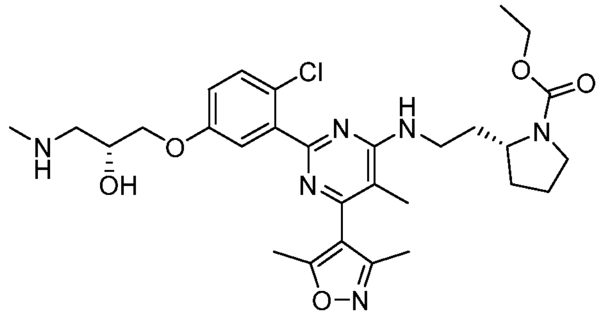

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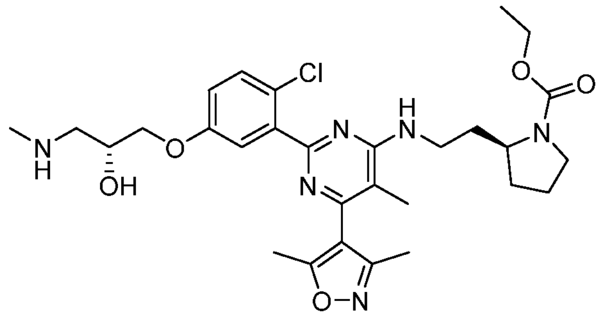

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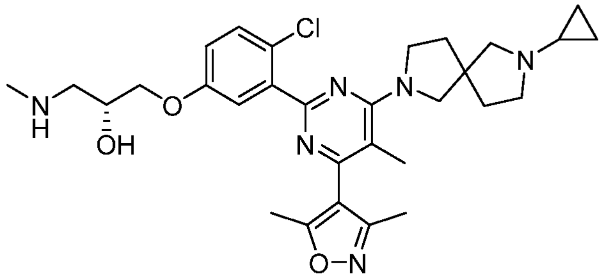

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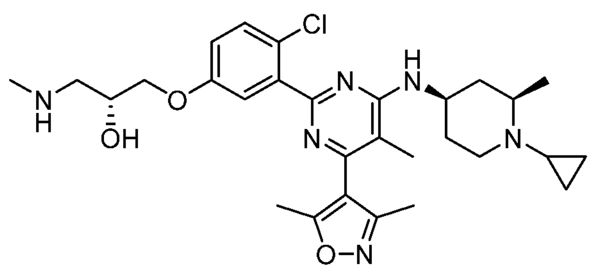

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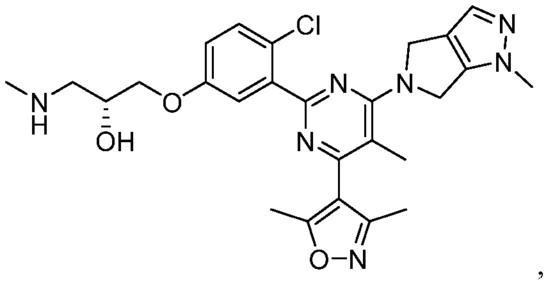

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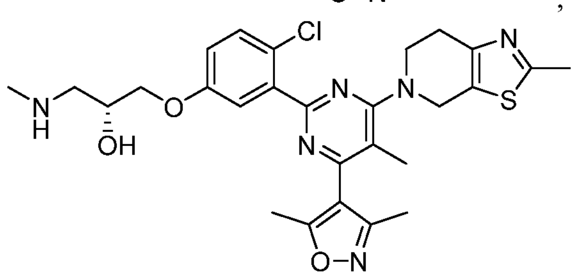

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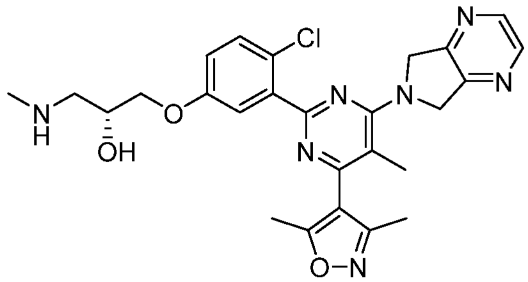

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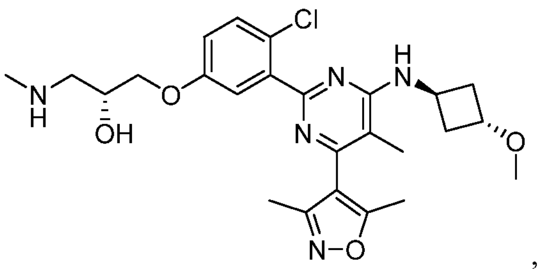

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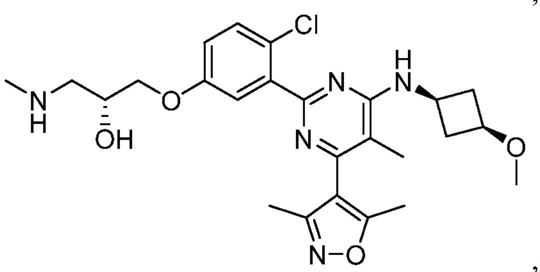

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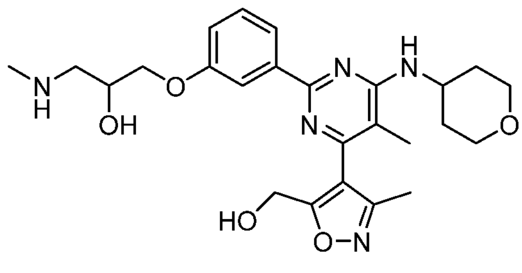

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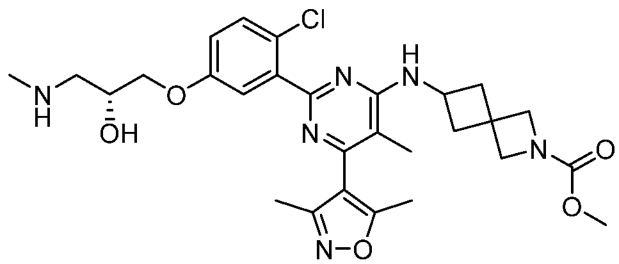

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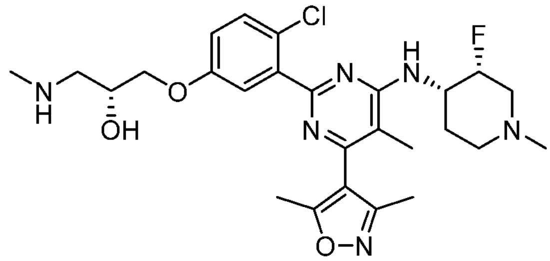

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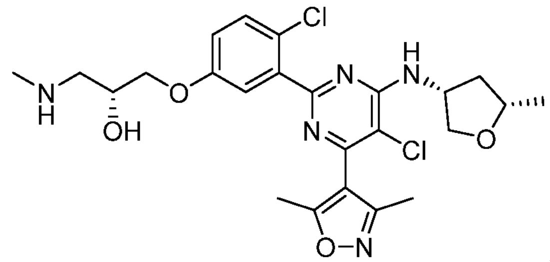

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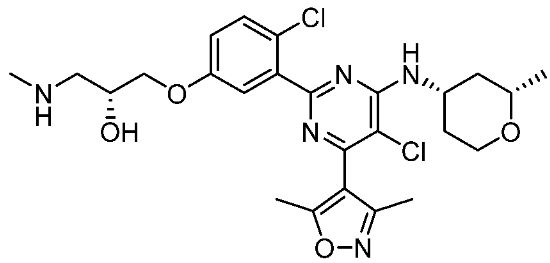

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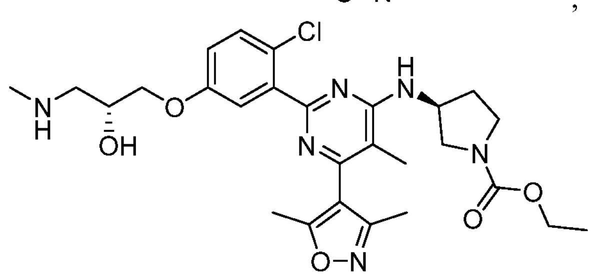

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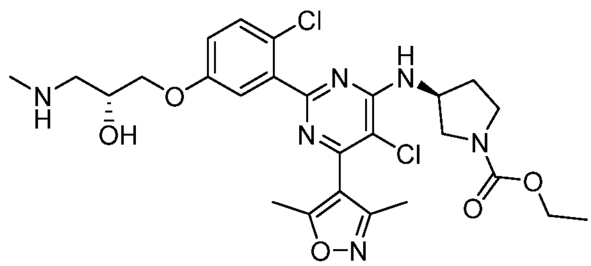

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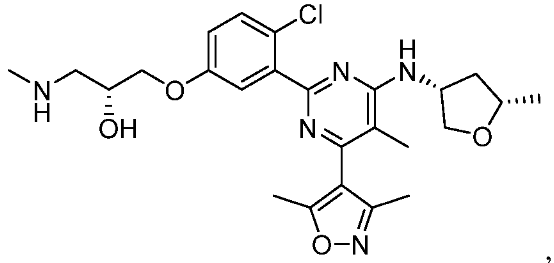

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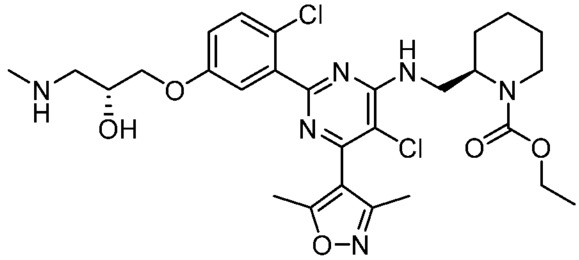

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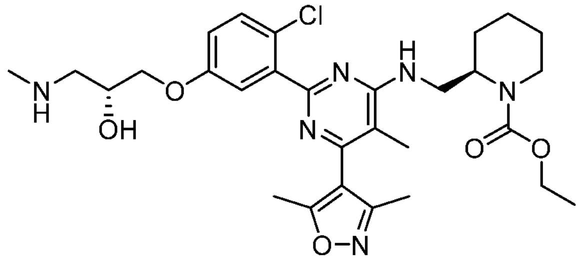

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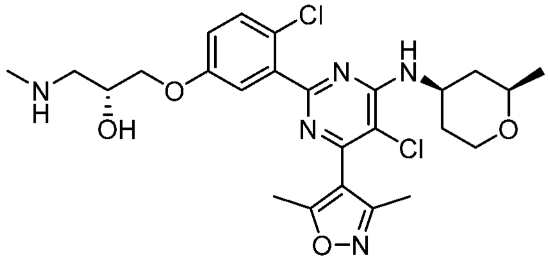

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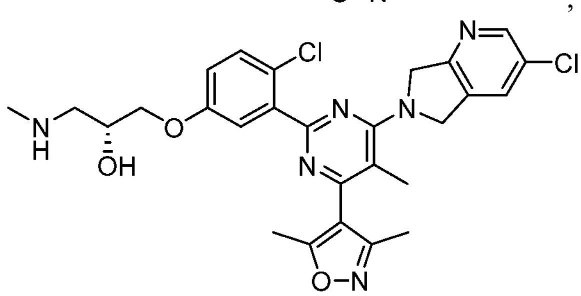

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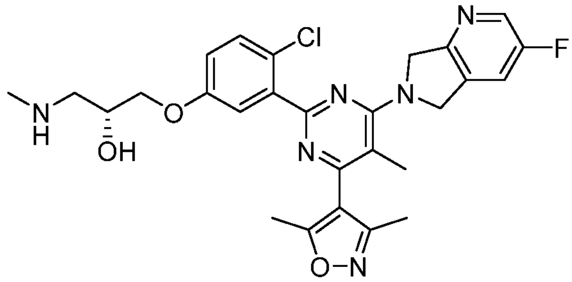

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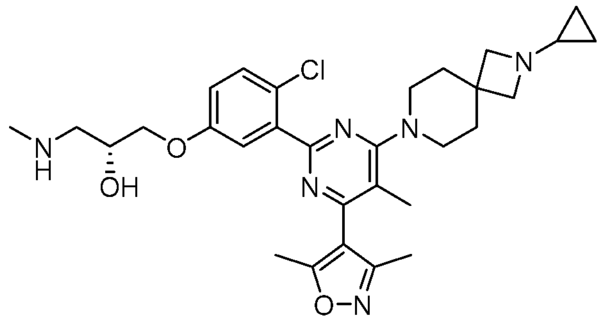

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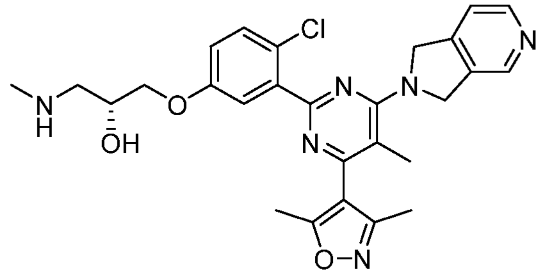

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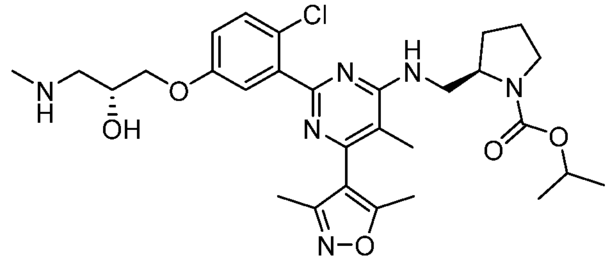

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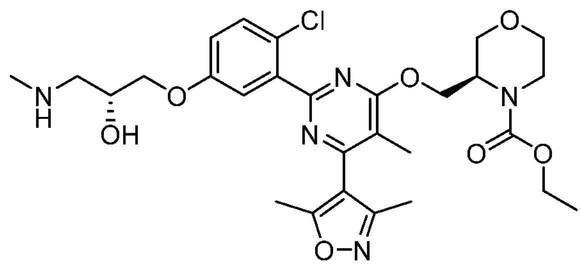

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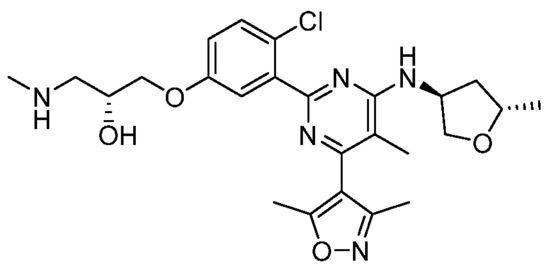

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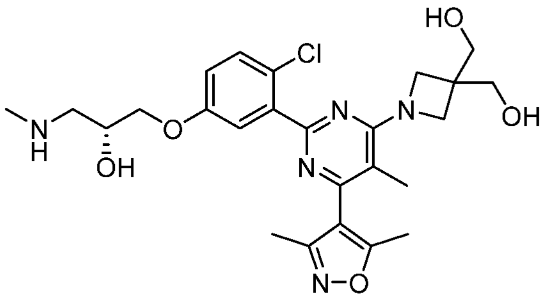

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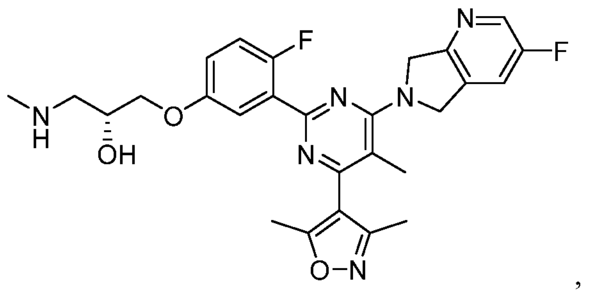

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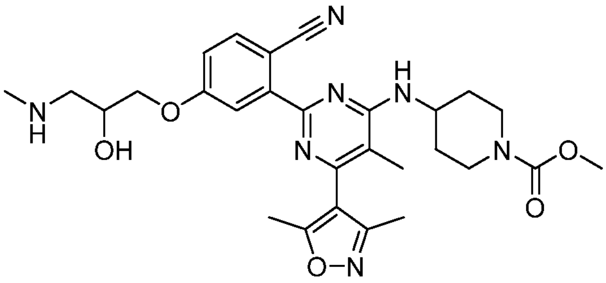

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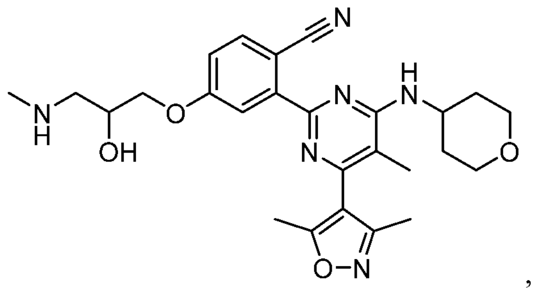

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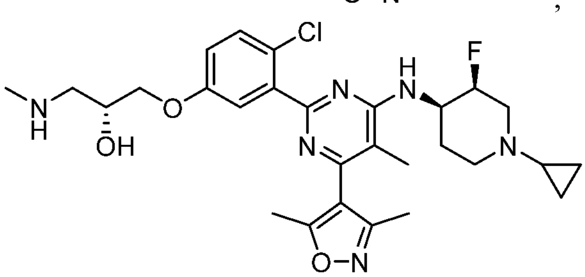

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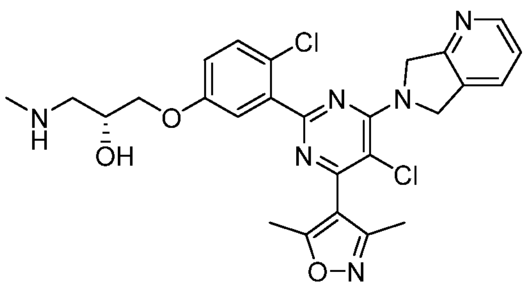

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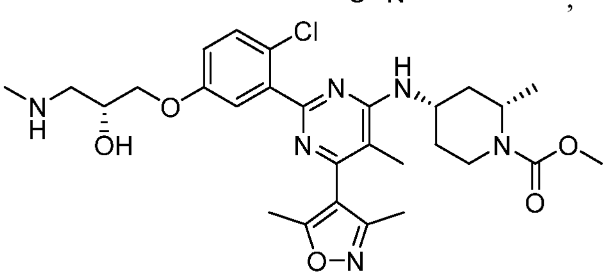

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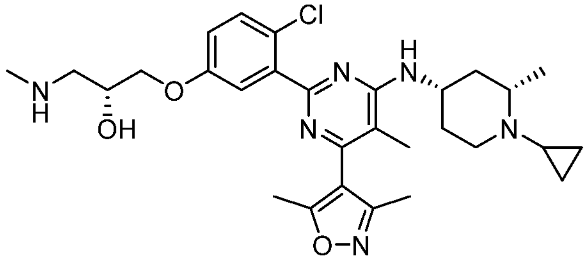

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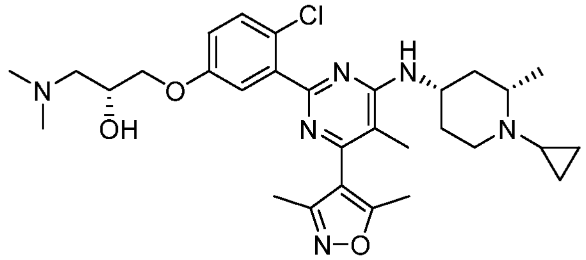

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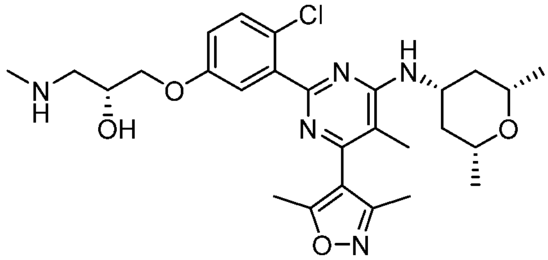

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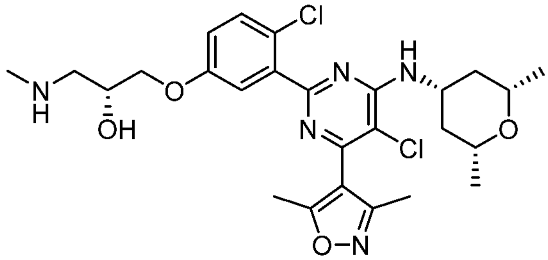

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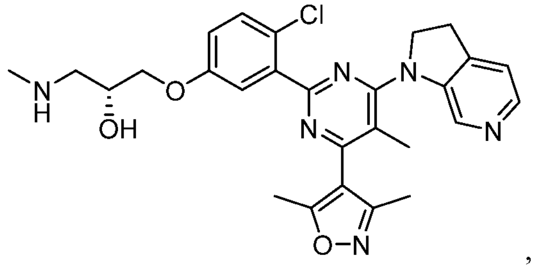

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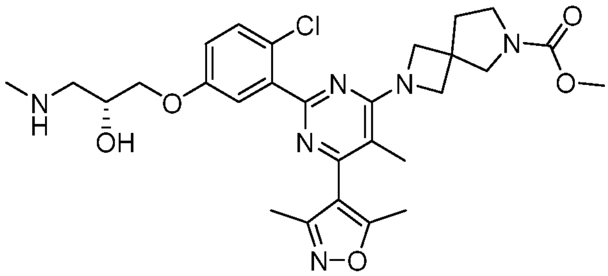

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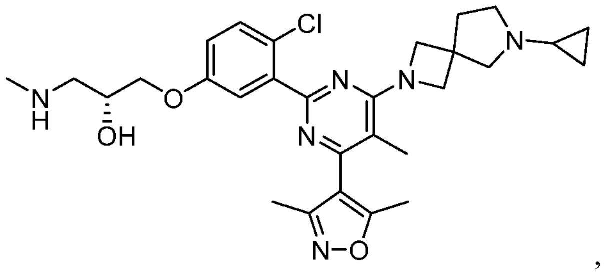

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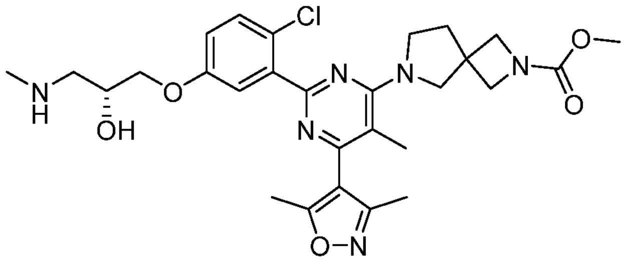

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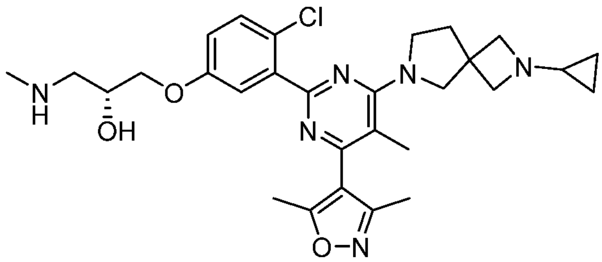

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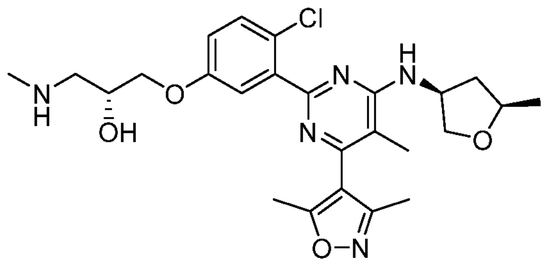

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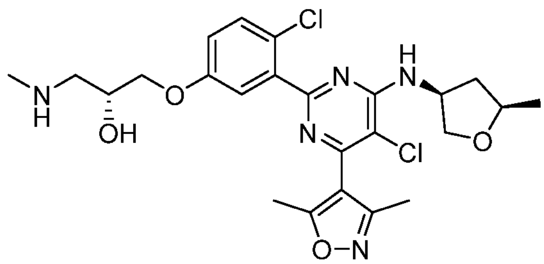

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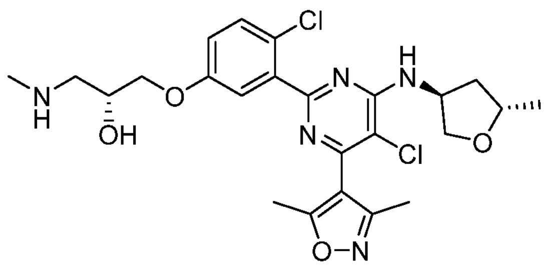

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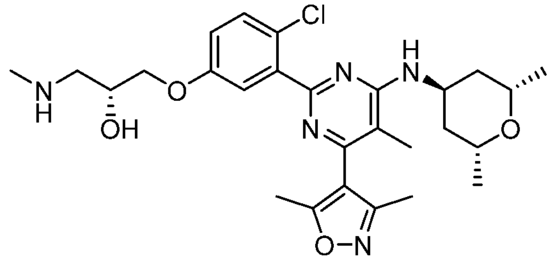

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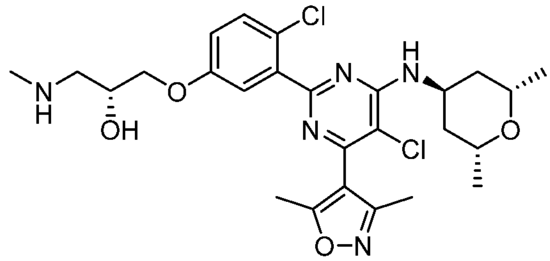

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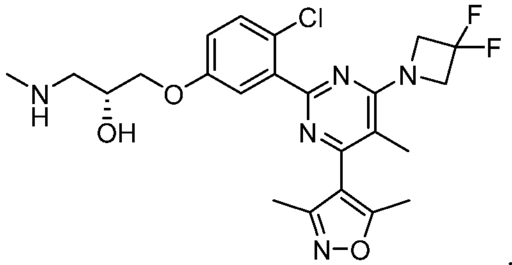

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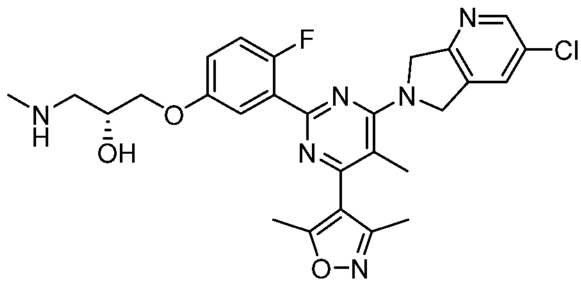

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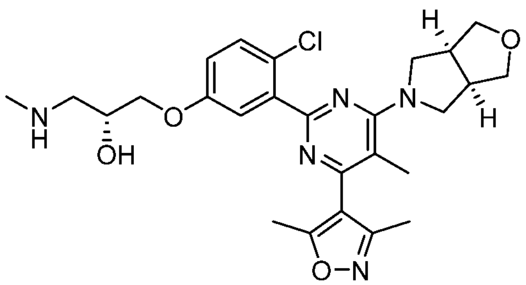

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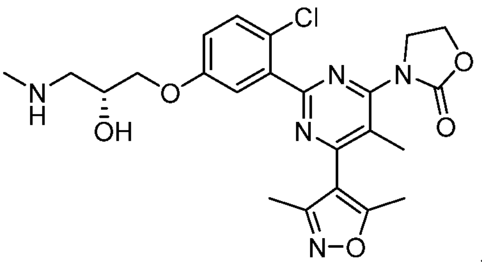

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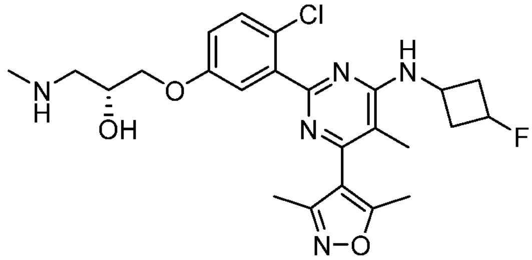
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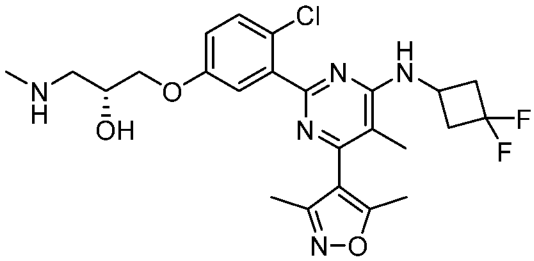
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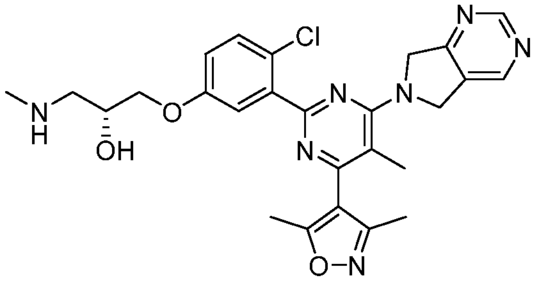
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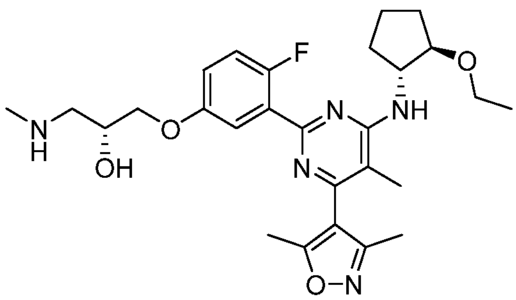
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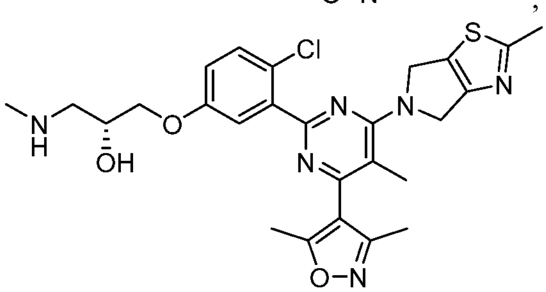
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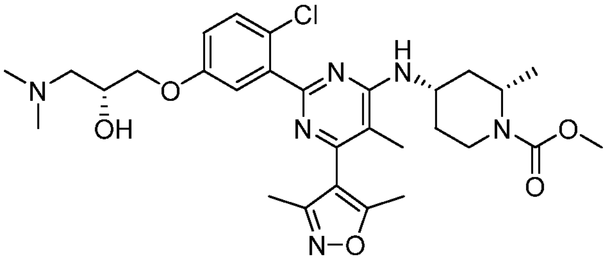
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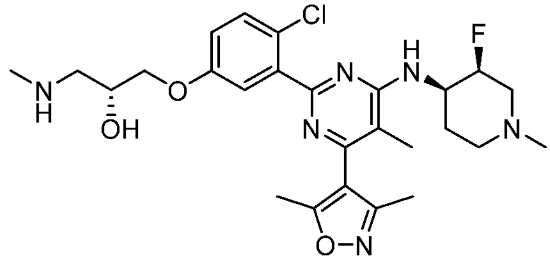

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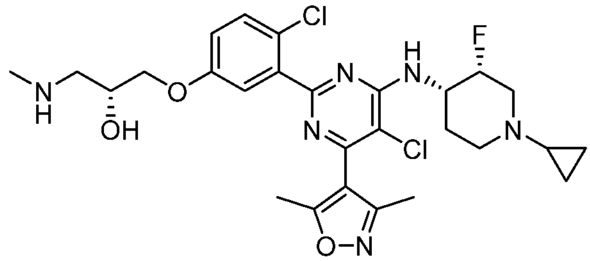

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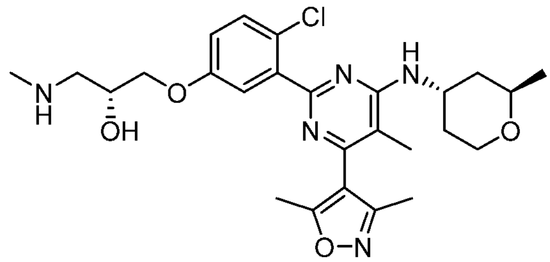

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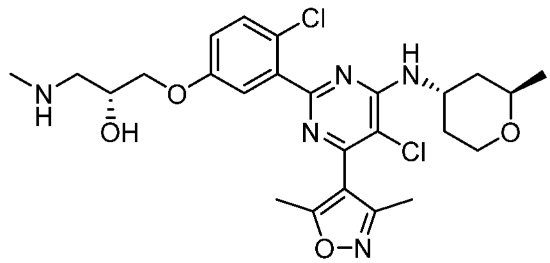

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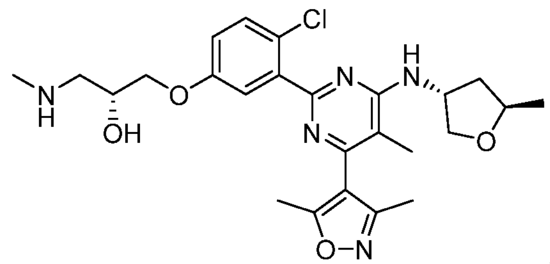

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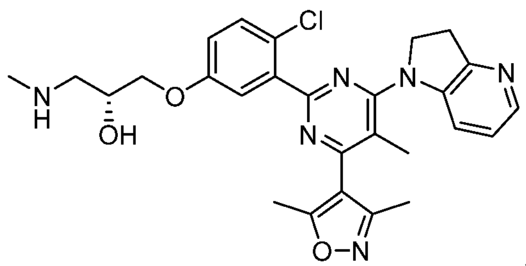

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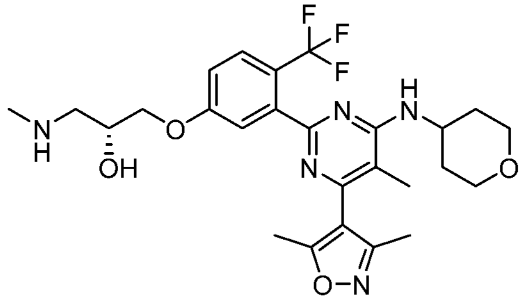

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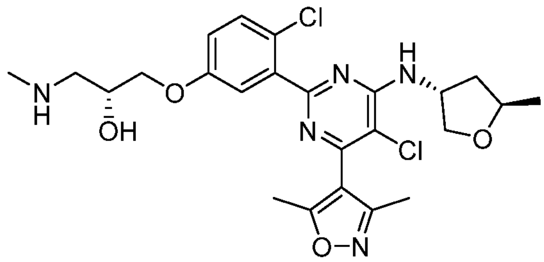

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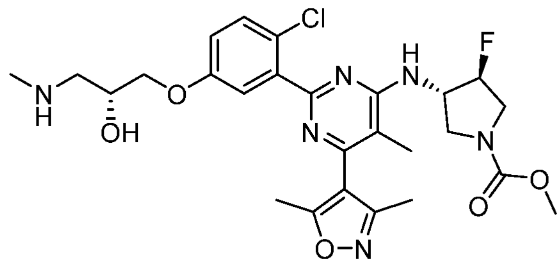

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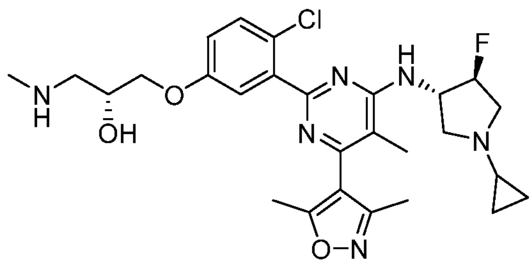

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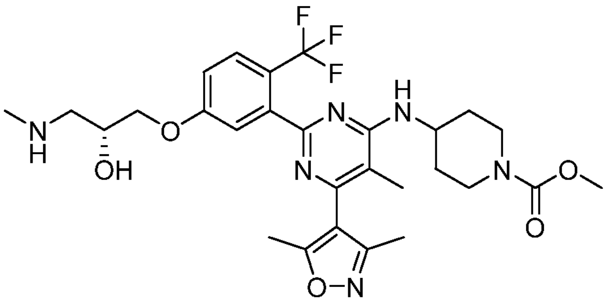

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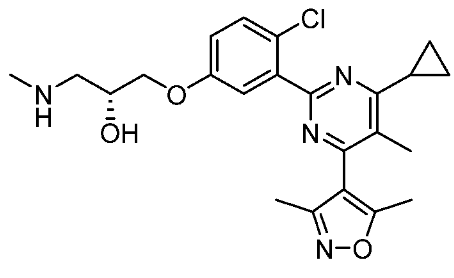

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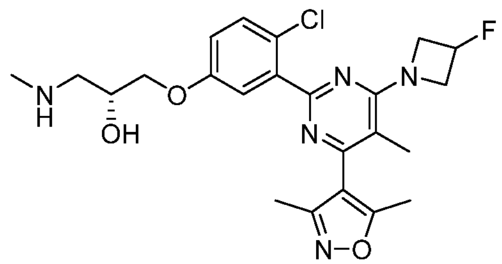
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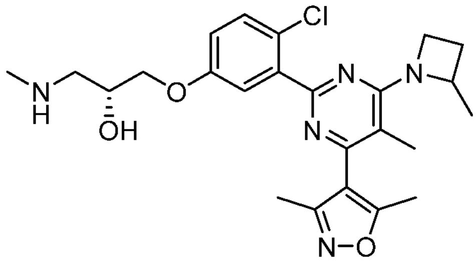
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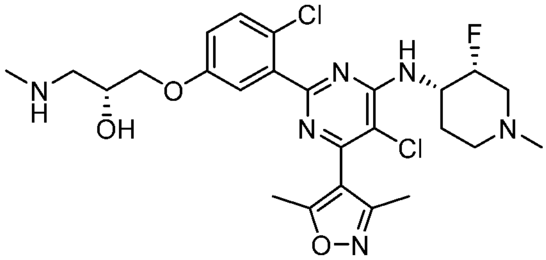
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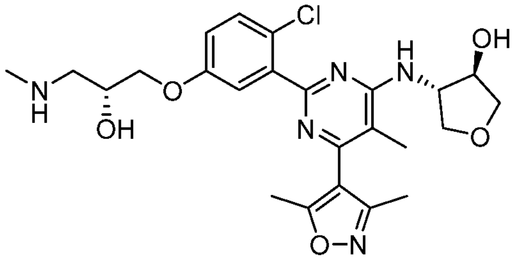
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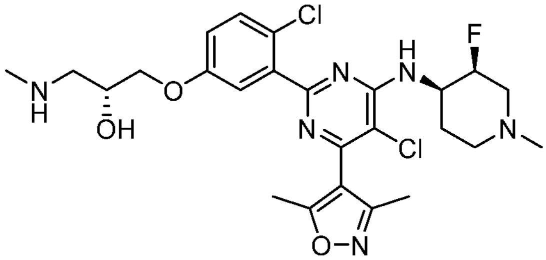
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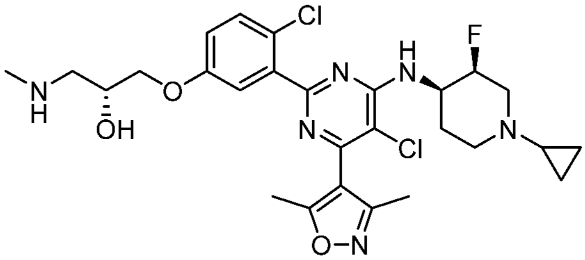
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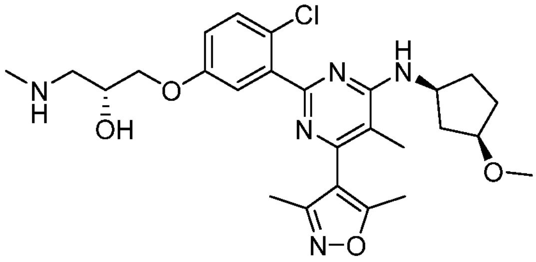

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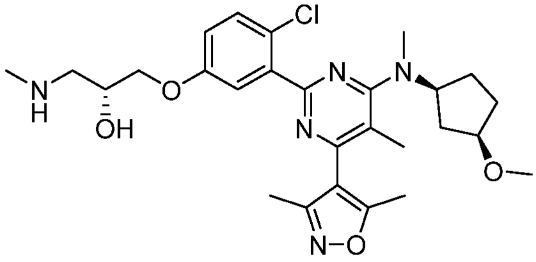

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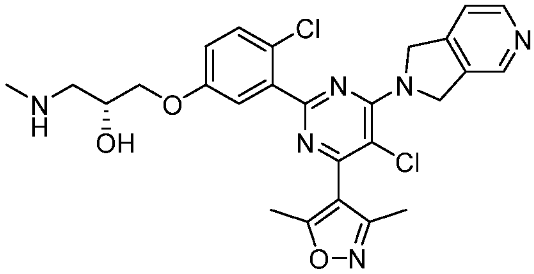

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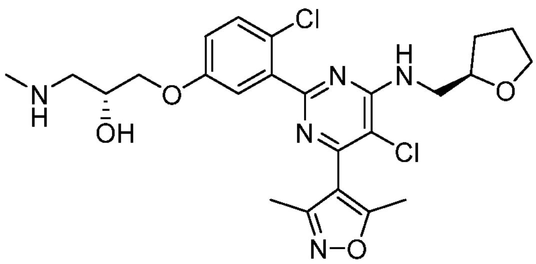

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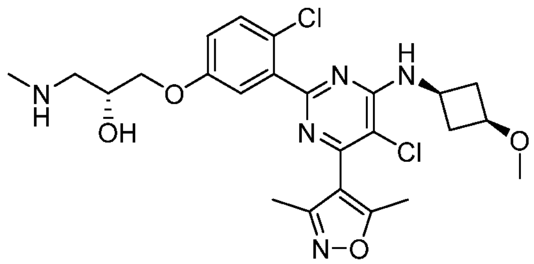

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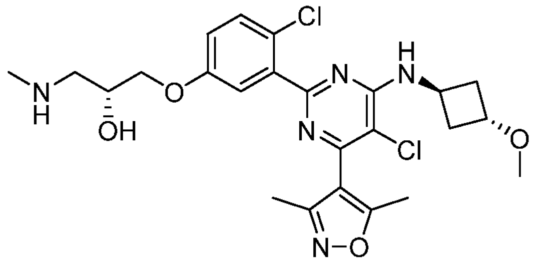

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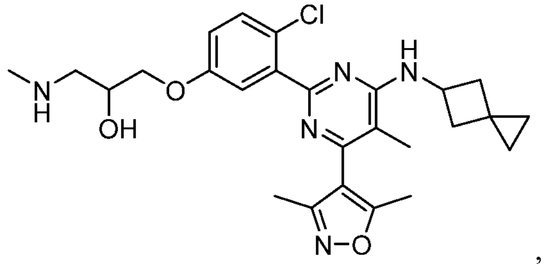

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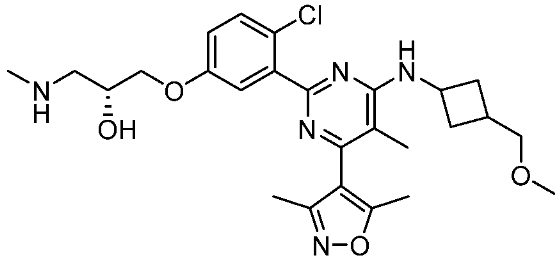

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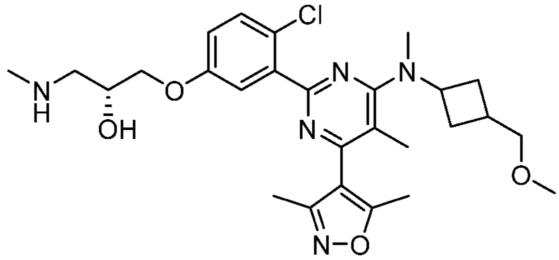

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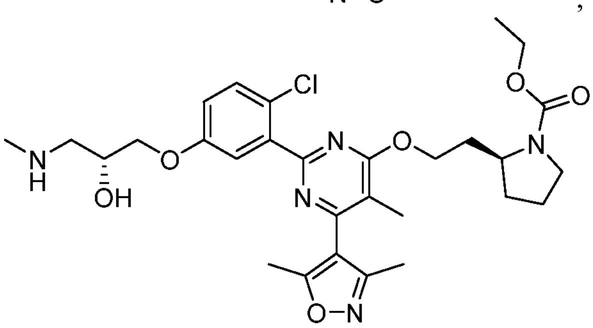

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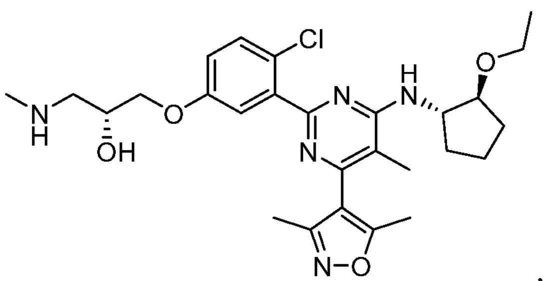

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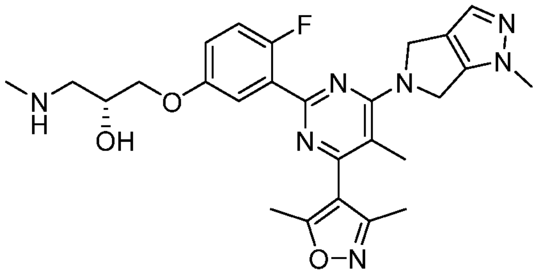

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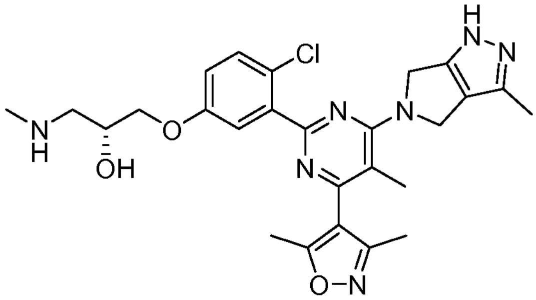

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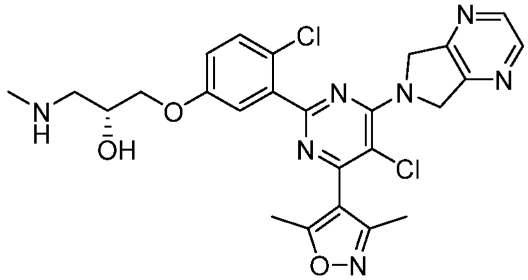

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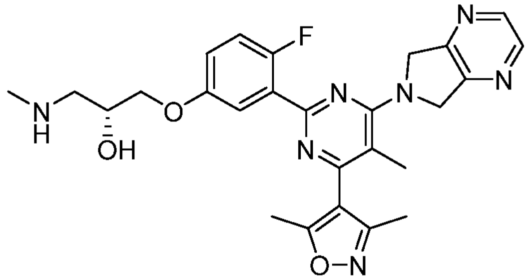

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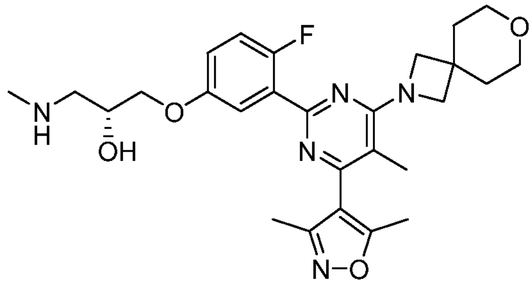

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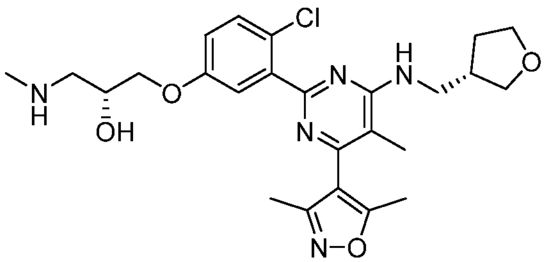

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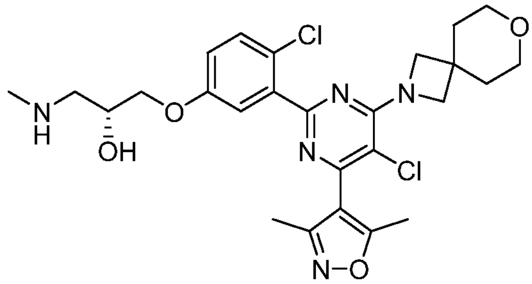

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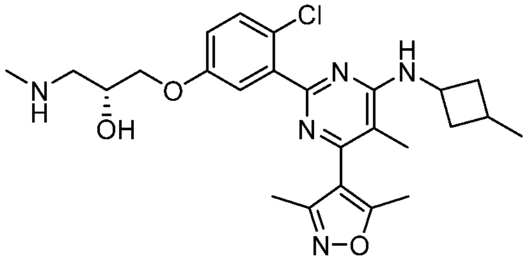

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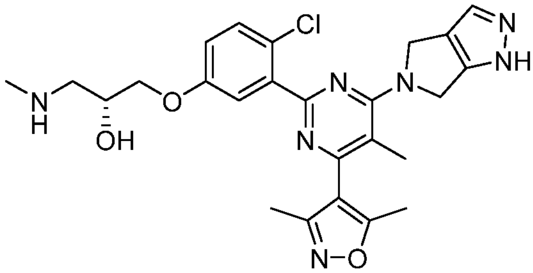

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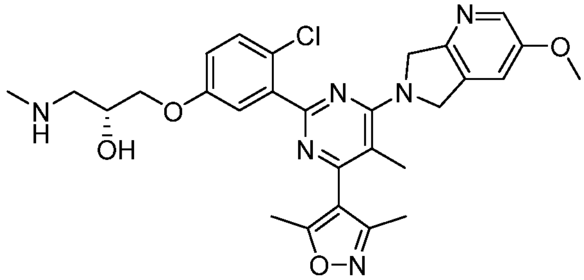

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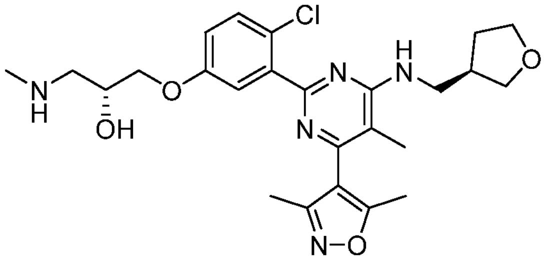

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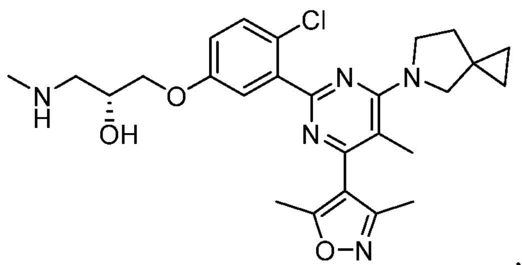

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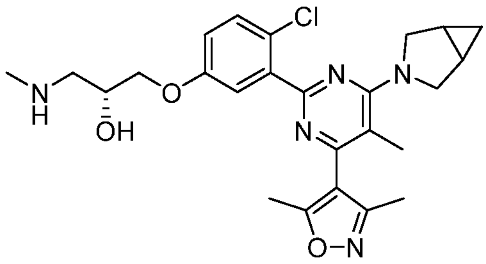

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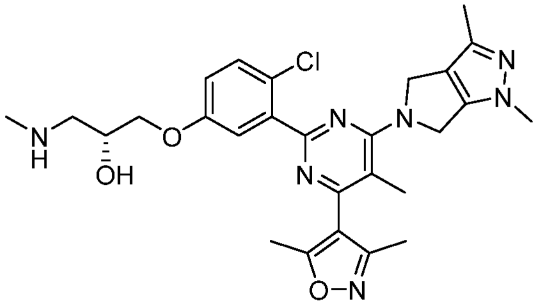

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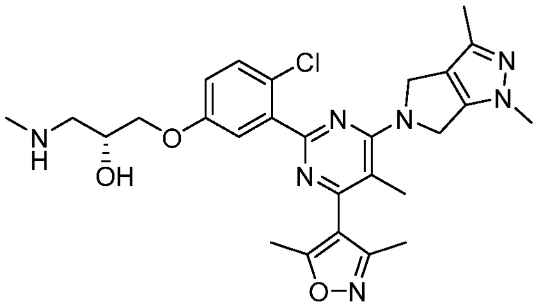

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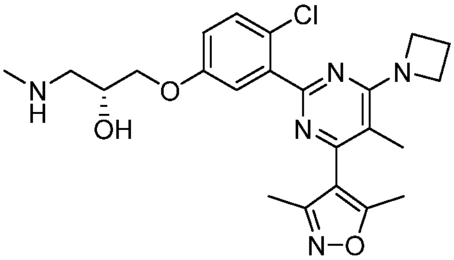

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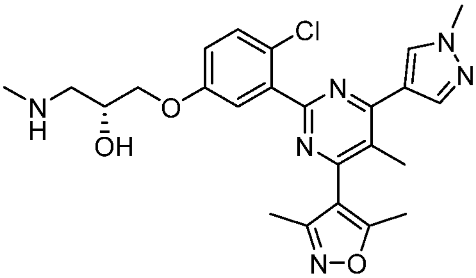

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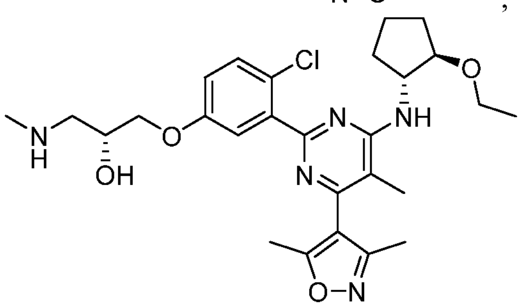

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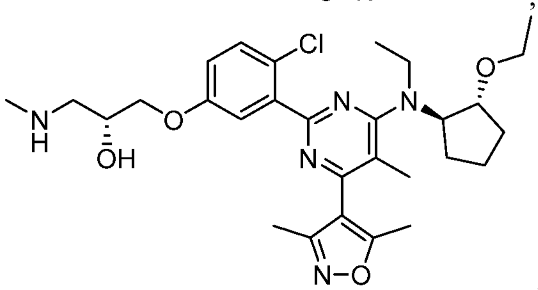

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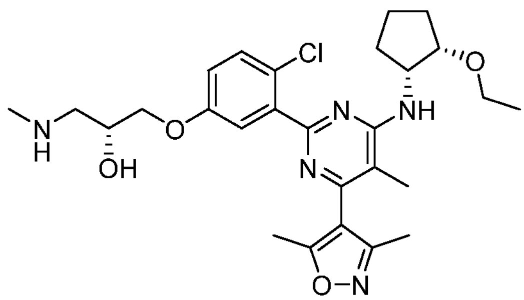

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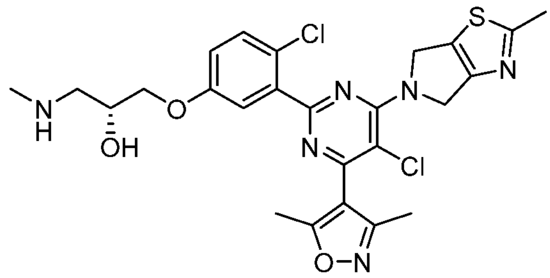

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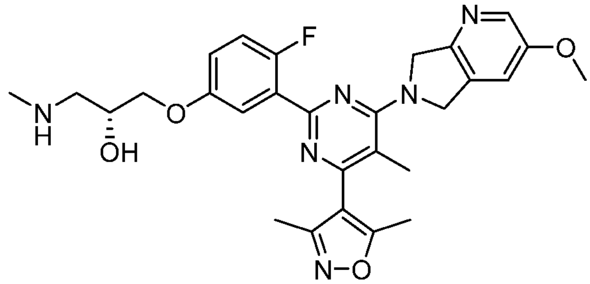

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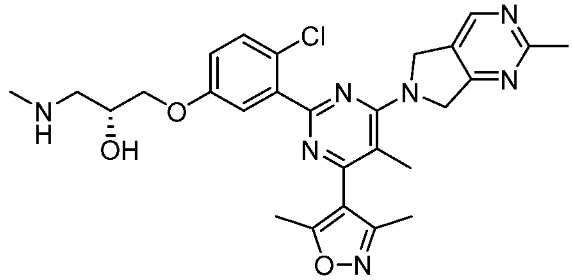

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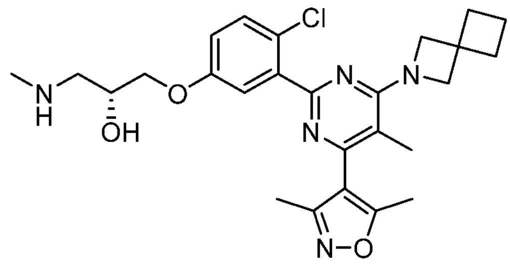

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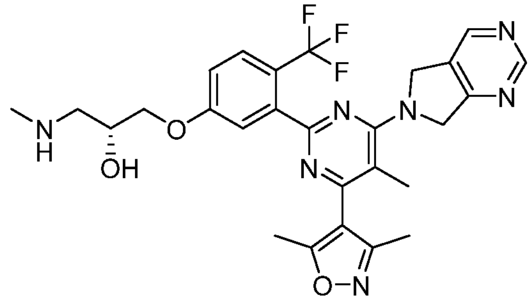

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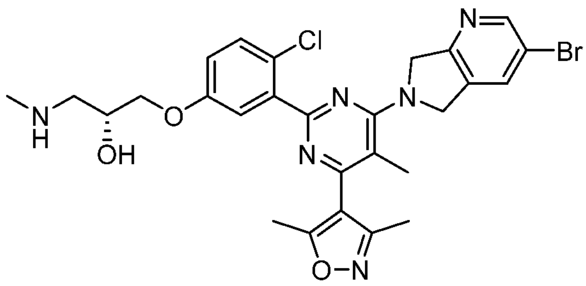

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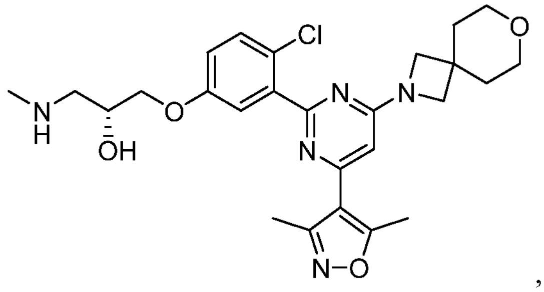

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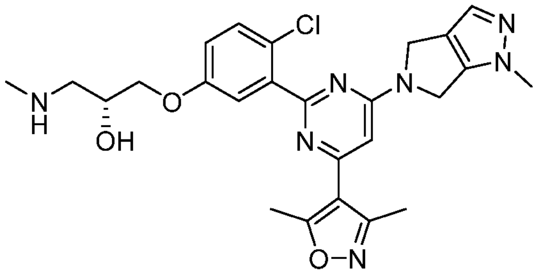

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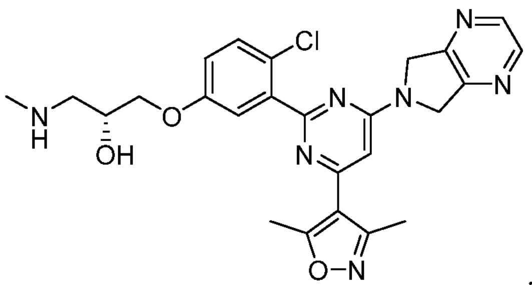

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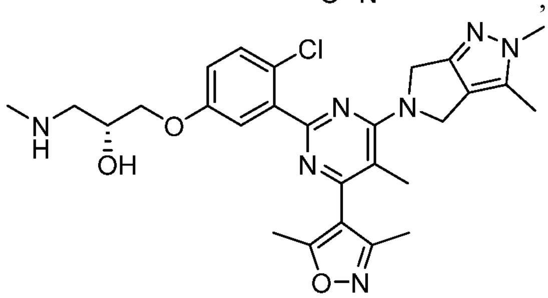

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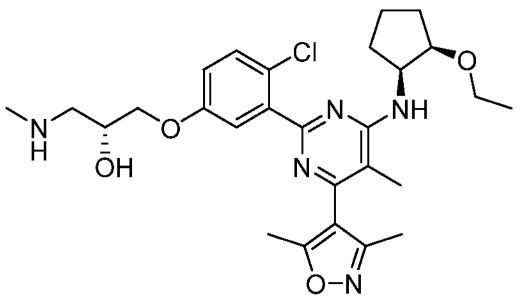

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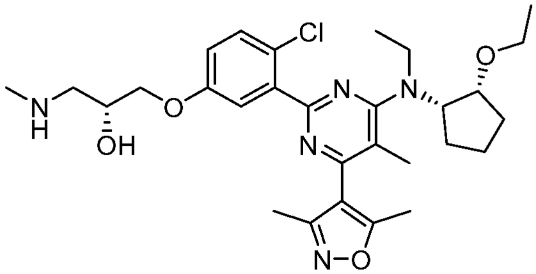

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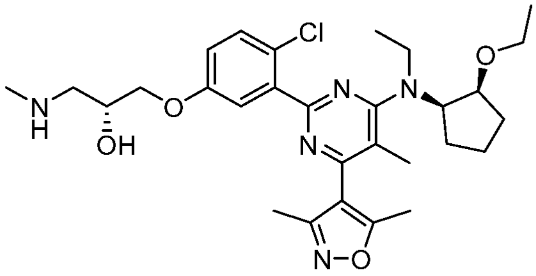

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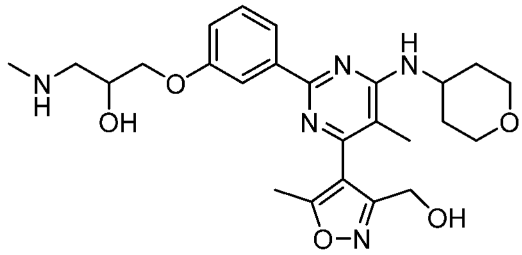

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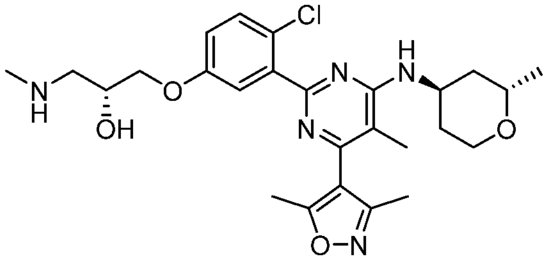

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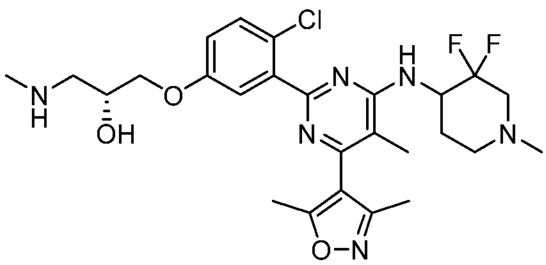

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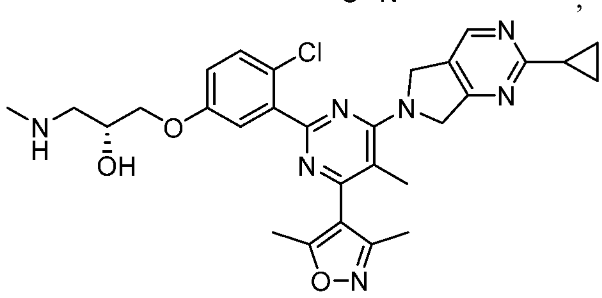

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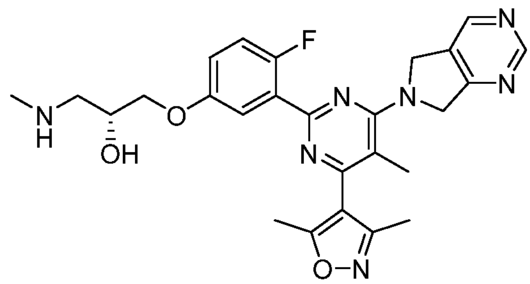

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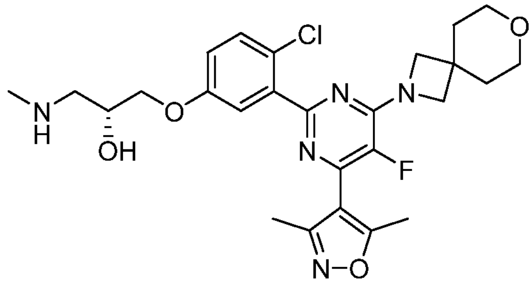

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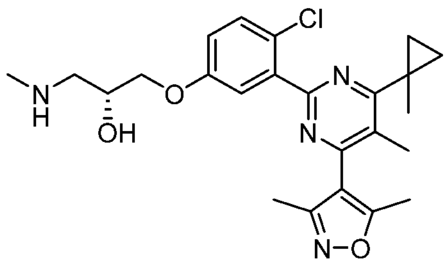

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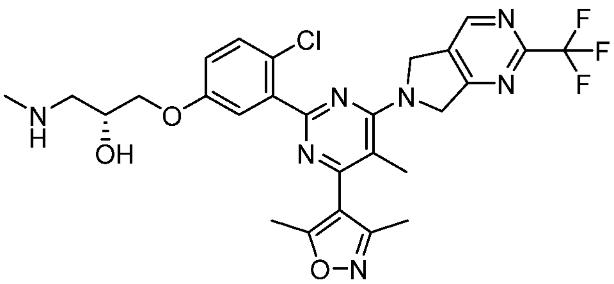

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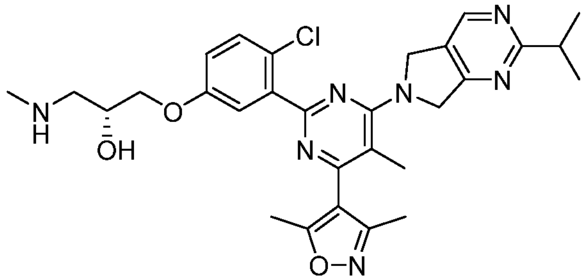

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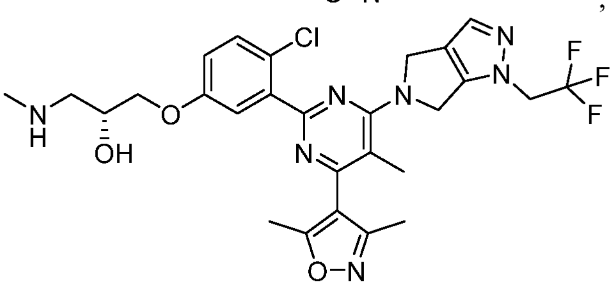

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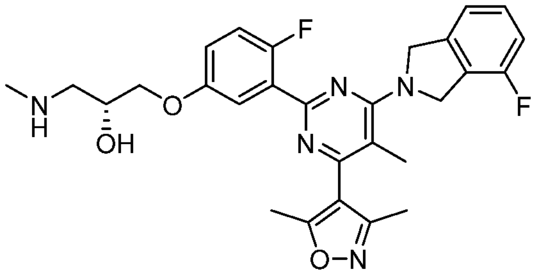

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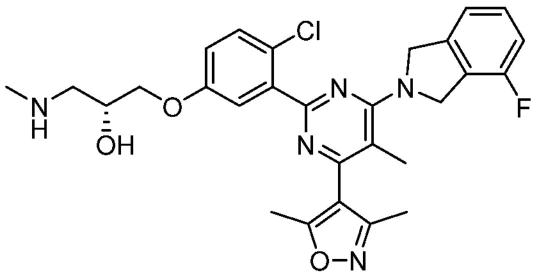

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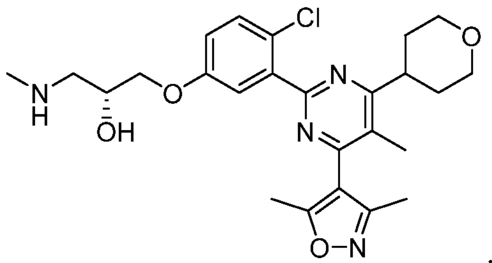

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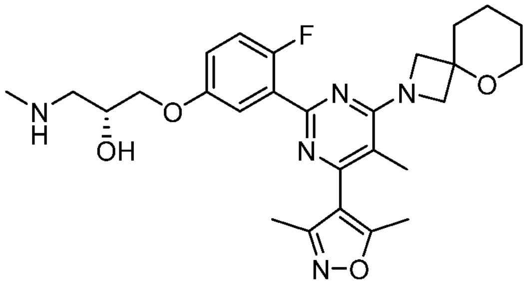

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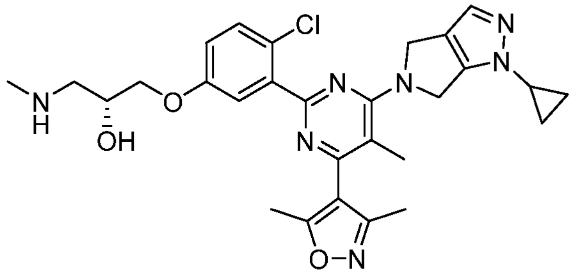

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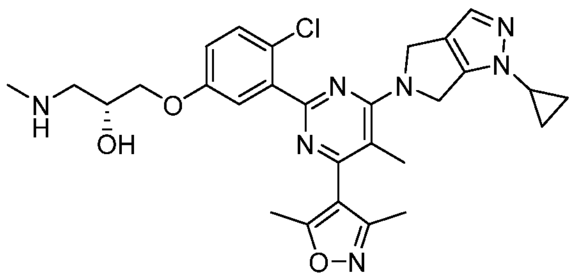

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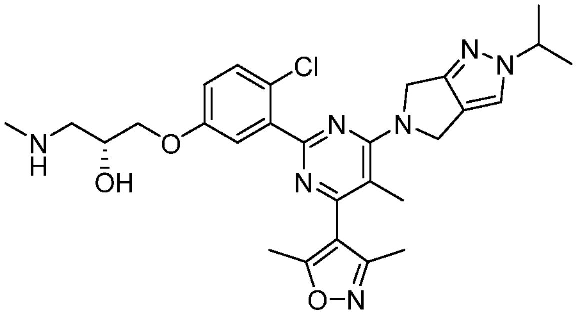

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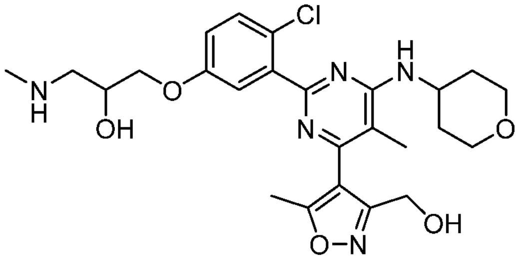

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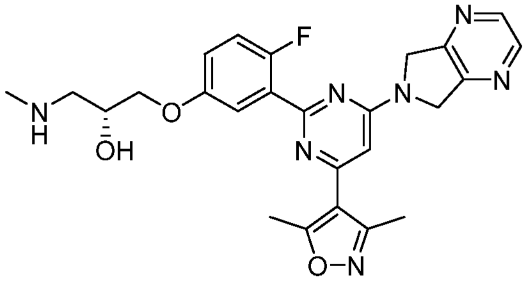

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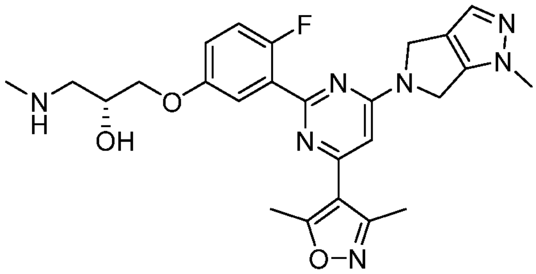

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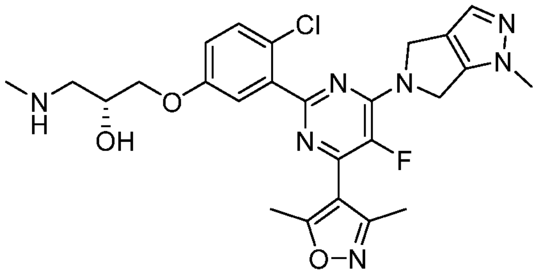

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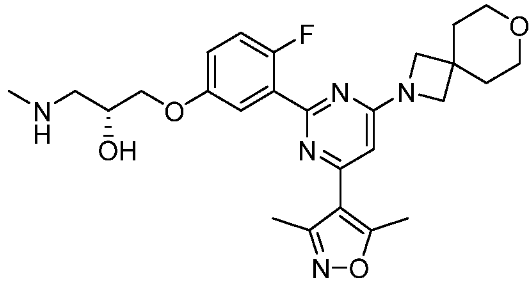

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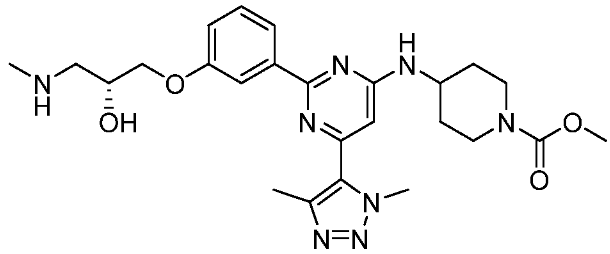

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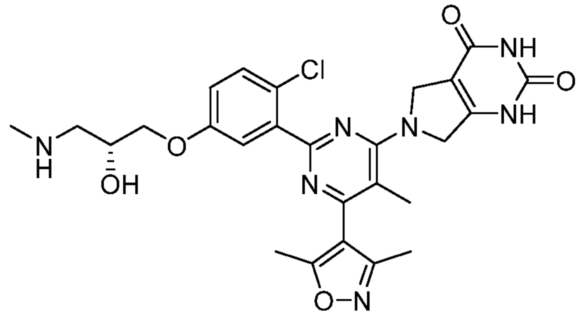

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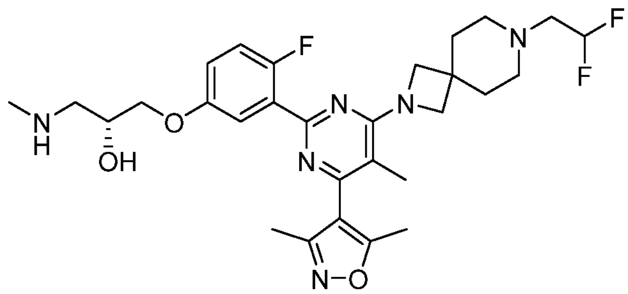

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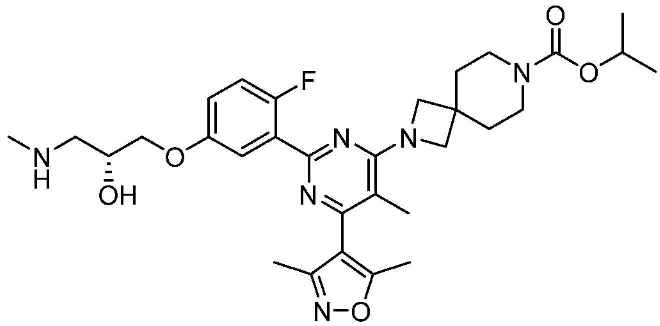

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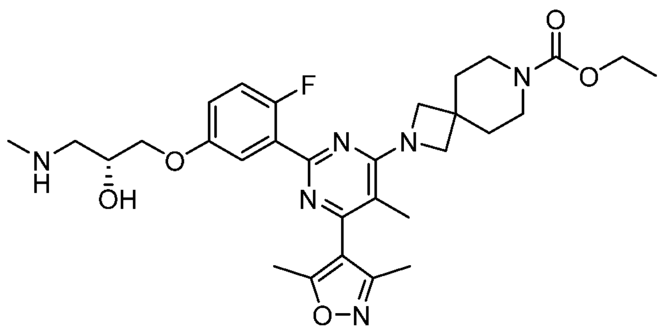

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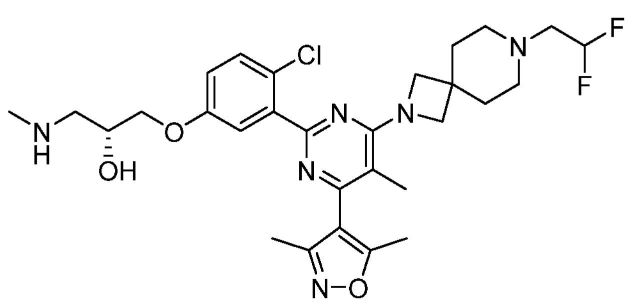

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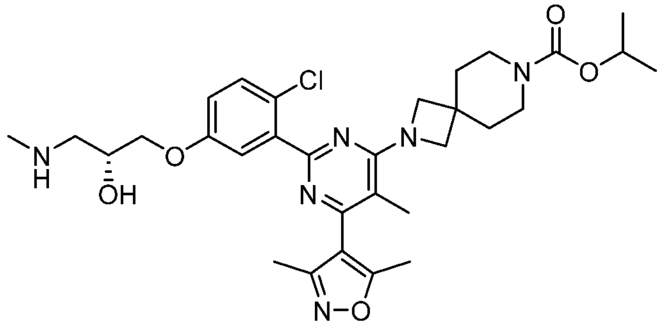
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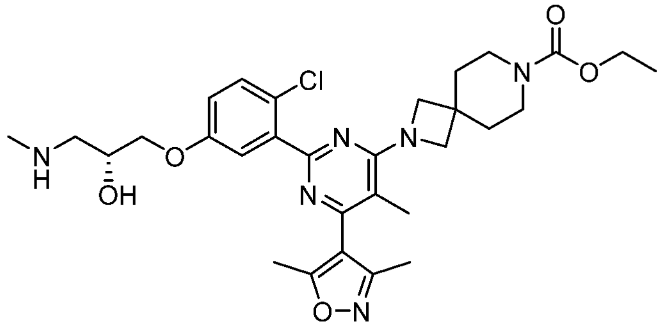
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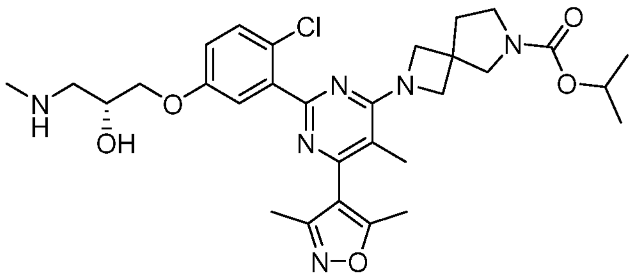
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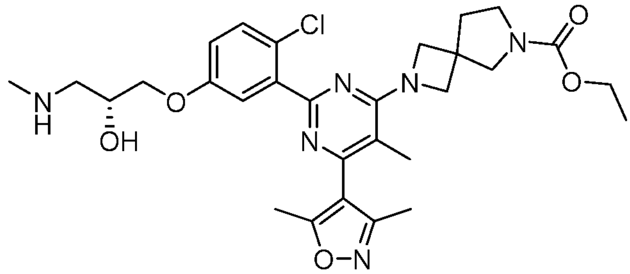
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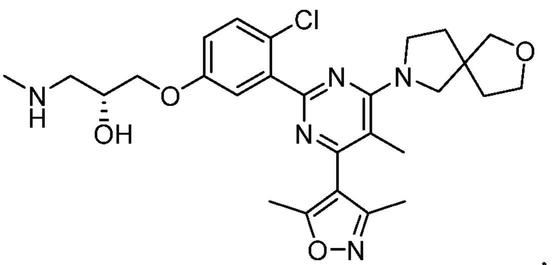
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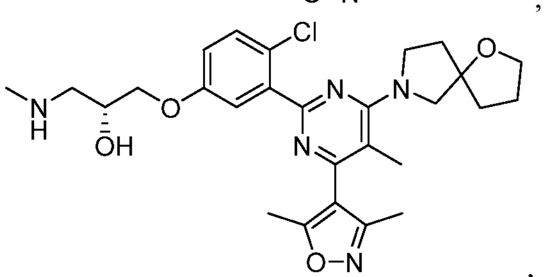
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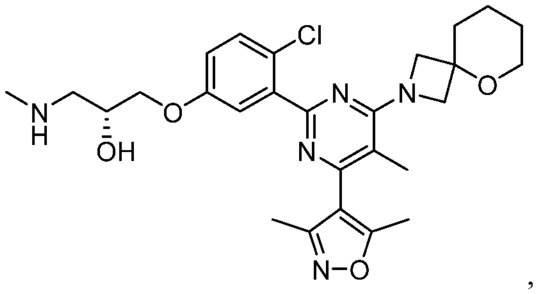

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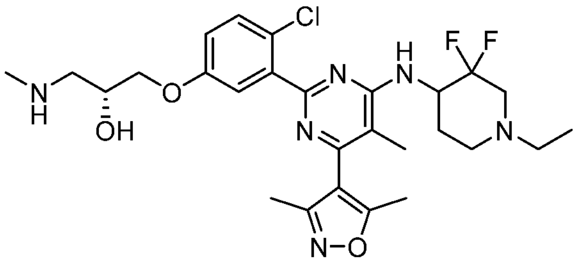

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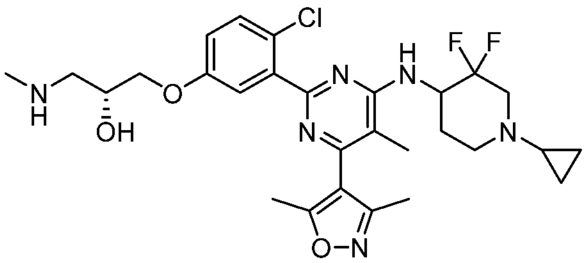

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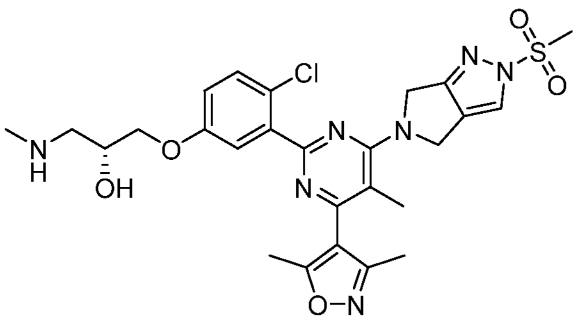

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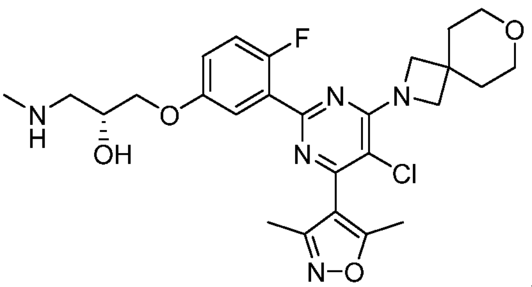

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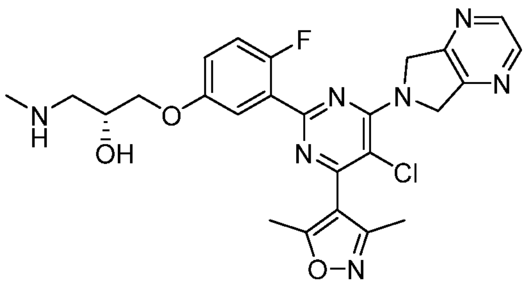

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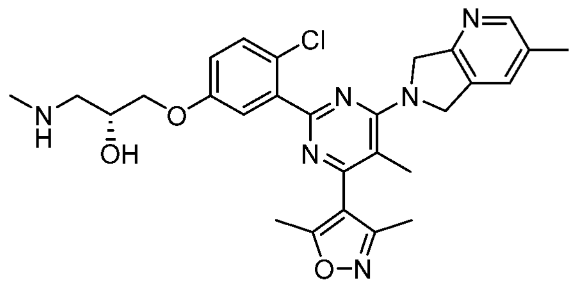

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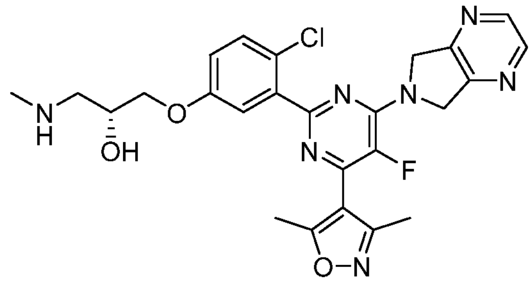

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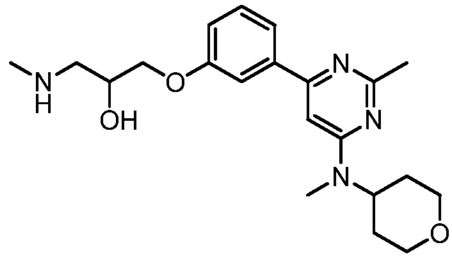

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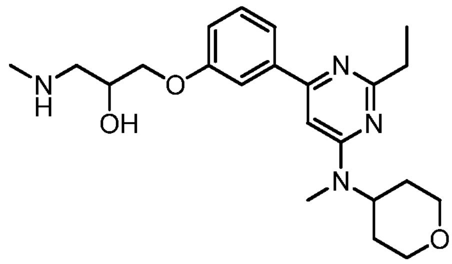

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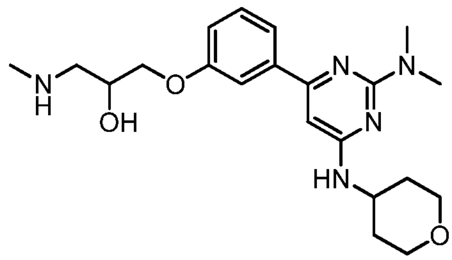

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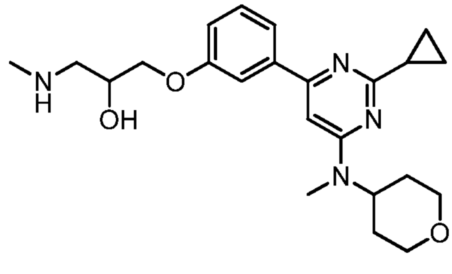

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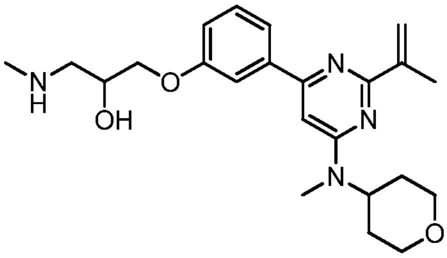

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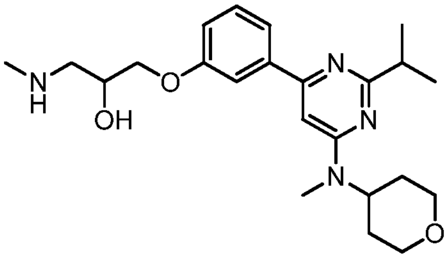

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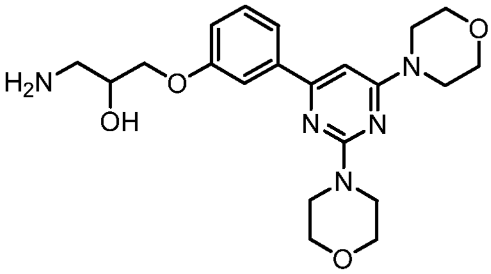

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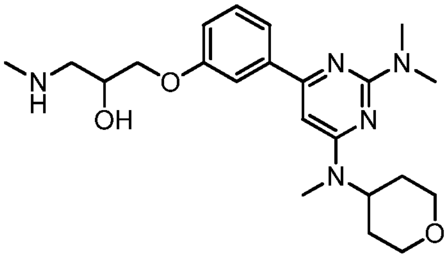

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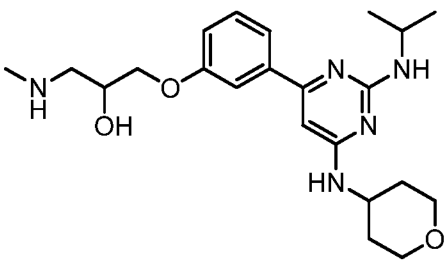

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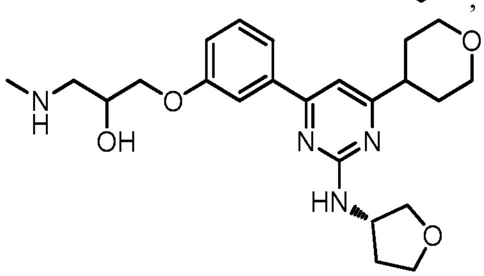

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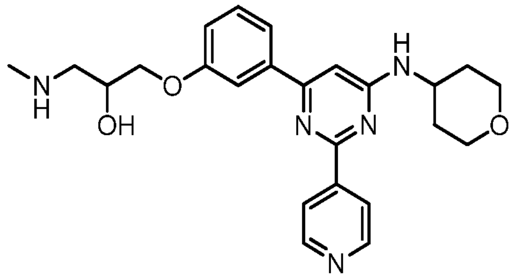

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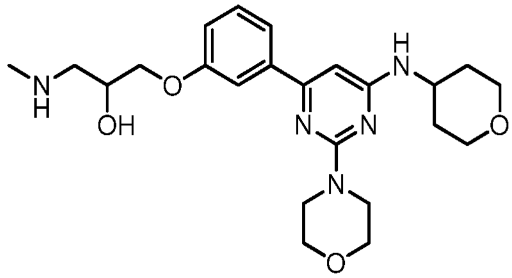

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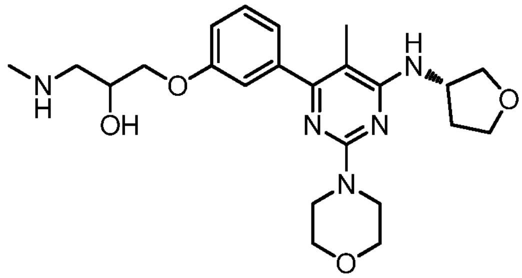

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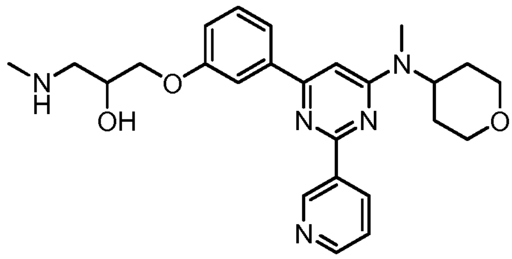

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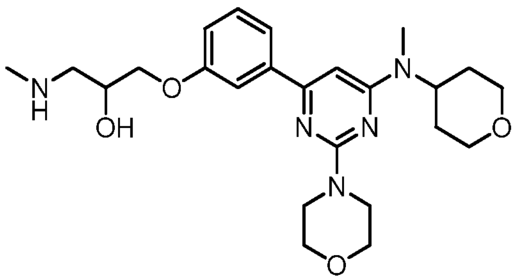

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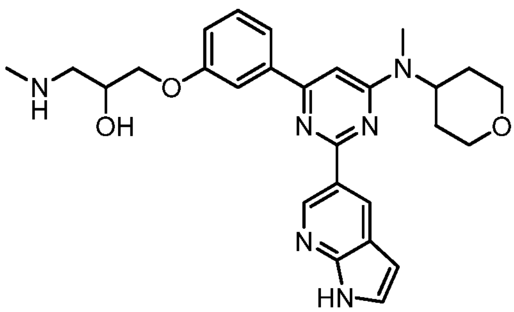

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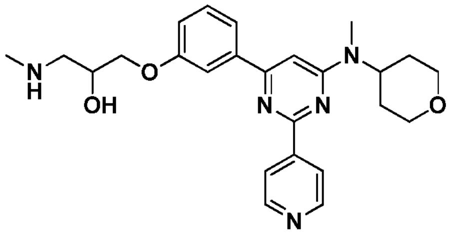
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and pharmaceutically acceptable salts thereof.

[00358] In certain embodiments, a provided compound inhibits CARM1. In certain embodiments, a provided compound inhibits wild-type CARM1. In certain embodiments, a provided compound inhibits a mutant CARM1. In certain embodiments, a provided compound inhibits CARM1, *e.g.*, as measured in an assay described herein. In certain embodiments, the CARM1 is from a human. In certain embodiments, a provided compound inhibits CARM1 at an IC_{50} less than or equal to 10 μM. In certain embodiments, a provided compound inhibits CARM1 at an IC_{50} less than or equal to 1 μM. In certain embodiments, a provided compound inhibits CARM1 at an IC_{50} less than or equal to 0.1 μM. In certain embodiments, a provided compound inhibits CARM1 in a cell at an EC_{50} less than or equal to 10 μM. In certain embodiments, a provided compound inhibits CARM1 in a cell at an EC_{50} less than or equal to 1 μM. In certain embodiments, a provided compound inhibits CARM1 in a cell at an EC_{50} less than or equal to 0.1 μM. In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 10 μM. In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 1 μM. In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 0.1 μM. In some embodiments, a provided compound is selective for CARM1 over other methyltransferases. In certain embodiments, a provided compound is at least about 10-fold selective, at least about 20-fold selective, at least about 30-fold selective, at least about 40-fold selective, at least about 50-fold selective, at least about 60-fold selective, at least about 70-fold selective, at least about 80-fold selective, at least about 90-fold selective, or at least about 100-fold selective for PRMT1 relative to one or more other methyltransferases.

[00359] It will be understood by one of ordinary skill in the art that the CARM1 can be wild-type CARM1, or any mutant or variant of CARM1.

[00360] The present disclosure provides pharmaceutical compositions comprising a compound described herein, *e.g.*, a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, as described herein, and optionally a pharmaceutically acceptable excipient. It will be understood by one of ordinary skill in the art that the compounds described herein, or salts thereof, may be present in various forms, such as amorphous, hydrates, solvates, or polymorphs. In certain embodiments, a provided composition comprises two or more compounds described herein. In certain embodiments, a compound described herein, or a pharmaceutically acceptable salt thereof, is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is an amount effective for inhibiting CARM1. In certain embodiments, the effective amount is an amount effective for treating a CARM1-mediated disorder. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the effective amount is an amount effective to prevent a CARM1-mediated disorder.

[00361] Pharmaceutically acceptable excipients include any and all solvents, diluents, or other liquid vehicles, dispersions, suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants, and the like, as suited to the particular dosage form desired. General considerations in formulation and/or manufacture of pharmaceutical compositions agents can be found, for example, in *Remington's Pharmaceutical Sciences*, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and *Remington: The Science and Practice of Pharmacy*, 21st Edition (Lippincott Williams & Wilkins, 2005).

[00362] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing a compound described herein (the "active ingredient") into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single– or multi–dose unit.

[00363] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one–half or one–third of such a dosage.

[00364] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the present disclosure will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

[00365] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[00366] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

[00367] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation–exchange resins, calcium carbonate, silicates, sodium carbonate, cross–linked poly(vinyl–pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross–linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[00368] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (*e.g.,* acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.,* bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (*e.g.,* stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.,* carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.,* carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.,* polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan (Tween 60), polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monopalmitate (Span 40), sorbitan monostearate (Span 60], sorbitan tristearate (Span

65), glyceryl monooleate, sorbitan monooleate (Span 80)), polyoxyethylene esters (*e.g.,* polyoxyethylene monostearate (Myrj 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.,* Cremophor™), polyoxyethylene ethers, (*e.g.,* polyoxyethylene lauryl ether (Brij 30)), poly(vinyl–pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F68, Poloxamer 188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

[00369] Exemplary binding agents include starch (*e.g.,* cornstarch and starch paste), gelatin, sugars (*e.g.,* sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.,* acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl–pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

[00370] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

[00371] Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[00372] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (*e.g.*, sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (*e.g.*, citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[00373] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[00374] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol. Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta–carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[00375] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti–oxidant. In other embodiments, the preservative is a chelating agent.

[00376] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D–gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen–free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[00377] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[00378] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut,

mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

[00379] Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3–butylene glycol, dimethylformamide, oils (*e.g.*, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the compounds described herein are mixed with solubilizing agents such as Cremophor™, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

[00380] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3–butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono– or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00381] The injectable formulations can be sterilized, for example, by filtration through a bacterial–retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00382] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[00383] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the compounds described herein with suitable non–irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

[00384] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may comprise buffering agents.

[00385] Solid compositions of a similar type can be employed as fillers in soft and hard–filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type can be employed as fillers in soft and hard–filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00386] The active ingredient can be in micro–encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets, and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

[00387] Dosage forms for topical and/or transdermal administration of a provided compound may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier and/or any desired preservatives and/or buffers as can be required. Additionally, the present disclosure encompasses the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

[00388] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi liquid preparations such as liniments, lotions, oil in water and/or water in oil emulsions such as creams, ointments and/or pastes, and/or solutions and/or suspensions. Topically–administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[00389] A provided pharmaceutical composition can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers or from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and/or using a self-propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low–boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[00390] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally the propellant may constitute 50 to 99.9% (w/w) of the composition, and the active ingredient may constitute 0.1 to 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid non–ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

[00391] Pharmaceutical compositions formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

[00392] Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an

average particle from about 0.2 to 500 micrometers. Such a formulation is administered by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[00393] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A provided pharmaceutical composition can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[00394] A provided pharmaceutical composition can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension of the active ingredient in an aqueous or oily liquid carrier. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other opthalmically–administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are contemplated as being within the scope of this disclosure.

[00395] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[00396] Compounds provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of provided compositions will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease, disorder, or condition being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[00397] The compounds and compositions provided herein can be administered by any route, including enteral (*e.g.*, oral), parenteral, intravenous, intramuscular, intra–arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically contemplated routes are oral administration, intravenous administration (*e.g.*, systemic intravenous injection), regional administration via blood and/or lymph supply, and/or direct administration to an affected site. In general the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (*e.g.*, its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (*e.g.*, whether the subject is able to tolerate oral administration).

[00398] The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[00399] In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

[00400] In certain embodiments, a compound described herein may be administered at dosage levels sufficient to deliver from about 0.001 mg/kg to about 1000 mg/kg, from about 0.01 mg/kg to about mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, or from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00401] In some embodiments, a compound described herein is administered one or more times per day, for multiple days. In some embodiments, the dosing regimen is continued for days, weeks, months, or years.

[00402] It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[00403] It will be also appreciated that a compound or composition, as described herein, can be administered in combination with one or more additional therapeutically active agents. In certain embodiments, a compound or composition provided herein is administered in combination with one or more additional therapeutically active agents that improve its bioavailability, reduce and/or modify its metabolism, inhibit its excretion, and/or modify its distribution within the body. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

[00404] The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional therapeutically active agents. In certain embodiments, the additional therapeutically active agent is a compound of Formula (**I**). In certain embodiments, the additional therapeutically active agent is not a compound of Formula (**I**). In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In will further be appreciated that the additional therapeutically active agent utilized in this combination can be administered together in a single composition or administered separately in different compositions. The particular combination to employ in a regimen will take into account compatibility of a provided compound with the additional therapeutically active agent and/or the desired therapeutic effect to be achieved. In general, it is expected that additional therapeutically active agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[00405] Exemplary additional therapeutically active agents include, but are not limited to, small organic molecules such as drug compounds (*e.g.*, compounds approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells.

[00406] Also encompassed by the present discosure are kits (*e.g.*, pharmaceutical packs). The kits provided may comprise a provided pharmaceutical composition or compound and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of a provided pharmaceutical composition or compound. In some embodiments, a provided pharmaceutical composition or compound provided in the container and the second container are combined to form one unit dosage form. In some embodiments, a provided kits further includes instructions for use.

[00407] Compounds and compositions described herein are generally useful for the inhibition of CARM1. In some embodiments, the CARM1 is human CARM1. In some embodiments, methods of treating CARM1-mediated disorder in a subject are provided which comprise administering an effective amount of a compound described herein (*e.g.*, a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof), to a subject in need of treatment. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the subject is suffering from a CARM1-mediated disorder. In certain embodiments, the subject is susceptible to a CARM1-mediated disorder.

[00408] As used herein, the term "CARM1-mediated disorder" means any disease, disorder, or other pathological condition in which CARM1 is known to play a role. Accordingly, in some embodiments, the present disclosure relates to treating or lessening the severity of one or more diseases in which CARM1 is known to play a role.

[00409] In some embodiments, the present disclosure provides a method of inhibiting CARM1 comprising contacting CARM1 with an effective amount of a compound described herein, *e.g.*, a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof. The CARM1 may be purified or crude, and may be present in a cell, tissue, or subject. Thus, such methods encompass both inhibition of *in vitro* and *in vivo* CARM1 activity. In certain embodiments, the method is an *in vitro* method, *e.g.,* such as an assay method. It will be understood by one of ordinary skill in the art that inhibition of CARM1 does not necessarily require that all of the CARM1 be occupied by an inhibitor at once. Exemplary levels of inhibition of CARM1 include at least 10% inhibition, about 10% to about 25% inhibition, about 25% to about 50% inhibition, about 50% to about 75% inhibition, at least 50% inhibition, at least 75% inhibition, about 80% inhibition, about 90% inhibition, and greater than 90% inhibition.

[00410] In some embodiments, provided is a method of inhibiting CARM1 activity in a subject in need thereof comprising administering to the subject an effective amount of a compound described herein (*e.g.*, a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[00411] In certain embodiments, provided is a method of modulating gene expression or activity in a cell which comprises contacting a cell with an effective amount of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof. In certain embodiments, the cell in culture *in vitro*. In certain embodiments, the cell is in an animal, *e.g.*, a human. In certain embodiments, the cell is in a subject in need of treatment.

[00412] In certain embodiments, provided is a method of modulating transcription in a cell which comprises contacting a cell with an effective amount of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof. In certain embodiments, the cell in culture *in vitro*. In certain embodiments, the cell is in an animal, *e.g.*, a human. In certain embodiments, the cell is in a subject in need of treatment.

[00413] In certain embodiments, a method is provided of selecting a therapy for a subject having a disease associated with CARM1-mediated disorder or mutation comprising the steps of determining the presence of CARM1-mediated disorder or gene mutation in the CARM1 gene or and selecting, based on the presence of CARM1-mediated disorder a gene mutation in the CARM1 gene a therapy that includes the administration of a provided compound. In certain embodiments, the disease is cancer.

[00414] In certain embodiments, a method of treatment is provided for a subject in need thereof comprising the steps of determining the presence of CARM1-mediated disorder or a gene mutation in the CARM1 gene and treating the subject in need thereof, based on the presence of a CARM1-mediated disorder or gene mutation in the CARM1 gene with a therapy that includes the administration of a provided compound. In certain embodiments, the subject is a cancer patient.

[00415] In some embodiments, a compound provided herein is useful in treating a proliferative disorder, such as cancer. For example, while not being bound to any particular mechanism, protein arginine methylation by CARM1 is a modification that has been implicated in signal transduction, gene transcription, DNA repair and mRNA splicing, among others; and overexpression of CARM1 within these pathways is often associated with various cancers. Thus, compounds which inhibit the action of PRMTs, and specifically CARM1, as provided herein, are effective in the treatment of cancer.

[00416] In some embodiments, compounds provided herein are effective in treating cancer through the inhibition of CARM1. For example, CARM1 levels have been shown to be elevated in castration-resistant prostate cancer (CRPC) (*e.g.*, see Di Lorenzo *et al.*, *Drugs* (2010) 70:983-1000), as well as in aggressive breast tumors (Hong *et al., Cancer* 2004 101, 83–89; El Messaoudi *et al.*, *Proc. Natl. Acad. Sci. U. S. A.* 2006, *103*, 13351-13356; Majumder *et al., Prostate* 2006 66, 1292–1301). Thus, in some embodiments, inhibitors of CARM1, as described herein, are useful in treating cancers associated with aberrant CARM1 activity, *e.g.,* CARM1 overexpression or aberrant protein methylation. For example, aberrant CARM1 activity has been found in prostate cancer (*e.g.*, see Hong *et al.*, *Cancer* (2004), 101:83-89); plays a coactivator role in the dysragulation of beta-catenin activity in colorectal cancer (*e.g.*, see Ou et al., *Mol. Cancer Res*. (2011) 9:660); and has been linked to estrogen signaling and estrogen related cancers such as breast cancer (see, *e.g.*, Teyssiewr *et al.*, *Trends in Endocrinology and Metabolism* (2010) 21:181-189). CARM1 has also been shown to affect estrogen receptor alpha (ER-alpha) dependent breast cancer cell differentiation and proliferation (Al−Dhaheri *et al., Cancer Res*. 2011 71, 2118–2128), thus in some aspects CARM1 inhibitors, as described herein, are useful in treating ERα-dependent breast cancer by inhibiting cell differentiation and proliferation. In another example, CARM1 has been shown to be recruited to the promoter of E2F1 (which encodes a cell cycle regulator) as a transcriptional co-activator (Frietze *et al., Cancer Res*. 2008 68, 301–306). Thus, CARM1-mediated upregulation of E2F1 expression may contribute to cancer progression and chemoresistance as increased abundance of E2F1 triggers invasion and metastasis by activating growth receptor signaling pathways, which in turn promote an antiapoptotic tumor environment (Engelmann and Pützer, *Cancer Res* 2012 72; 571). Accordingly, in some embodiments, the inhibition of CARM1, *e.g.,* by compounds provided herein, is useful in treating cancers associated with E2F1 upregulation, *e.g.*, such as lung cancer (see, *e.g.*, Eymin *et al.*, *Oncogene* (2001) 20:1678-1687), and breast cancer (see, *e.g.*, Brietz *et al.*, *Cancer Res.* (2008) 68:301-306). Thus, without being bound by any particular mechanism, the inhibition of CARM1, *e.g.*, by compounds described herein, is beneficial in the treatment of cancer. CARM1 overexpression has also been demonstrated to be elevated in 75% of colorectal cancers (Kim *et al.*, BMC Cancer, 10, 197). It has been additionally been determined that depletion of CARM1 in WNT/β-catenin dysregulated colorectal cancer suppressed anchorage independent growth (Ou *et al.*, Mol. Cancer. Res., 2011 9, 660-670). This, in some embodiments, the inhibition of CARM1, *e.g.* by compounds provided herein, is useful in colorectal cancer associated with elevated CARM1 expression or dysregulated WNT/β-catenin signaling.

[00417] In some embodiments, compounds described herein are useful for treating a cancer including, but not limited to, acoustic neuroma, adenocarcinoma, adrenal gland cancer, anal cancer, angiosarcoma (*e.g.,* lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma), appendix cancer, benign monoclonal gammopathy, biliary cancer (*e.g.,* cholangiocarcinoma), bladder cancer, breast cancer (*e.g.,* adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast), brain cancer (*e.g.,* meningioma; glioma, *e.g.,* astrocytoma, oligodendroglioma; medulloblastoma), bronchus cancer, carcinoid tumor, cervical cancer (*e.g.,* cervical adenocarcinoma), choriocarcinoma, chordoma, craniopharyngioma, colorectal cancer (*e.g.,* colon cancer, rectal cancer, colorectal adenocarcinoma), epithelial carcinoma, ependymoma, endotheliosarcoma (*e.g.,* Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma), endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma), esophageal cancer (*e.g.,* adenocarcinoma of the esophagus, Barrett's adenocarinoma), Ewing sarcoma, eye cancer (*e.g.,* intraocular melanoma, retinoblastoma), familiar hypereosinophilia, gall bladder cancer, gastric cancer (*e.g.,* stomach adenocarcinoma), gastrointestinal stromal tumor (GIST), head and neck cancer (*e.g.,* head and neck squamous cell carcinoma, oral cancer (*e.g.,* oral squamous cell carcinoma (OSCC), throat cancer (*e.g.,* laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)), hematopoietic cancers (*e.g.,* leukemia such as acute lymphocytic leukemia (ALL) (*e.g.,* B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.,* B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.,* B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (*e.g.,* B-cell CLL, T-cell CLL); lymphoma such as Hodgkin lymphoma (HL) (*e.g.,* B-cell HL, T-cell HL) and non–Hodgkin lymphoma (NHL) (*e.g.*, B-cell NHL such as diffuse large cell lymphoma (DLCL) (*e.g.,* diffuse large B–cell lymphoma (DLBCL)), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (*e.g.,* mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (*i.e.,* "Waldenström's macroglobulinemia"), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (*e.g.,* cutaneous T-cell lymphoma (CTCL) (*e.g.,* mycosis fungiodes, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease), hemangioblastoma, inflammatory myofibroblastic tumors, immunocytic amyloidosis, kidney cancer (*e.g.,* nephroblastoma *a.k.a.* Wilms' tumor, renal cell carcinoma), liver cancer (*e.g.,* hepatocellular cancer (HCC), malignant hepatoma), lung cancer (*e.g.,* bronchogenic carcinoma, small cell lung cancer (SCLC), non–small cell lung cancer (NSCLC), adenocarcinoma of the lung), leiomyosarcoma (LMS), mastocytosis (*e.g.,* systemic mastocytosis), myelodysplastic syndrome (MDS), mesothelioma, myeloproliferative disorder (MPD) (*e.g.,* polycythemia Vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)), neuroblastoma, neurofibroma (*e.g.,* neurofibromatosis (NF) type 1 or type 2, schwannomatosis), neuroendocrine cancer (*e.g.,* gastroenteropancreatic neuroendoctrine tumor (GEP-NET), carcinoid tumor), osteosarcoma, ovarian cancer (*e.g.,* cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma), papillary adenocarcinoma, pancreatic cancer (*e.g.,* pancreatic andenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors), penile cancer (*e.g.,* Paget's disease of the penis and scrotum), pinealoma, primitive neuroectodermal tumor (PNT), prostate cancer (*e.g.,* prostate adenocarcinoma), rectal cancer, rhabdomyosarcoma, salivary gland cancer, skin cancer (*e.g.,* squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)), small bowel cancer (*e.g.,* appendix cancer), soft tissue sarcoma (*e.g.,* malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma), sebaceous gland carcinoma, sweat gland carcinoma, synovioma, testicular cancer (*e.g.,* seminoma, testicular embryonal carcinoma), thyroid cancer (*e.g.,* papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer), urethral cancer, vaginal cancer, and vulvar cancer (*e.g.*, Paget's disease of the vulva).

[00418] In certain embodiments, the cancer is a solid cancer. In certain embodiments, the cancer is a liquid cancer.

[00419] In certain embodiments, the cancer is breast cancer, prostate cancer, colorectal cancer, or a hematopoietic cancer (*e.g.,* multiple myeloma).

[00420] CARM1 is also the most abundant PRMT expressed in skeletal muscle cells, and has been found to selectively control the pathways modulating glycogen metabolism, and associated AMPK (AMP-activated protein kinase) and p38 MAPK (mitogen-activated protein kinase) expression. See, *e.g.,* Wang *et al.,* Biochem (2012) 444:323-331. Thus, in some embodiments, inhibitors of CARM1, as described herein, are useful in treating metabolic disorders, *e.g.,* for example skeletal muscle metabolic disorders, *e.g.,* glycogen and glucose metabolic disorders. Exemplary skeletal muscle metabolic disorders include, but are not limited to, Acid Maltase Deficiency (Glycogenosis type 2; Pompe disease), Debrancher deficiency (Glycogenosis type 3), Phosphorylase deficiency (McArdle's; GSD 5), X-linked syndrome (GSD9D), Autosomal recessive syndrome (GSD9B), Tarui's disease (Glycogen storage disease VII; GSD 7), Phosphoglycerate Mutase deficiency (Glycogen storage disease X; GSDX; GSD 10), Lactate dehydrogenase A deficiency (GSD 11), Branching enzyme deficiency (GSD 4), Aldolase A (muscle) deficiency, β-Enolase deficiency, Triosephosphate isomerase (TIM) deficiency, Lafora's disease (Progressive myoclonic epilepsy 2), Glycogen storage disease (Muscle, Type 0, Phosphoglucomutase 1 Deficiency (GSD 14)), and Glycogenin Deficiency (GSD 15).

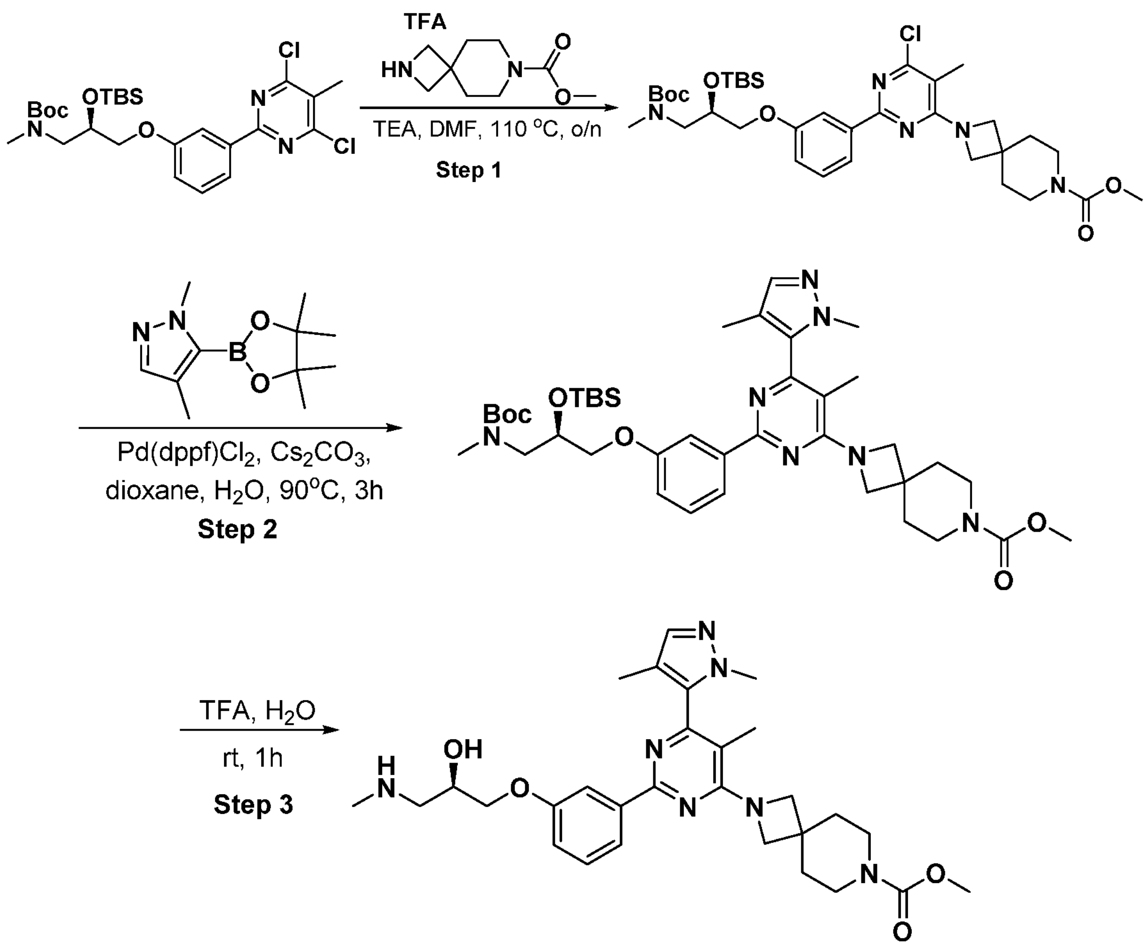
EXAMPLES

[00421] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

Synthetic Methods

[00422] The synthesis of an exemplary set of compounds of Formula (**I**) is provided below. These compounds are also provided in Table 1.

Example 1. Preparation of methyl 2-(2-(5-((R)-2-hydroxy-3-(methylamino)propoxy)phenyl)- 6-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-4-yl)-2,7-diazaspiro[3.5] nonane-7-carboxylate



[00423] **Step 1: methyl 2-(2-(3-((R)-3-(tert-butoxycarbonyl(methyl)amino) -2-(tert-butyldimethylsilyloxy)propoxy)phenyl)-6-chloro-5-methylpyrimidin-4-yl)-2,7-diazaspiro [3.5]nonane-7-carboxylate.** To a solution of (R)-tert-butyl 2-(tert-butyldimethylsilyloxy)-3-(3-(4,6-dichloro-5- methylpyrimidin-2-yl)phenoxy)propyl(methyl)carbamate (1 g, 1.8 mmol) in DMF (20 mL) was added methyl 2,7-diazaspiro[3.5]nonane-7-carboxylate TFA salt (2.15 g, 7.2 mmol) and triethylamine (909 mg, 9 mmol) at room temperature. The reaction mixture was heated at 110 °C for 16h, cooled down to room temperature, diluted with EtOAc (120 mL) and then washed with water (80 mL x 2) and brine (80 mL). The organic layer was dried

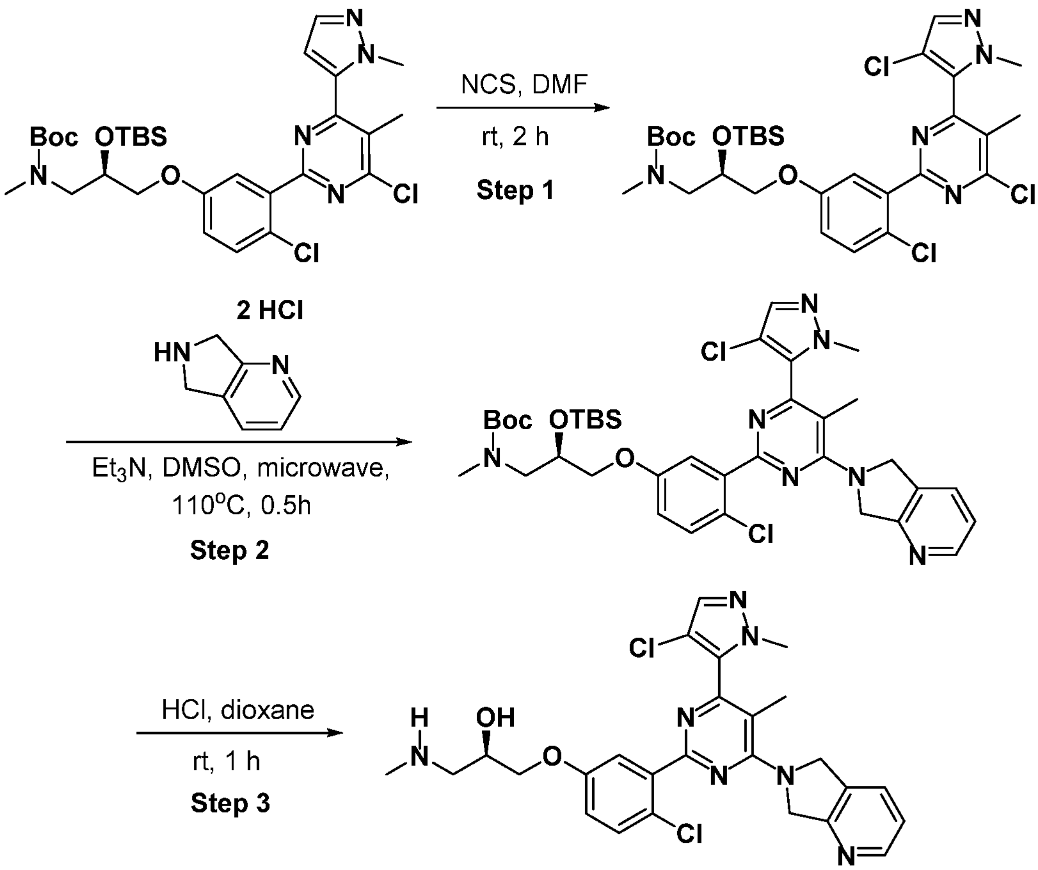
over Na_2SO_4, filtered and concentrated in vacuo to render a residue which was purified by column chromatography over silicagel to give methyl 2-(2-(3-((R)-3-(tert-butoxycarbonyl(methyl)amino)-2-(tert-butyldimethylsilyloxy) propoxy)phenyl)-6-chloro-5-methylpyrimidin-4-yl)-2,7-diazaspiro [3.5] nonane-7-carboxylate as a yellow solid (1.2 g, 95% yield). ESI-LCMS (m/z): 704.3 found for $[M+1]^+$.

[00424] Step **2: methyl 2-(2-(3-((R)-3-(tert-butoxycarbonyl(methyl)amino)-2 -(tert-butyldimethylsilyloxy)propoxy)phenyl)-6-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl pyrimidin-4-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate.** To a solution of methyl 2-(2-(3-((R)-3-(tert-butoxycarbonyl(methyl)amino)-2-(tert- butyldimethylsilyloxy)propoxy)phenyl)-6-chloro-5-methylpyrimidin-4-yl)-2,7-diaza- spiro[3.5] nonane-7-carboxylate (160 mg, 0.23 mmol) in degassed dioxane:H_2O (5:1, 6 mL) was added 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (78 mg, 0.35 mmol), Pd(dppf)Cl_2 (16 mg, 0.02mmol) and Na_2CO_3 (73 mg, 0.69 mmol) at room temperature. The system was purged with N_2 and the mixture was stirred at 90°C for 3h. After being cooled down to room temperature the mixture was filtered through a pad of celite. The filtrate was concentrated and the resulting residue was purified by preparative-TLC on silicagel eluting with petroleum ether/EtOAc = 2/1 to give methyl 2-(2-(3- ((R)-3-(tert-butoxycarbonyl (methyl)amino)-2-(tert-butyldimethylsilyloxy)propoxy) phenyl)-6-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-4-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate (130 mg, 74% yield) as a white solid. ESI-LCMS (m/z): 764.1 found for $[M+1]^+$.

[00425] **Step 3: methyl 2-(2-(5-((R)-2-hydroxy-3-(methylamino)propoxy) phenyl)-6-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-4-yl)-2,7-diazaspiro[3.5] nonane-7-carboxylate.** A solution of methyl 2-(2-(3-((R)-3-(tert-butoxycarbonyl(methyl)amino)-2-(tert-butyldimethyl- silyloxy)propoxy)phenyl)-6-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-4-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate (130 mg, 0.17 mmol) in 90% TFA (2 mL), was stirred at room-temperature for 1h. The solvent was then removed in vacuo and the resulting residue was dissolved in MeOH (5 mL). The solution was adjusted pH 7-8 with aqueous K_2CO_3 and concentrated. The residue was purified by preparative-HPLC to give methyl 2-(6-(1,4-dimethyl-1H-pyrazol-5-yl)-2-(3-((R)-2-hydroxy-3-(methylamino) propoxy) phenyl)-5-methylpyrimidin-4-yl)-2,7-diazaspiro[3.5]nonane-7-carboxylate as a white solid (20 mg, 21%). ESI-LCMS (m/z): 550.2 found for $[M+1]^+$; ^{1}HNMR (400 MHz, CD_3OD) δ ppm: 7.92-7.87 (m, 2H), 7.38 (s, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.03 (dd, J = 2.0 and 7.6 Hz, 1H), 4.23-4.12 (m, 4H), 4.10-4.07 (m, 1H), 4.03-3.98 (m, 2H), 3.73 (s, 3H), 3.67

(s, 3H), 3.55-3.45 (m, 4H), 2.86-2.70 (m, 2H), 2.44 (s, 3H), 2.08 (s, 3H), 1.98 (s, 3H) , 1.86-1.78 (m, 4H).

Example 2. Preparation of (2R)-1-(4-chloro-3-(4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-6-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl)phenoxy)-3-(methyl - amino)propan-2-ol.

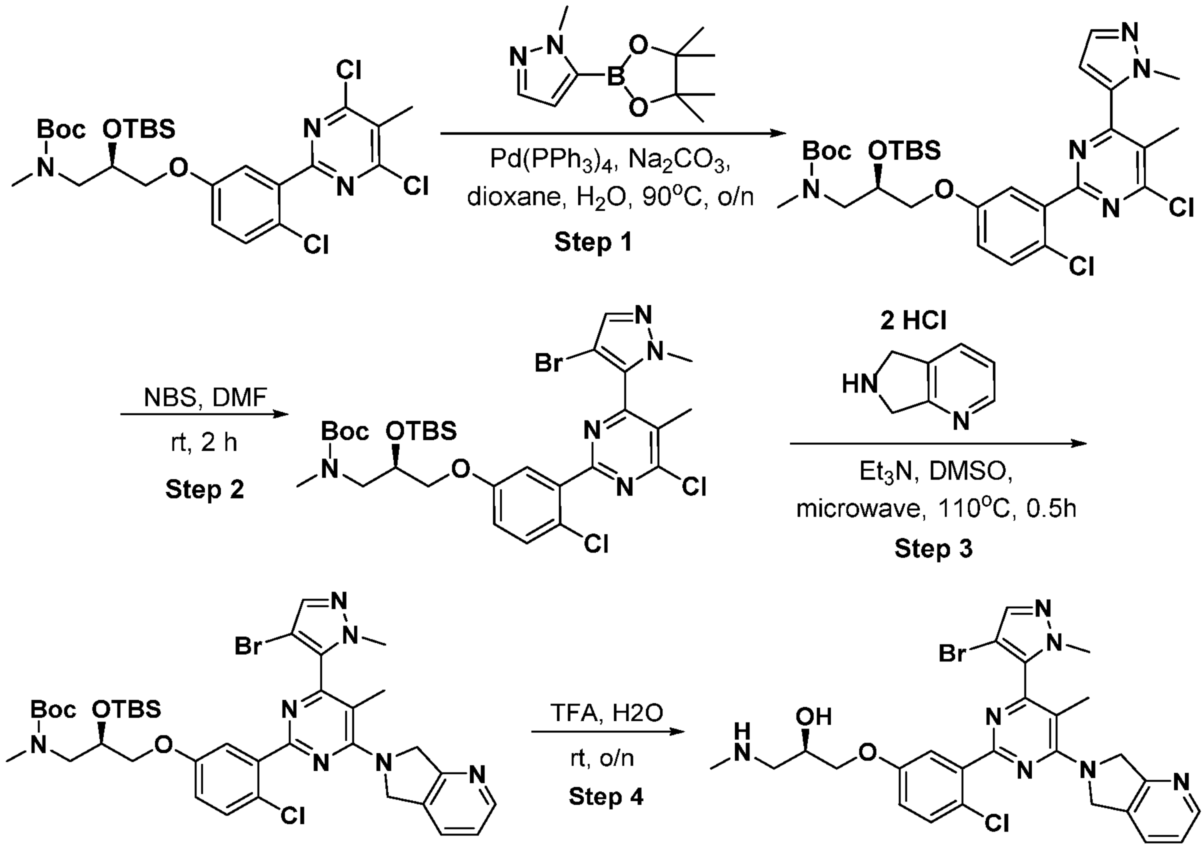


[00426] Step 1: tert-butyl (2R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3- (4-chloro-6-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl) phenoxy)propyl(methyl)carbamate . A solution of (R)-tert-butyl 2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-chloro- 5-methyl-6-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)phenoxy)propyl(methyl) carbamate (120 mg, 0.19 mmol) and NCS (45 mg, 0.34 mmol) in DMF (2 ml) was stirred at room temperature for 2 h; the mixture was then diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated to give tert-butyl (2R)-2-(tert-butyl- dimethylsilyloxy)-3-(4-chloro-3-(4-chloro-6-(4-chloro-1-methyl-1H-pyrazol-5-yl) -5-methylpyrimidin-2-yl)phenoxy)propyl (methyl)carbamate (120 mg, 94% yield) as white solid. ESI-LCMS (m/z): 670 found for $[M+1]^+$.

[00427] **Step 2: tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3- (4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-6-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl) pyrimidin-2-yl)phenoxy)propyl(methyl)carbamate.** A reaction pressure vessel was charged with a mixture of tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-chloro- 6-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl)phenoxy)propyl (methyl)carbamate (90 mg, 0.13 mmol); 6,7-dihydro -5H-pyrrolo[3,4-b]pyridine dihydrochloride (or any other suitably substituted primary or secondary amine, 0.15 mmol), triethylamine (30 mg, 0.3 mmol) and n-BuOH (2 mL). The vessel was capped, placed in a microwave reactor and irradiated for 30 min. at external temperature of 110 ℃. After being cooled down to room temperature, the mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated to give tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3- (4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-6-(5H-pyrrolo[3,4-b]pyridin-6(7H) -yl)pyrimidin-2-yl)phenoxy)propyl(methyl)carbamate as a yellow solid (120 mg, crude), which was used directly into next step without further purification. ESI-LCMS (m/z): 754.0 found for $[M+1]^+$.

[00428] **Step 3: (2R)-1-(4-chloro-3-(4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5- methyl-6-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl)phenoxy)-3-(methyl-amino)propan-2-ol.** A solution of tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-(4-chloro-1-methyl -1H-pyrazol-5-yl)-5-methyl-6-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl) phenoxy) propyl(methyl)carbamate (120 mg, crude, from step 2) in a 4N HCl solution in dioxane (6 mL), was stirred at room temperature for 1 h. The solvent was then removed in vacuo and the resulting residue was purified by preparative HPLC to give (2R)-1-(4-chloro-3-(4-(4-chloro-1- methyl-1H-pyrazol-5-yl)-5-methyl-6-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl) phenoxy)-3-(methylamino)propan-2-ol as a white solid (22 mg, 31% yield for 2 steps). ESI-LCMS (m/z): 540.2 found for $[M+H]^+$; ^{1}HNMR (400 MHz, CD_3OD) δ ppm: 8.50 (d, J = 4.8 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.61 (s, 1H), 7.44-7.38 (m, 2H), 7.35 (d, J = 3.2 Hz, 1H), 7.05(dd, J = 2.8 and 8.8 Hz, 1H), 5.44 (t, J = 14.8 Hz, 2H), 5.23 (t, J = 16.8 Hz, 2H), 4.15-4.08 (m, 1H), 4.06-3.98 (m, 2H), 3.89 (s, 3H), 2.86-2.73 (m, 2H), 2.51 (s, 3H), 2.47 (s, 3H).

Example 3. Preparation of (2R)-1-(3-(4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-6-(5H -pyrrolo[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl)-4-chlorophenoxy)-3-(methyl-amino)propan-2-ol



[00429] **Step 1: (R)-tert-butyl 2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4 -chloro-5-methyl-6-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)phenoxy)propyl (methyl)carbamate.** To a solution of (R)-tert-butyl 2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4,6-di- chloro-5-methylpyrimidin-2-yl)phenoxy)propyl(methyl)carbamate (1.0 g, 1.7 mmol) in degassed dioxane and H_2O (3/1, 24 mL) was added Na_2CO_3 (541 mg, 5.1 mmol), $Pd(PPh_3)_4$ (98 mg, 0.08 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxa-borolan-2-yl)-1H-pyrazole (707 mg, 3.4 mmol) at room temperature. The system was purged with N_2 and the mixture was stirred at 90 °C for 16h. After being cooled down to room temperature the solvent was removed in vacuo. The residue was diluted with water (30 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography over silicagel (petroleum ether/EtOAc = 4/1) to give (R)-tert-butyl 2-(tert-butyldimethylsilyloxy)-3- (4-chloro-3-(4-chloro-5-methyl-6-(1-methyl-

1H-pyrazol-5-yl)pyrimidin-2-yl)phenoxy)propyl(methyl)carbamate (420 mg, 39 % yield). ESI-LCMS (m/z): 658.2 found for $[M+23]^{+}$.

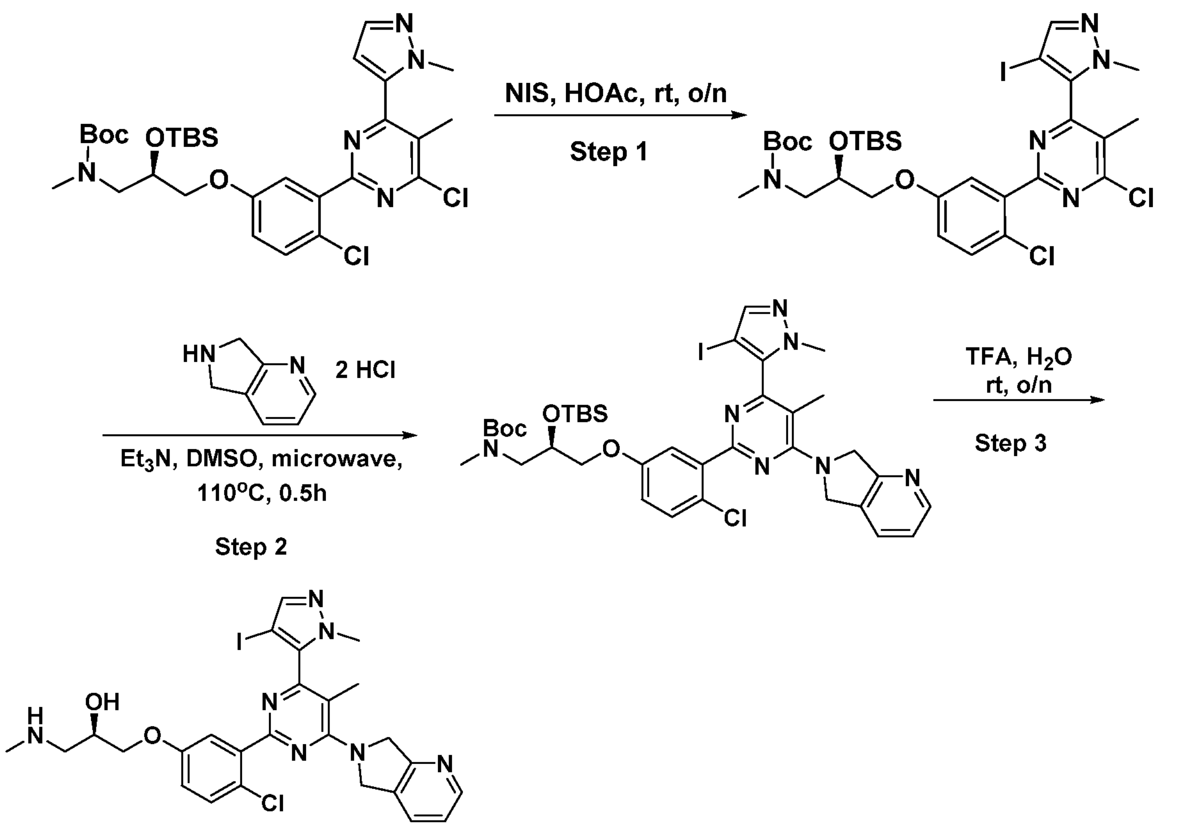
[00430] **Step 2: tert-butyl (2R)-3-(3-(4-(4-bromo-1-methyl-1H-pyrazol-5-yl)- 6-chloro-5-**methylpyrimidin**-2-yl)-4-chlorophenoxy)-2-(tert-butyldimethyl-silyloxy)propyl(methyl)carbamate.** A solution of (R)-tert-butyl 2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-chloro- 5-methyl-6-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)phenoxy)propyl(methyl) carbamate (120 mg, 0.19 mmol) and NBS (50 mg, 0.28 mmol) in DMF (3 ml) was stirred at room temperature for 2 h. After the reaction was complete the mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated to give tert-butyl (2R)-3-(3-(4-(4- bromo-1-methyl-1H-pyrazol-5-yl)-6-chloro-5-methylpyrimidin-2-yl)-4-chloro- phenoxy)-2-(tert-butyl dimethylsilyloxy)propyl(methyl)carbamate (120 mg, 88% yield). ESI-LCMS (m/z): 736.1 found for $[M+23]^{+}$.

[00431] **Step 3: tert-butyl (2R)-3-(3-(4-(4-bromo-1-methyl-1H-pyrazol-5-yl)- 5-methyl-6-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl)-4-chlorophenoxy)-2-(tert-**butyldimethylsilyloxy)**propyl(methyl)carbamate.** A reaction pressure vessel was charged with a mixture of tert-butyl (2R)-3-(3-(4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-6- chloro-5-methylpyrimidin-2-yl)-4-chlorophenoxy)-2-(tert-butyl dimethylsilyloxy)-propyl(methyl)carbamate (120 mg, 0.17 mmol); 6,7-dihydro -5H-pyrrolo[3,4-b]pyridine dihydrochloride (or any other suitably substituted primary or secondary amine, 0.34 mmol), triethylamine (0.5 mL, 3.5 mmol) and DMSO (3 mL). The vessel was capped, placed in a microwave reactor and irradiated for 30 min. at external temperature of 110 ℃. After being cooled down to room temperature, the mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography over silicagel to give tert-butyl (2R)-3-(3-(4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-6-(5H-pyrrolo [3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl)-4-chlorophenoxy)-2-(tert-butyldimethyl- silyloxy)propyl(methyl)carbamate (120 mg, 89% yield) as white solid. ESI-LCMS (m/z): 798.2found for $[M+H]^{+}$.

[00432] **Step 4: (2R)-1-(3-(4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl- 6-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl)-4-chlorophenoxy)-3-(methylamino)propan-2-ol.** A solution of tert-butyl (2R)-3-(3-(4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-6-(5H- pyrrolo[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl)-4-

chlorophenoxy)-2-(tert-butyldi- methylsilyl oxy)propyl(methyl)carbamate (120 mg, 0.15 mmol) in 90% TFA (2 mL) was stirred at room temperature for 16h; concentrated in vacuo and the residue was dissolved in MeOH (2 ml); the resulting solution was adjusted to pH 7-8 with aqueous K_2CO_3 solution, filtered and the filtrate was concentrated again. The residue was purified by preparative-HPLC to give (2R)-1-(3-(4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-6-(5H-pyrrolo[3,4-b] pyridin-6(7H)-yl)pyrimidin -2-yl)-4-chlorophenoxy)-3-(methylamino)propan-2-ol (26 mg, 30% yield) as white solid. ESI-LCMS (m/z): 584.1 found for $[M+H]^+$; ^{1}HNMR (400 MHz, CD_3OD) δ ppm: : 8.50 (d, J = 5.2 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.64 (s, 1H), 7.45-7.39 (m, 2H) , 7.35 (d, J = 3.2 Hz, 1H), 7.07 (dd, J = 2.8 and 8.8 Hz, 1H), 5.43 (t, J = 14.8 Hz, 2H), 5.24 (t, J = 16.8 Hz, 2H), 4.14-4.10 (m, 1H), 4.05-4.01 (m, 2H), 3.89 (s, 3H), 2.90-2.75 (m, 2H), 2.50 (s, 3H), 2.48 (s, 3H).

Example 4. Preparation of (2R)-1-(4-chloro-3-(4-(4-iodo-1-methyl-1H-pyrazol-5-yl)-5-methyl-6-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl)phenoxy)-3-(methyl-amino)propan-2-ol



[00433] Step 1: tert-butyl (2R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3- (4-chloro-6-(4-iodo-1-methyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-

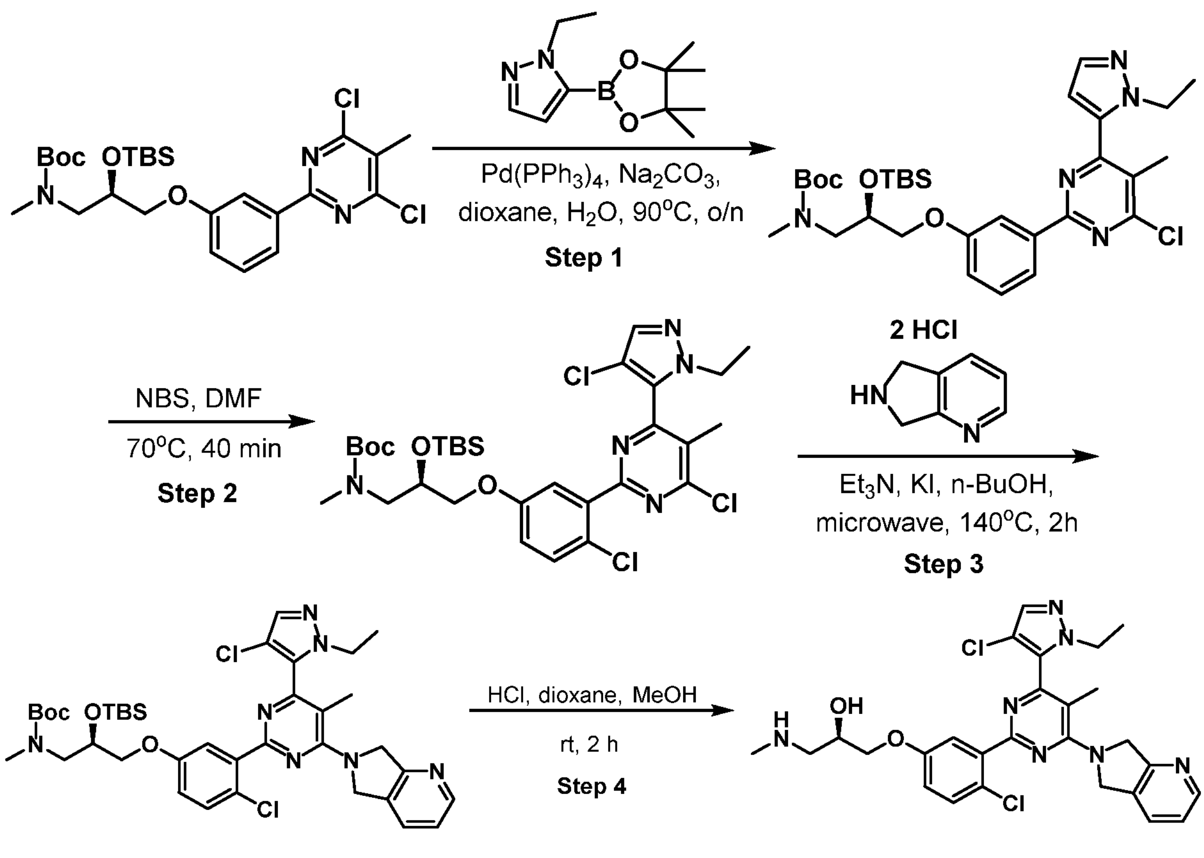
yl)phenoxy)propyl(methyl)carbamate. To a solution of (R)-tert-butyl 2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-chloro -5-methyl-6-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)phenoxy)propyl(methyl) carbamate (220 mg, 0.35 mmol) in HOAc (3 ml) was added NIS (117 mg, 0.52 mmol). The mixture was stirred at room temperature for 16h., diluted with water (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated to give tert-butyl (2R)-2-(tert- butyldimethylsilyloxy)-3-(4-chloro-3-(4-chloro-6-(4-iodo-1-methyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl)phenoxy)propyl(methyl)carbamate (160 mg, 60% yield). ESI-LCMS (m/z): 784.0 found for $[M+Na]^+$.

[00434] **Step 2: tert-butyl (2R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3- (4-(4-iodo-1-methyl-1H-pyrazol-5-yl)-5-methyl-6-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl)phenoxy)propyl(methyl)carbamate.** A reaction pressure vessel was charged with a mixture of tert-butyl (2R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-chloro-6-(4-iodo-1-methyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl)phenoxy)propyl(methyl)carbamate (160 mg, 0.2 mmol); 6,7-dihydro -5H-pyrrolo[3,4-b]pyridine dihydrochloride (or any other suitably substituted primary or secondary amine, 0.4 mmol), triethylamine (0.5 mL, 3.5 mmol) and DMSO (3 mL). The vessel was capped, placed in a microwave reactor and irradiated for 30 min. at external temperature of 110 ℃. After being cooled down to room temperature, the mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography over silicagel to give tert-butyl (2R)-2-(tert-butyldimethyl-silyloxy)-3-(4-chloro-3-(4-(4-iodo-1-methyl-1H-pyrazol-5-yl)-5-methyl-6-(5H- pyrrolo[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl)phenoxy)propyl(methyl)carbamate (160 mg, 95% yield). ESI-LCMS (m/z): 846 found for $[M+H]^+$.

[00435] **Step 3: (2R)-1-(4-chloro-3-(4-(4-iodo-1-methyl-1H-pyrazol-5-yl)-5- methyl-6-(5H-**pyrrolo**[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl)phenoxy)-3-(methyl-amino)propan-2-ol .** A solution of tert-butyl (2R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-(4-iodo-1-methyl -1H-pyrazol-5-yl)-5-methyl-6-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl) phenoxy)propyl(methyl)carbamate (160 mg, 0.19 mmol) was treated with 90% TFA (2.2 mL), and the mixture was stirred at room temperature for 16h. The mixture was concentrated in vacuo and the residue was dissolved in MeOH (2 ml). The solution was adjusted to pH 7-8 with aqueous K_2CO_3 solution, then the mixture was filtered. The filtrate was concentrated,

and the residue was purified by preparative HPLC to give (2R)-1-(4-chloro-3-(4-(4-iodo-1-methyl-1H -pyrazol-5-yl)-5-methyl-6-(5H- pyrrolo[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl)phenoxy)-3-(methylamino) propan-2-ol (91 mg, 76% yield). ESI-LCMS (m/z): 632.1 found for $[M+H]^+$; ^{1}HNMR (400 MHz, CD_3OD) δ ppm: 8.50 (d, J = 4.8 Hz, 1H), 7.89 (d, J = 7.2 Hz, 1H), 7.65 (s, 1H), 7.43-7.38 (m, 2H) , 7.37 (d, J = 3.2 Hz, 1H), 7.05 (dd, J = 3.2 and 8.8 Hz, 1H), 5.45-5.37 (m, 2H), 5.30-5.21 (m, 2H), 4.12-4.09 (m, 1H), 4.06-3.98 (m, 2H), 3.90 (s, 3H), 2.84-2.71 (m, 2H), 2.47 (s, 3H), 2.46 (s, 3H).

Example 5. Preparation of (2R)-1-(4-chloro-3-(4-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-5-methyl-6-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl)phenoxy)-3-(methyl-amino)propan-2-ol



[00436] Step **1: tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(3-(4-chloro- 6-(1-ethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl)phenoxy)propyl(methyl) carbamate.** To a solution of (R)-tert-butyl 2-(tert-butyldimethylsilyloxy)-3-(3-(4,6-dichloro-5- methyl-pyrimidin-2-yl)phenoxy)propyl(methyl)carbamate (1.0 g, 1.7 mmol) in degassed dioxane / H_2O (5/1, 30 mL) was added 1-ethyl-5-(4,4,5,5-tetra- methyl-1,2-oxaborolan-2-yl)-1H-pyrazole (420 mg, 1.9 mmol); $Pd(PPh_3)_4$ (104 mg, 0.09 mmol) and Na_2CO_3 (572 mg, 5.4

mmol) at room temperature. The system was purged with N_2 and the mixture was stirred at 90 °C for 16h. After being cooled down to room temperature, the solvent was removed in vacuo. The residue was diluted with water (30 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography over silicagel (petroleum ether/EtOAc = 2/1) to give tert-butyl (R)-2-(tert-butyldimethyl-silyloxy)-3-(3-(4-chloro-6-(1-ethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl) phenoxy)propyl(methyl)carbamate (540 mg, white solid, 49% yield). ESI-LCMS (m/z): 638.4 found for $[M+23]^+$.

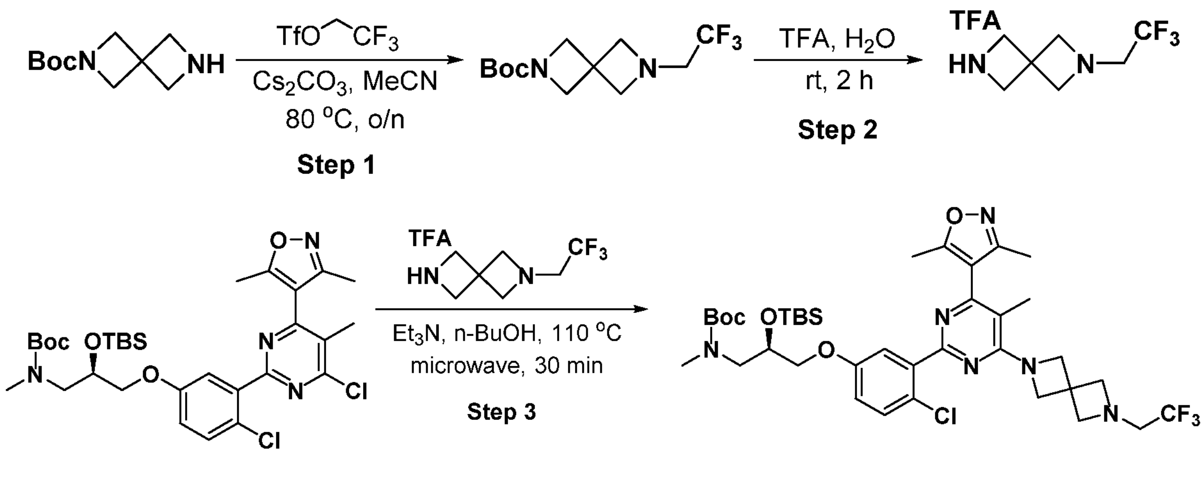
[00437] **Step 2: tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3- (4-chloro-6-(4-**chloro**-1-ethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl)phenoxy) propyl(methyl) carbamate.** To a solution of tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(3-(4-chloro-6-(1- ethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl)phenoxy)propyl(methyl)carbamate (400 mg, 0.65 mmol) in 30 mL of DMF was added NCS (389 mg, 2.92 mmol) and the mixture was heated at 70°C for 40 min; cooled down to room temperature, diluted with EtOAc (30 mL) and washed with water (30 mL x 2) and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated and the resulting residue was purified by preparative TLC (petroleum ether/EtOAc = 3/1) to give tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-chloro-6- (4-chloro-1-ethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl)phenoxy)propyl(methyl) carbamate (390 mg, white solid, 88% yield). ESI-LCMS (m/z): 630.4 found for $[M-56]^+$.

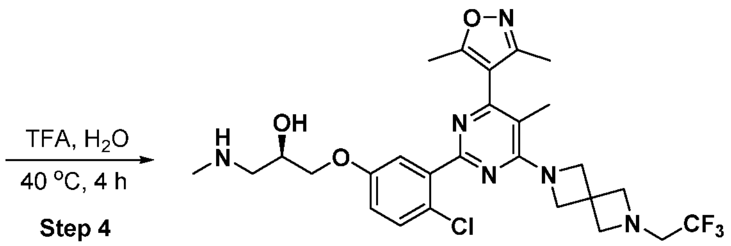
[00438] **Step 3: tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3- (4-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-5-methyl-6-(5H-pyrrolo[3,4-b]pyridin-6 (7H)-yl)pyrimidin-2-yl)phenoxy)propyl(methyl)carbamate.** A reaction pressure vessel was charged with a mixture of tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-chloro-6-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl)phenoxy)propyl (methyl) carbamate (100 mg, 0.15 mmol); 6,7-dihydro -5H-pyrrolo[3,4-b]pyridine dihydrochloride (or any other suitably substituted primary or secondary amine, 0.35 mmol), KI (30 mg, 0.18 mmol), triethylamine (2 mL) and n-BuOH (4 mL). The vessel was capped, placed in a microwave reactor and irradiated for 2h. at external temperature of 140 °C. After being cooled down to room temperature, 30 mL of water was added and the mixture was extracted with EtOAc (40 mL x 3). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated to give tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-(4-chloro-1- ethyl-1H-pyrazol-5-yl)-5-methyl-

6-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)pyrimidin-2- yl)phenoxy)propyl (methyl) carbamate (128 mg, crude), which was used for next step directly without further purification. ESI-LCMS (m/z): 768.4 found for $[M+1]^+$.

[00439] Step 4: (2R)-1-(4-chloro-3-(4-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-5- methyl-6-(5H-pyrrolo**[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl)phenoxy)-3-(methyl-amino)propan-2-ol** . A solution of tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-(4-chloro - 1-ethyl-1H-pyrazol-5-yl)-5-methyl-6-(5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)pyrimidin-2-yl)phenoxy) propyl(methyl)carbamate (128 mg, crude from step 3) in MeOH (2 mL) was treated with 2 mL of 4N HCl solution in dioxane and the mixture was stirred at room temperature for 2 h. The solvent was then removed in vacuo, the resulting residue was dissolved in MeOH (5 mL) and treated with ammonia till pH 8-9. The mixture was concentrated under vacuum and the residue was purified by preparative HPLC to give (2R)-1-(4-chloro-3-(4-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-5-methyl-6-(5H-pyrrolo[3,4-b]pyridine-6(7H)-yl) pyrimidin-2-yl)phenoxy)-3-(methylamino)propan-2-ol as white solid (60 mg, 72 % yield for two steps). ESI-LCMS: 554.0 found for $[M+1]^+$; ^{1}HNMR (400 MHz, CD_3OD) δ ppm: 8.49 (d, J = 4.8 Hz, 1H), 7.87 (d, J = 7.2 Hz, 1H), 7.62 (s, 1H), 7.44-7.37 (m, 2H), 7.34 (d, J = 3.2 Hz, 1H), 7.05 (dd, J = 2.8 and 8.8 Hz, 1H), 5.43 (t, J = 15.2 Hz, 2H), 5.20 (t, J = 17.6 Hz, 2H), 4.35-4.26 (m, 1H), 4.21-4.10 (m, 2H), 4.06-3.98 (m, 2H), 2.88-2.74 (m, 2H), 2.49 (s, 3H), 2.48 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H).

Example 6. Preparation of (2R)-1-(4-chloro-3-(4-(3,5-dimethylisoxazol-4-yl)-5-methyl-6-(6- (2,2,2-trifluoroethyl**)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-2-yl)phenoxy)-3-(methylamino)propan-2-ol**





[00440] **Step 1: tert-butyl 6-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptane -2-carboxylate.** To a solution of tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (200 mg, 1.01 mmol) in MeCN (6 mL) was added 3,3,3-trifluoropropyl trifluoromethanesulfonate (403 mg, 1.65 mmol) and Cs_2CO_3 (804 mg, 2.47 mmol) at room temperature. The reaction mixture was stirred at 80 °C overnight, cooled down to room temperature, diluted with water (80 mL) and extracted with EtOAc (60 mL x 3). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give tert-butyl 6-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate as white solid (250 mg, crude), which was used into next step directly without further purification. ESI-LCMS (m/z): 281.1 found for $[M+1]^+$.

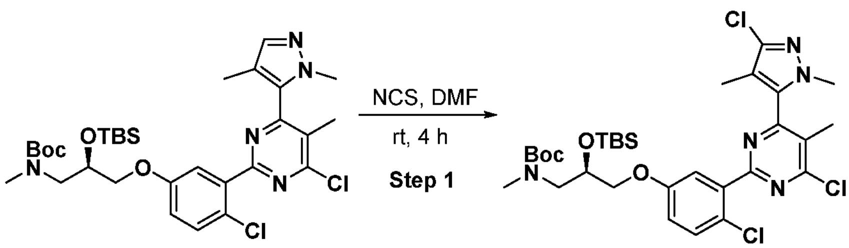
[00441] **Step 2: 2-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptane TFA salt.** A solution of tert-butyl 6-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (250 mg, crude from step 1) in TFA (5 mL) and water (0.5 ml) was stirred at room temperature for 2 h. The solvent was then removed in vacuo to give 2-(2,2,2-trifluoroethyl)-2,6-diaza-spiro[3.3]heptane 2,2,2-trifluoroacetate trifluoroacetate salt as brown solid (920 mg, crude), which was used into next step directly without further purification. ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm: 4.36 (s, 4H), 4.29(s, 4H), 3.97-3.90 (m, 2H).

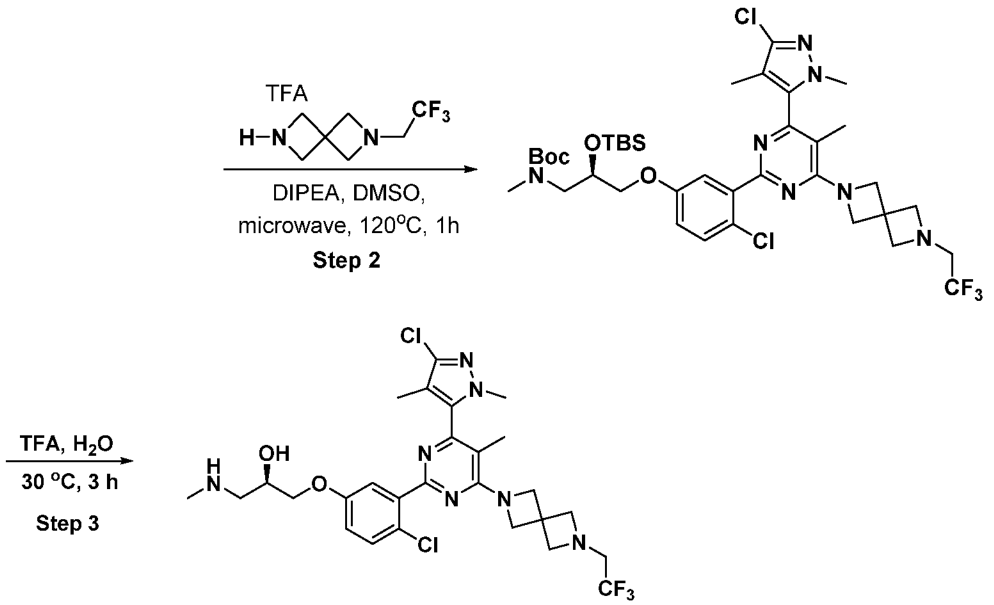
[00442] **Step 3: tert-butyl (2R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3- (4-(3,5-dimethylisoxazol-4-yl)-5-methyl-6-(6-(2,2,2-trifluoroethyl)-2,6-diazaspiro [3.3]heptan-2-yl) pyrimidin-2-yl)phenoxy)propyl(methyl)carbamate.** A reaction pressure vessel was charged with a mixture of tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-chloro -6-(3,5-dimethylisoxazol-4-yl)-5-methyl pyrimidin-2-yl)phenoxy)propyl(methyl) carbamate (100 mg, 0.15 mmol); 2-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptane TFA salt (or any other suitably substituted primary or secondary amine, 1.54 mmol), triethylamine (186 mg, 1.85 mmol) and n-BuOH (1 mL). The vessel was capped, placed in a microwave reactor and irradiated for 30 min. at external temperature of 110 °C; cooled down to room temperature, diluted with water (70 mL) and extracted with EtOAc (60 mL x 3). The organic layers were combined, concentrated in vacuo and the residue was purified by preparative TLC developed with petroleum ether/EtOAc = 2/1 to give tert-butyl (2R)-2-(tert-

butyldimethyl- silyloxy)-3-(4-chloro-3-(4-(3,5-dimethylisoxazol-4-yl)-5-methyl-6-(6-(2,2,2-trifluoro-ethyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-2-yl)phenoxy)propyl(methyl) carbamate as light yellow solid (110 mg, 89.7 %). ESI-LCMS (m/z): 795.3 found for $[M+1]^+$.

[00443] **Step 4: (2R)-1-(4-chloro-3-(4-(3,5-dimethylisoxazol-4-yl)-5-methyl-6 -(6-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-2-yl)phenoxy)-3-(methylamino)propan-2-ol.** A solution of tert-butyl (2R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-(3,5-dimethyl- isoxazol-4-yl)-5-methyl-6-(6-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptan-2-yl) pyrimidin-2-yl) phenoxy)propyl(methyl)carbamate (110 mg, 0.14 mmol) in TFA (5 mL) and water (0.5 ml), was stirred at 40 °C for 8 h. The solvent was then removed in vacuo, the residue was dissolved in MeOH (3 ml) and the solution was adjusted to pH 9 with ammonia. The solvent was removed in rotary evaporator and the residue was purified by preparative HPLC to give (2R)-1-(4-chloro-3-(4-(3,5-dimethylisoxazol-4-yl)-5-methyl-6-(6-(2,2,2-trifluoroethyl) -2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-2-yl)phenoxy)-3-(methylamino) propan-2-ol as a white solid (26 mg, 32%). ESI-LCMS (m/z): 581.1 found for $[M+H]^+$; ^{1}HNMR (400 MHz, CD_3OD) δ ppm: 7.39 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 2.8 Hz, 1H), 7.05 (dd, J = 3.2 and 8.8 Hz, 1H), 4.50 (s, 4H), 4.14-4.07 (m, 1H), 4.05-3.96 (m, 2H), 3.65 (s, 4H), 3.20-3.12 (m, 2H), 2.85-2.70 (m, 2H), 2.46 (s, 3H), 2.37 (s, 3H), 2.24 (s, 3H), 2.14 (s, 3H).

Example 7. Preparation of (2R)-1-(4-chloro-3-(4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-6-(6-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-2-yl)phenoxy)-3-(methylamino)propan-2-ol



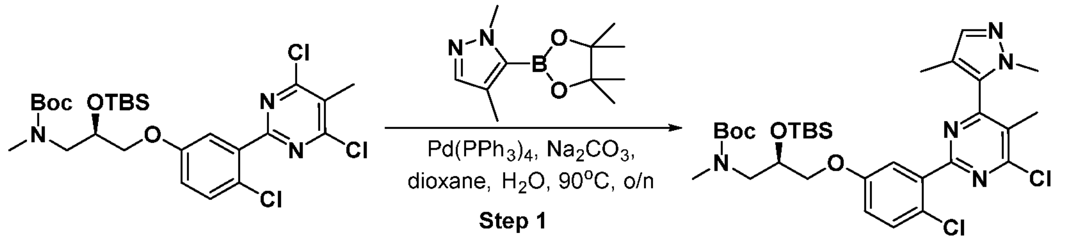


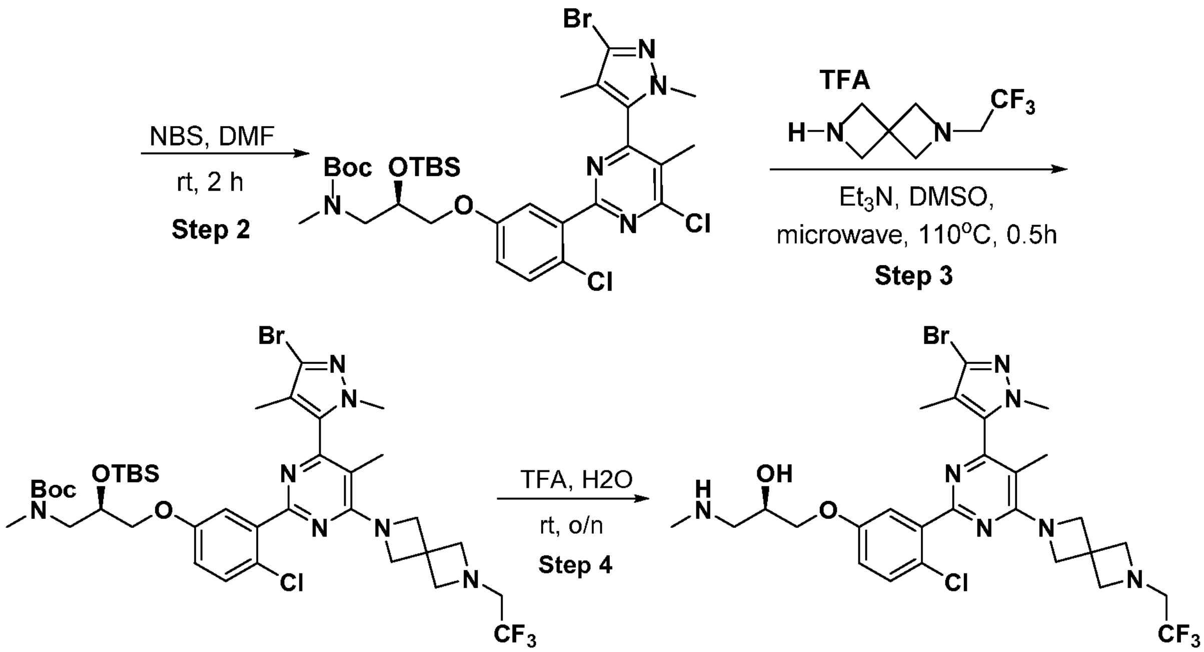
[00444] Step 1: tert-butyl (2R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-chloro-6-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl) phenoxy)propyl(methyl)carbamate. A solution of tert-butyl (2R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-chloro-6-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl)phenoxy)propyl(methyl) carbamate (1.66 g, 2.55 mmol) and N-chlorosuccinimide (509 mg, 3.83 mmol) in DMF (20 mL) was stirred at room temperature for 12 h. After the reaction was complete, water (50 mL) and ethyl acetate (50 mL) were added. The organic layer was separated and washed with water (50 mL x 4) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography over silicagel eluted with petroleum ether/ethyl acetate = 5:1 to give tert-butyl (2R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-chloro -6-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl)phenoxy)propyl(methyl)carbamate (420 mg, 24% yield) as a colorless oil. ESI-LCMS (m/z): 706.2 found for $[M+Na]^+$.

[00445] Step 2: tert-butyl (2R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-6-(6-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-2-yl)phenoxy)propyl(methyl)carbamate. A reaction pressure vessel was charged with a mixture of tert-butyl (2R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-chloro-6-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl)phenoxy)propyl(methyl)carbamate (200 mg, 0.29 mmol); 2-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptane TFA salt (or any other suitably substituted primary or secondary amine, 0.35 mmol), DIPEA (151 mg, 1.17 mmol) and DMSO (4 mL). The veseel was capped, placed in a microwave reactor and irradiated for 30 min. at external temperature of 140 °C. After being cooled down to room temperature, the mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with water (50 mL x 4) and brine (40 mL), dried over Na_2SO_4, filtered and concentrated to give tert-butyl (2R)-2-(tert-butyl dimethyl silyloxy)-3-(4- chloro-3-(4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-6-(6-(2,2,2-trifluoro- ethyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-2-yl)phenoxy)propyl (methyl) carbamate (270 mg, crude) as a brown oil, which was used directly in the next step without further purification. ESI- LCMS (m/z): 828.0 found for $[M+H]^+$.

[00446] **Step 3: (2R)-1-(4-chloro-3-(4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-6-(6-(2,2,2-trifluoroethyl)-2,6-diazaspiro 3.3]heptan-2-yl)pyrimidin-2-yl)phenoxy)-3-(methylamino)propan-2-ol**. A solution of tert-butyl(2R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-6-(6-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-2-yl)phenoxy)propyl(methyl)carbamate (270 mg, crude, from step 2) in 90% TFA (5 mL) was stirred at 30 °C for 3h. The solvent was then removed in vacuo, the residue was dissolved in MeOH (5 ml) and the solution was adjusted to pH 7-8 with ammonia. The solvent was removed in rotary evaporator and the residue was purified by preparative HPLC to give (2R)-1-(4-chloro-3-(4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-6- (6-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-2-yl)phenoxy)-3-(methylamino)propan-2-ol as a white solid (27 mg, 15% yield for 2 steps). ESI-LCMS (m/z): 614.0 found for $[M+H]^+$; ^{1}HNMR (400 MHz, MeOD) δ ppm: 7.39 (d, J = 8.8 Hz, 1H), 7.21 (d, J = 3.2 Hz, 1H), 7.04 (dd, J = 3.2 and 8.8 Hz, 1H), 4.58-4.49 (m, 4H), 4.13-4.07 (m, 1H), 4.05-3.96 (m, 2H), 3.72 (s, 3H), 3.65 (s, 4H), 3.16 (q, J = 9.6 Hz, 2H), 2.86-2.72 (m, 2H), 2.48 (s, 3H), 2.13 (s, 3H), 1.95 (s, 3H).

Example 8. Preparation of (2R)-1-(3-(4-(3-bromo-1,4-dimethyl-1H-pyrazol-5-yl)- 5-methyl-6 -(6-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-2-yl)-4-chloro-phenoxy)-3-(methylamino)propan-2-ol





[00447] Step 1: tert-butyl (2R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3- (4-chloro-6-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl)phenoxy) propyl(methyl)carbamate. To a solution of (R)-tert-butyl 2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4,6- dichloro-5-methylpyrimidin-2-yl)phenoxy)propyl(methyl)carbamate (1.0 g, 1.7 mmol) in degassed dioxane and H_2O (3/1, 20 mL) was added Na_2CO_3 (541 mg, 5.1 mmol), $Pd(PPh_3)_4$ (98 mg, 0.08 mmol) and 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxa-borolan-2-yl)-1H-pyrazole (755 mg, 3.4 mmol). The system was purged with N_2 and the mixture was stirred at 90 °C for 16h. After being cooled down to room temperature, the solvent was removed in vacuo. The residue was diluted with water (30 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography over silicagel (petroleum ether/EtOAc = 4/1) to give tert-butyl (2R)-2-(tert-butyldimethylsilyloxy)- 3-(4-chloro- 3-(4-chloro-6-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl)phenoxy)propyl(methyl) carbamate (520 mg, 47 % yield) as white solid. ESI-LCMS (m/z): 650 found for $[M+1]^+$.

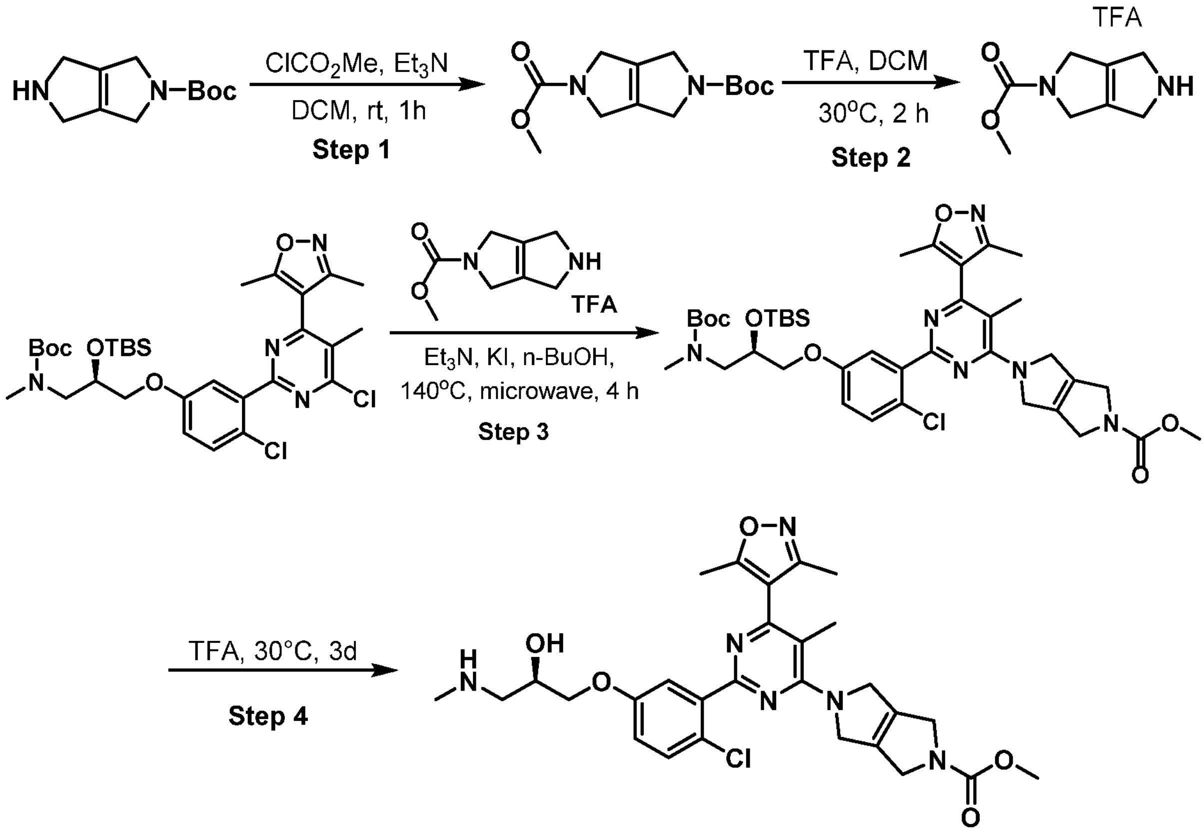
[00448] Step 2: tert-butyl (2R)-3-(3-(4-(3-bromo-1,4-dimethy l-1H-pyrazol-5 -yl)-6-chloro-5-methylpyrimidin-2-yl)-4-chlorophenoxy)-2-(tert-butyldimethyl-silyloxy)propyl(methyl)carbamate. A solution of (2R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-chloro-6-(1,4- dimethyl-1H-pyrazol-5-yl)-5-methylpyrimidin-2-yl)phenoxy)propyl(methyl) carbamate (520 mg, 0.8 mmol) and NBS (470 mg, 2.64 mmol) in DMF (5 ml) was stirred at room temperature for 2h. The mixture was diluted with water (50 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated to give tert-butyl (2R)-3-(3-(4-(3-bromo-1,4-dimethyl-1H-pyrazol-5-yl)-6-chloro-5-methylpyrimidin-2-yl)-4-chlorophenoxy)-2-(tert-butyldimethylsilyloxy)propyl(methyl)carbamate (600 mg, 103% yield). ESI-LCMS (m/z): 750 found for $[M+23]^+$.

[00449] **Step 3: tert-butyl (2R)-3-(3-(4-(3-bromo-1,4-dimethyl-1H-pyrazol-5- yl)-5-methyl-6-(6-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-2-yl)-4-chlorophenoxy)-2-(tert-butyldimethylsilyloxy)propyl(methyl)carbamate.** A reaction pressure vessel was charged with a mixture of tert-butyl (2R)-3-(3-(4-(3-bromo-1,4-dimethyl-1H-pyrazol-5-yl)-6- chloro-5-methylpyrimidin-2-yl)-4-chlorophenoxy)-2-(tert-butyldimethylsilyloxy) propyl(methyl)carbamate (130 mg, 0.18 mmol); 2-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptane TFA salt (or any other suitably substituted primary or secondary amine, 0.36 mmol), triethylamine (0.5 mL, 3.5 mmol).and DMSO (3 mL). The vessel was capped, placed in a microwave reactor and irradiated for 30 min. at external temperature of 110 ℃. After being cooled down to room temperature, the mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated and the residue was submitted to purification by column chromatography over silicagel to give tert-butyl (2R)-3-(3-(4-(3-bromo-1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-6-(6-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3] heptan-2-yl)pyrimidin-2-yl)-4-chlorophenoxy)-2-(tert-butyldimethylsilyloxy) propyl (methyl) carbamate (120 mg, 76% yield) as white solid. ESI-LCMS (m/z): 872.2found for $[M+H]^+$.

[00450] **Step 4: (2R)-1-(3-(4-(3-bromo-1,4-dimethyl-1H-pyrazol-5-yl)-5- methyl-6-(6-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-2-yl)-4-chlorophenoxy)-3-(methylamino)propan-2-ol.** A solution of tert-butyl (2R)-3-(3-(4-(3-bromo-1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-6-(6- (2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-2-yl)-4-chlorophenoxy)-2-(tert-butyldimethylsilyloxy)propyl(methyl)carbamate (100 mg, 0.11 mmol) in 90% TFA (2 mL) was stirred at room temperature for 16h. After removal of voltiles in vacuo, the residue was dissolved in MeOH (2 ml), the solution pH was adjusted to 7-8 with aqueous K_2CO_3 solution; the mixture was filtered and the filtrate was concentrated. The resulting residue was purified by preparative HPLC to give (2R)-1-(3-(4-(3-bromo-1,4-dimethyl-1H-pyrazol-5-yl) -5-methyl-6-(6-(2,2,2-trifluoroethyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-2-yl)-4-chlorophenoxy)-3-(methyl amino)propan-2-ol (23 mg, 32% yield) as white solid. ESI-LCMS (m/z): 658.1 found for $[M+H]^+$; ^{1}HNMR

(400 MHz, CD_3OD) δ ppm: : 7.39 (d, J = 8.8 Hz, 1H), 7.21 (d, J = 2.8 Hz, 1H), 7.04 (dd, J =2.8 and 8.8 Hz, 1H) , 4.60-4.50 (m, 4H), 4.13-4.08 (m, 1H), 4.04-3.98 (m, 2H), 3.75 (s, 3H), 3.65 (s, 4H), 3.21-3.12 (m, 2H), 2.88-2.75 (m, 2H), 2.49 (s, 3H), 2.12 (s, 3H), 1.94 (s, 3H).

Example 9. Preparation of methyl (R)-5-(2-(2-chloro-5-(2-hydroxy-3-(methylamino)propoxy)phenyl)-6-(3,5-dimethylisoxazol-4-yl)-5-methylpyrimidin-4-yl)-3,4,5,6-tetrahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate



[00451] **Step 1: 2-(tert-butyl) 5-methyl 4,6-dihydropyrrolo[3,4-c]pyrrole-2,5(1H,3H)-dicarboxylate.** To a solution tert-butyl 3,4,5,6-tetrahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (100 mg, 0.404 mmol) and triethylamine (82 mg, 0.80 mmol) in 5 mL of DCM was added and $ClCO_2Me$ (58 mg, 0.61 mmol) and the mixture was stirred at room temperature for 1h. After the reaction was complete, water (10 mL) was added and the mixture was extracted with DCM (15 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated to give 2-(tert-butyl) 5-methyl 4,6-dihydropyrrolo[3,4-c]pyrrole-2,5(1H,3H)-dicarboxylate (98 mg, 90% yield). ESI-LCMS (m/z): 269.7 found for $[M+1]^+$.

[00452] **Step 2: methyl 3,4,5,6-tetrahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate TFA salt.** A solution of 2-(tert-butyl) 5-methyl 4,6-dihydropyrrolo[3,4-c]pyrrole-2,5(1H,3H)-

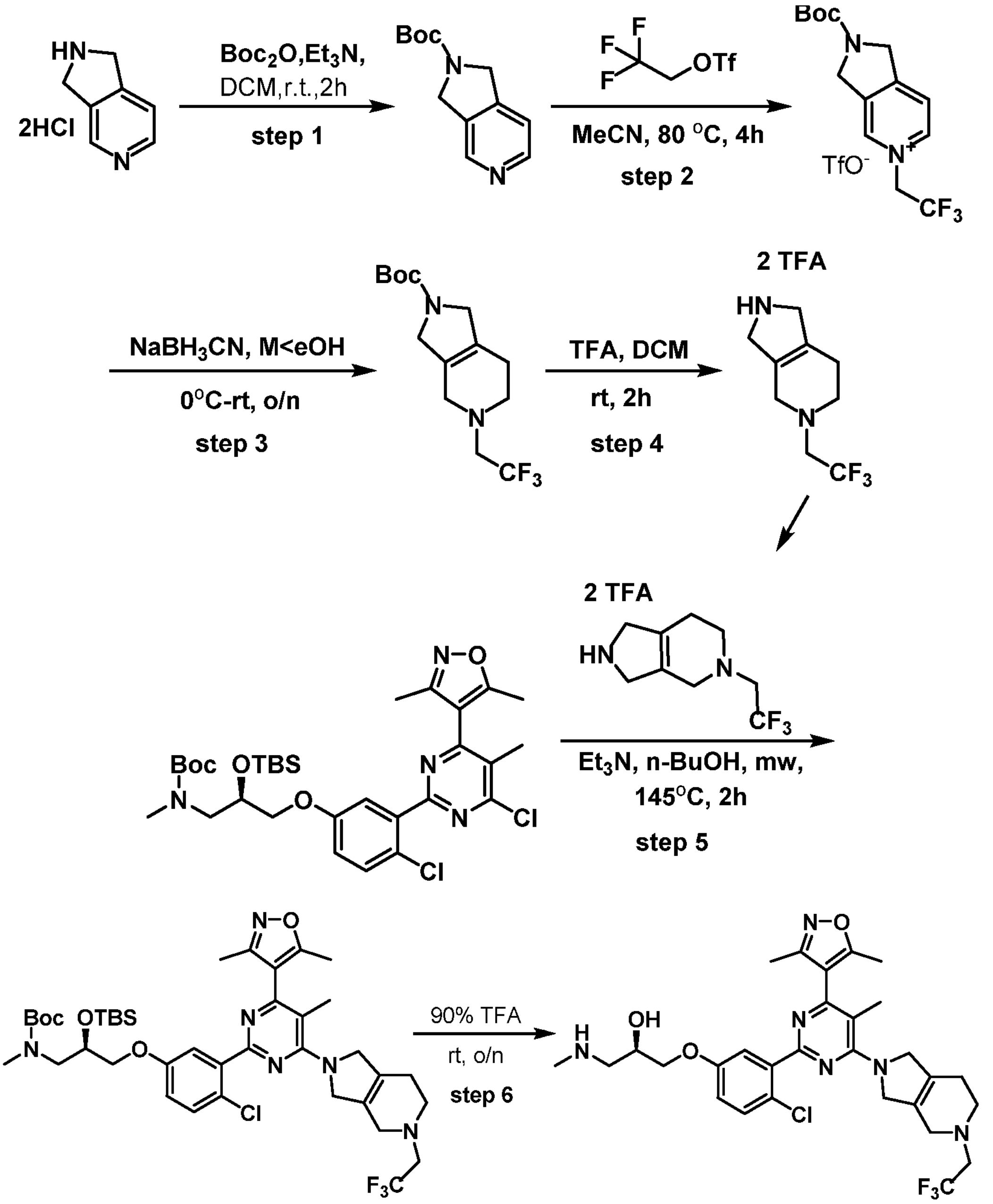
dicarboxylate (98 mg, 0.37 mmol) in DCM (3 mL) was treated with TFA (2 mL) and the mixture was stirred at 30℃ for 2 h. The solvent was removed in vacuo to give methyl 3,4,5,6-tetrahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate TFA salt (210 mg, 100% yield), which was used directly for the next step without further purification. ESI-LCMS (m/z): 169.7 found for $[M+1]^+$.

[00453] **Step 3: methyl (R)-5-(2-(5-(3-((tert-butoxycarbonyl)(methyl)amino)-2-((tert-butyldimethylsilyl)oxy)propoxy)-2-chlorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-5-methyl pyrimidin-4-yl)-3,4,5,6-tetrahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate.** A reaction pressure vessel was charged with a mixture of tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4- chloro-6-(3,5-dimethylisoxazol-4-yl)-5-methyl pyrimidin-2-yl)phenoxy)propyl(methyl) carbamate (150 mg, 0.23 mmol); methyl 3,4,5,6-tetrahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate TFA salt, (or any other suitably substituted primary or secondary amine, 0.79 mmol), KI (30 mg, 0.18 mmol), triethylamine (2 mL).and n-BuOH (3 mL). The vessel was capped, placed in a microwave reactor and irradiated for 2h. at external temperature of 140 ℃. After being cooled down to room temperature, 20 mL of water was added and the mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative TLC ($MeOH/CH_2Cl_2$ = 1/25) to give methyl (R)-5-(2-(5-(3-((tert-butoxycarbonyl)(methyl)amino)-2-((tert-butyldimethylsilyl)oxy)propoxy)-2-chloro phenyl)-6-(3,5-dimethylisoxazol-4-yl)-5-methylpyrimidin-4-yl)-3,4,5,6-tetrahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (145 mg, 81% yield). ESI-LCMS (m/z): 783.4 found for $[M+1]^+$.

[00454] **Step 4: methyl (R)-5-(2-(2-chloro-5-(2-hydroxy-3-(methylamino)propoxy)phenyl)-6-(3,5-dimethylisoxazol-4-yl)-5-methylpyrimidin-4-yl)-3,4,5,6-tetrahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate.** A solution of methyl (R)-5-(2-(5-(3-((tert-butoxycarbonyl)(methyl)amino)-2-((tert-butyldimethylsilyl)oxy) propoxy)-2-chlorophenyl)-6-(3,5-dimethylisoxazol-4-yl)-5-methyl pyrimidin-4-yl)-3,4,5,6-tetrahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (100 mg, 0.12 mmol) in 90% TFA (3 ml) was stirred at 30℃ for 72 h. The solvent was then removed in vacuo and the residue was dissolved in MeOH (5 mL). Ammonia was added to adjust the pH to 8-9; the mixture was concentrated under vacuum and the residue was purified by preparative HPLC to give methyl (R)-5-(2-(2-chloro-5-(2-hydroxy-3-(methylamino) propoxy)phenyl)-6-(3,5-dimethylisoxazol-4-yl)-5-methylpyrimidin-4-yl)-3,4,5,6-tetrahydro pyrrolo[3,4-c]pyrrole-2(1H)-carboxylate

(45 mg, 62 % yield). ESI-LCMS: 569.1 found for $[M+1]^+$; ^{1}HNMR (400 MHz, CD_3OD) δ ppm: 7.39 (d, J = 8.8 Hz, 1H), 7.27 (d, J = 2.8 Hz, 1H) 7.06-7.00 (m, 1H), 4.71 (br s, 4H), 4.25 (br s, 4H), 4.13-4.08 (m, 1H), 4.06-3.98 (m, 2H), 3.76 (s, 3H), 2.84-2.70 (m, 2H), 2.47 (s, 3H), 2.41 (s, 3H), 2.36 (s, 3H), 2.27 (s, 3H).

Example 10. Preparation of (R)-1-(4-chloro-3-(4-(3,5-dimethylisoxazol-4-yl)-5-methyl-6-(5-(2,2,2-trifluoroethyl)-1,3,4,5,6,7-hexahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)pyrimidin-2-yl) phenoxy)-3-(methylamino)propan-2-ol



[00455] Step 1: tert-butyl 1H-pyrrolo[3,4-c]pyridine-2(3H)-carboxylate. A solution of 2,3-dihydro-1H-pyrrolo[3,4-c]pyridine dihydrochloride (1.0 g, 5.2 mmol) and Et_3N (1.1 g, 10.9 mmol) in DCM (50 mL) was treated with slow addition of Boc_2O (1.2 g, 5.5 mmol). The mixture was stirred at room temperature for 2h, concentrated in rotary evaporator and the residue was purified by column chromatography over silicagel (petroleum ether/EtOAc = 1/1) to give tert-butyl 1H-pyrrolo[3,4-c]pyridine-2(3H)-carboxylate (0.9 g, 78 % yield). ESI-LCMS (m/z): 221.1 found for $[M+H]^+$.

[00456] **Step 2: 2-(tert-butoxycarbonyl)-5-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-5-ium trifluoromethanesulfonate.** A solution of tert-butyl 1H-pyrrolo[3,4-c]pyridine-2(3H)-carboxylate (500 mg, 2.3 mmol) in MeCN (10 mL) was treated with 2,2,2-trifluoroethyl trifluoromethane sulfonate (1.1 g, 4.7 mmol) and the reaction mixture was stirred at external temperature of 80℃ for 4 h. After being cooled down to room temperature, the mixture was concentrated to give 2-(tert- butoxycarbonyl)-5-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-5-ium trifluoro methanesulfonate (0.7 g, crude), which was used directly without further purification. ESI-LCMS (m/z): 303.1 found for $[M+H]^+$.

[00457] **Step 3: tert-butyl 5-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydro-1H-pyrrolo[3,4-c]pyridine-2(3H)-carboxylate.** A solution of 2-(tert-butoxycarbonyl)-5-(2,2,2-trifluoroethyl)-2,3-dihydro-1H- pyrrolo[3,4-c]pyridin-5-ium trifluoromethanesulfonate (700 mg, crude from step 2) in MeOH (100 mL) was treated with $NaBH_3CN$ (302 mg, 4.8 mmol) and the reaction mixture was stirred at room temperature for 16h. and then concentrated under vacuum. The residue was dissolved in DCM (50 ml) and the solution was washed with water (50 ml). The organic layer was concentrated and the residue was purified by column chromatography over silicagel (petroleum ether/EtOAc = 1/3) to give tert-butyl 5- (2,2,2-trifluoroethyl)-4,5,6,7-tetrahydro-1H-pyrrolo[3,4-c]pyridine-2(3H)-carboxylate (white solid, 350 mg, 50% yield for two steps). ESI-LCMS (m/z): 307.0 found for $[M+H]^+$.

[00458] **Step 4: 5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1H-pyrrolo[3,4-c]pyridine trifluoroacetate salt.** A solution of tert-butyl 5-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydro-1H-pyrrolo[3,4-c]pyridine-2(3H)-carboxylate (200 mg, 0.65 mmol) in TFA/DCM (v/v=1/3, 10 ml) was stirred at room temperature for 2h. and then the solvent was removed under vacuo to afford 5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7- hexahydro-1H-pyrrolo[3,4-c]pyridine as trifluoroacetate salt, which was used directly without further purification. Assumed quantitative yield. ESI-LCMS (m/z): 207.1 found for $[M+H]^+$.

[00459] **Step 5: tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4- (3,5-dimethylisoxazol-4-yl)-5-methyl-6-(5-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydro-1H-**

pyrrolo[3,4-c]pyridin-2(3H)-yl)pyrimidin-2-yl)phenoxy)propyl(methyl) carbamate. A reaction pressure vessel was charged with a mixture of tert-butyl (R)-2-(tert-butyl dimethylsilyloxy)-3-(4-chloro-3-(4-chloro-6-(3,5-dimethylisoxazol-4-yl)-5-methylpyrimidin-2-yl)phenoxy)propyl(methyl)carbamate (364 mmol, 0.56 mmol); 5-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1H-pyrrolo[3,4-c] pyridine TFA salt, (or any other suitably substituted primary or secondary amine, 0.65 mmol), Et_3N (226 mg, 2.24 mmol) and n-BuOH (5 mL). The vessel was capped, placed in a microwave reactor and irradiated for 2h. at external temperature of 145 °C. The solvent was then concentrated in vacuo and the residue was purified by preparative TLC to afford tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-(3,5-dimethylisoxazol- 4-yl)-5-methyl-6-(5-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydro-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)pyrimidin-2-yl)phenoxy)propyl(methyl)carbamate (450 mg, 98 % yield). ESI-LCMS (m/z): 821.0 found for $[M+H]^+$.

[00460] **Step 6: (2R)-1-(4-chloro-3-(4-(3,5-dimethylisoxazol-4-yl)-5-methyl-6-(5-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydro-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)pyrimidin-2-yl)phenoxy)-3-(methylamino)propan-2-ol.** A solution of tert-butyl (R)-2-(tert-butyldimethylsilyloxy)-3-(4-chloro-3-(4-(3,5-dimethyl- isoxazol-4-yl)-5-methyl-6-(5-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydro-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)pyrimidin-2-yl)phenoxy)propyl(methyl)carbamate (150 mg, 0.18 mmol) in TFA/water (20:1 v/v, 10.5 mL) was stirred at room temperature for 16h. The mixture was concentrated under vacuum, the residue was dissolved in MeOH (10 ml), and the solution was adjusted to pH 7-8 with ammonia. The mixture was concentrated, and the residue was purified by preparative HPLC to give (2R)-1-(4-chloro-3-(4-(3,5-dimethylisoxazol-4-yl)-5-methyl-6-(5-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydro-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)pyrimidin-2-yl) phenoxy)-3-(methyl amino)propan-2-ol (white solid, 38 mg, 35% yield). ESI-LCMS (m/z): 607.2 found for $[M+H]^+$; ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm: 7.26 (d, J = 8.8 Hz, 1H), 7.22(d, J = 3.2 Hz, 1H), 6.81 (dd, J = 8.8 and 3.2 Hz, 1H), 4.50 (br s, 4H), 4.02-3.97 (m, 1H), 3.91 (d, J = 5.2 Hz, 2H), 3.23 (s, 2H), 3.13-3.04 (m, 2H), 2.87-2.83 (m, 2H), 2.76-2.63 (m, 2H), 2.40 (s, 3H), 2.32 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 2.20-2.15 (m, 2H).

<u>Biological Assays</u>

General Materials

[00461] S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), bicine, Tween20, dimethylsulfoxide (DMSO), bovine skin gelatin (BSG), sodium butyrate and Tris(2-

carboxyethyl)phosphine hydrochloride solution (TCEP) were purchased from Sigma-Aldrich at the highest level of purity possible. ^{3}H-SAM was purchase from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well streptavidin Flashplates were purchased from PerkinElmer.

Substrates

[00462] Peptide representative of human histone H3 residues 16-30 was synthesized with an N-terminal linker-affinity tag motif and a C-terminal amide cap by 21st Century Biochemicals. The peptide was purified by high-performance liquid chromatography (HPLC) to greater than 95% purity and confirmed by liquid chromatography mass spectrometry (LC-MS). The sequence was Biot-Ahx-PRKQLATKAARKSAP-amide and contained a monomethylated arginine at position 26 (**SEQ ID NO.:1**).

Molecular Biology

[00463] Human CARM1 (PRMT4) (NM_199141.1) transcript clone was amplified from an HEK 293 cDNA library, incorporating a flanking 5' sequence encoding a FLAG tag (MDYKDDDDK) (**SEQ ID NO.:2**) fused directly to Ala 2 of CARM1 and 3' sequence encoding a hexa His sequence (EGHHHHHH) (**SEQ ID NO.:3**) fused directly to Ser 608. The gene sequence encoding isoform1 containing a deletion of amino acids 539-561 was amplified subsequently and subcloned into pFastBacMam (Viva Biotech).

Protein Expression

[00464] Recombinant baculovirus were generated according to Bac-to-Bac kit instructions (Life Technologies). Protein over-expression was accomplished by infecting exponentially growing HEK 293F cell culture at $1.3X10^{6}$cell/ml with virus (MOI = 10) in the presence of 8 mM sodium butyrate. Infections were carried out at 37°C for 48 hours, harvested by centrifugation, and stored at -80°C for purification.

Protein Purification

[00465] Expressed full-length human Flag- and His-tagged CARM1 protein was purified from cell paste by anti-flag M2 affinity chromatography with resin equilibrated with buffer containing 20 mM Tris, 150 mM NaCl, 5% glycerol, pH 7.8. Column was washed with 500 mM NaCl in buffer A and Flag-CARM1-His was eluted with 200 ug/ml FLAG peptide in buffer A. Pooled fractions were dialyzed in 20 mM Tris, 150 mM NaCl, 5% glycerol and 1 mM DTT, pH 7.8. The purity of recovered protein was 94.

Predicted Translations

[00466] Flag-CARM1-His (**SEQ ID NO.: 4**)

[00467] MDYKDDDDKAAAAAAVGPGAGGAGSAVPGGAGPCATVSVFPGARLLTI GDANGEIQRHAEQQALRLEVRAGPDSAGIALYSHEDVCVFKCSVSRETECSRVGKQS FIITLGCNSVLIQFATPNDFCSFYNILKTCRGHTLERSVFSERTEESSAVQYFQFYGYLS QQQNMMQDYVRTGTYQRAILQNHTDFKDKIVLDVGCGSGILSFFAAQAGARKIYAV EASTMAQHAEVLVKSNNLTDRIVVIPGKVEEVSLPEQVDIIISEPMGYMLFNERMLES YLHAKKYLKPSGNMFPTIGDVHLAPFTDEQLYMEQFTKANFWYQPSFHGVDLSALR GAAVDEYFRQPVVDTFDIRILMAKSVKYTVNFLEAKEGDLHRIEIPFKFHMLHSGLV HGLAFWFDVAFIGSIMTVWLSTAPTEPLTHWYQVRCLFQSPLFAKAGDTLSGTCLLI ANKRQSYDISIVAQVDQTGSKSSNLLDLKNPFFRYTGTTPSPPPGSHYTSPSENMWNT GSTYNLSSGMAVAGMPTAYDLSSVIASGSSVGHNNLIPLGSSGAQGSGGGSTSAHYA VNSQFTMGGPAISMASPMSIPTNTMHYGSEGHHHHHH

General Procedure for CARM1 Enzyme Assays on Peptide Substrates

[00468] The assays were all performed in a buffer consisting of 20 mM Bicine (pH=7.6), 1 mM TCEP, 0.005% BSG, and 0.002% Tween 20, prepared on the day of use. Compounds in 100% DMSO (1ul) were spotted into a polypropylene 384-well V-bottom plates (Greiner) using a Platemate Plus outfitted with a 384-channel head (Thermo Scientific). DMSO (1ul) was added to Columns 11, 12, 23, 24, rows A-H for the maximum signal control and 1ul of SAH, a known product and inhibitor of CARM1, was added to columns 11, 12, 23, 24, rows I-P for the minimum signal control. A cocktail (40ul) containing the CARM1 enzyme was added by Multidrop Combi (Thermo-Fisher). The compounds were allowed to incubate with CARM1 for 30 min at room temperature, then a cocktail (10ul) containing ^{3}H-SAM and peptide was added to initiate the reaction (final volume = 51ul). The final concentrations of the components were as follows: CARM1 was 0.25 nM, ^{3}H-SAM was 30 nM, peptide was 250 nM, SAH in the minimum signal control wells was 1 mM, and the DMSO concentration was 2%. The assays were stopped by the addition of non-radiolabeled SAM (10ul) to a final concentration of 300 uM, which dilutes the ^{3}H-SAM to a level where its incorporation into the peptide substrate is no longer detectable. 50ul of the reaction in the 384-well polypropylene plate was then transferred to a 384-well Flashplate and the biotinylated peptides were allowed to bind to the streptavidin surface for at least 1 hour before being washed once with 0.1%Tween20 in a Biotek ELx405 plate washer. The plates were then read in a PerkinElmer TopCount plate reader to measure the quantity of ^{3}H-labeled peptide bound to the Flashplate surface, measured as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

% inhibition calculation

$$\% \, inh = 100 - \left(\frac{dpm_{cmpd} - dpm_{min}}{dpm_{max} - dpm_{min}}\right) \times 100$$

where dpm = disintegrations per minute, cmpd = signal in assay well, and min and max are the respective minimum and maximum signal controls.

parameter IC50 fit

$$Y = Bottom + \frac{(Top - Bottom)}{(1 + (\frac{X}{IC_{50}})^{Hill\ Coefficient}}$$

where top and bottom are the normally allowed to float, but may be fixed at 100 or 0 respectively in a 3-parameter fit. The Hill Coefficient normally allowed to float but may also be fixed at 1 in a 3-parameter fit. Y is the % inhibition and X is the compound concentration.

RKO methylation assay

[00469] RKO adherent cells were purchased from ATCC (American Type Culture Collection), Manassas, VA, USA. DMEM/Glutamax medium, penicillin-streptomycin, heat inactivated fetal bovine serum, 0.05% trypsin and D-PBS were purchased from Life Technologies, Grand Island, NY, USA. Odyssey blocking buffer, 800CW goat anti-rabbit IgG (H+L) antibody, and Licor Odyssey infrared scanner were purchased from Licor Biosciences, Lincoln, NE, USA. Asymmetric di-methyl PABP1 antibody was purchased from Cell Signaling Technology, Danvers, MA, USA. Methanol was purchased from VWR, Franklin, MA, USA. 10% Tween 20 was purchased from KPL, Inc., Gaithersburg, Maryland, USA. Paraformaldehyde (PFA) was purchased from EM Sciences. DRAQ5 was purchased from Biostatus Limited, Leicestershire, UK.

[00470] RKO adherent cells were maintained in growth medium (DMEM/Glutamax medium supplemented with 10% v/v heat inactivated fetal bovine serum and 100 units/mL penicillin-streptomycin) and cultured at 37 °C under 5% CO_2.

[00471] Cell treatment, In Cell Western (ICW) for detection of asymmetric di-methyl PABP1 and DNA content: RKO cells were seeded in assay medium at a concentration of

30,000 cells per mL to a poly-D-lysine coated 384 well culture plate (BD Biosciences 356697) with 50 µL per well. Compound (100 nL) from a 96-well source plate was added directly to 384 well cell plate. Plates were incubated at 37°C, 5% CO_2 for 48 hours. After two days of incubation, plates were brought to room temperature outside of the incubator for ten minutes and blotted on paper towels to remove cell media. Cells were fixed for 20 minutes at room temperature by adding 50 ul of 8% PFA followed by aspiration of supernatant with the Biotek EL406 plate washer. Cells were then permeabilized by addition of 50 µL of ice cold 100% methanol directly to each well and incubated for 30 min at room temperature. After 30 min, plates were transferred to a Biotek EL406 plate washer and washed 2 times with 100 µL per well of wash buffer (1X PBS). Next 60 µL per well of Odyssey blocking buffer (Odyssey Buffer with 0.1% Tween 20 (v/v)) were added to each plate and incubated 1 hour at room temperature. Blocking buffer was removed and 20 µL per well of primary antibody was added (asymmetric-methyl PABP1) diluted 1:400 in Odyssey buffer with 0.1% Tween 20 (v/v)) and plates were incubated overnight (16 hours) at 4°C. Plates were washed 5 times with 100 µL per well of wash buffer. Next 20 µL per well of secondary antibody was added (1:800 800CW goat anti-rabbit IgG (H+L) antibody, 1:2000 DRAQ5 in Odyssey buffer with 0.1% Tween 20 (v/v)) and incubated for 1 hour at room temperature. The plates were washed 5 times with 100 µL per well wash buffer then 2 times with 100 µL per well of water. Plates were allowed to dry at room temperature then imaged on the Licor Odyssey machine which measures integrated intensity at 700nm and 800nm wavelengths. Both 700 and 800 channels were scanned.

[00472] **Calculations.** First, the ratio for each well was determined by:

$$\left(\frac{asymmetric\ di\text{-}methyl\ PABP1\ 800nm\ value}{DRAQ5\ 700nm\ value}\right)$$

[00473] Each plate included fourteen control wells of DMSO only treatment (minimum inhibition) as well as fourteen control wells for maximum inhibition treated with 20 µM of a reference compound. The average of the ratio values for each control type was calculated and used to determine the percent activation for each test well in the plate. Reference compound was serially diluted three-fold in DMSO for a total of nine test concentrations, beginning at 20 µM.

[00474] Percent inhibition was determined and IC_{50} curves were generated using triplicate wells per concentration of compound.

$$\text{Percent Inhibition} = 100 - \left(\left(\frac{\text{(Minimum Inhibition Ratio)} - \text{(Individual Test Sample Ratio)}}{\text{(Minimum Inhibition Ratio)} - \text{(Maximum Inhibition Ratio)}}\right) * 100\right)$$

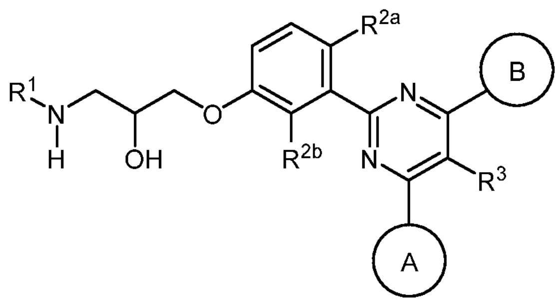
OTHER EMBODIMENTS

[00475] The foregoing has been a description of certain non–limiting embodiments of the invention. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



(I)

or pharmaceutically acceptable salt thereof;

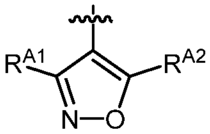
wherein:

R^1 is hydrogen, -CHO, or unsubstituted C_{1-3}alkyl;

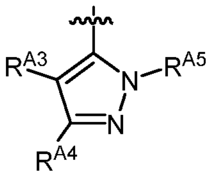
each instance of R^{2a} and R^{2b} is independently hydrogen, halogen, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl;

R^3 is unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, or halogen;

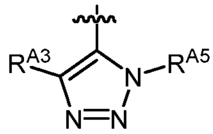
Ring A is of formula (A-i), (A-ii), or (A-iii):



(A-i)



(A-ii)



(A-iii)

wherein:

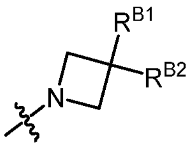
each instance of R^{A1} and R^{A2} is independently unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, or unsubstituted cyclopropyl;

R^{A3} is unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, halogen, or –CN;

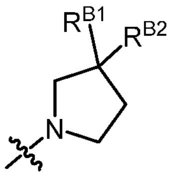
R^{A4} is hydrogen, unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, halogen, or –CN; and

R^{A5} is unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl;

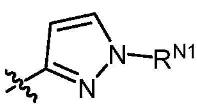
Ring B is any one of formula (i) to (xxviii):



(i)



(ii)



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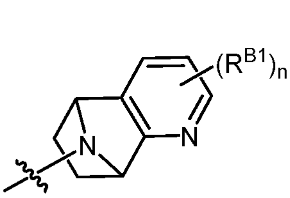
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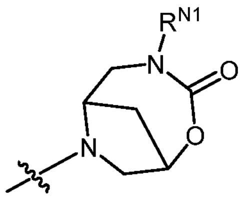
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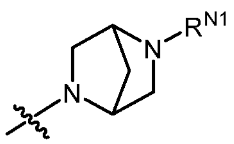
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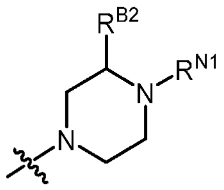
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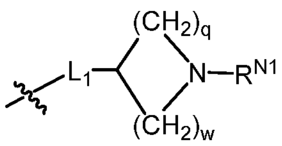
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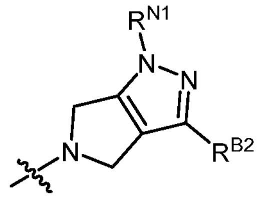
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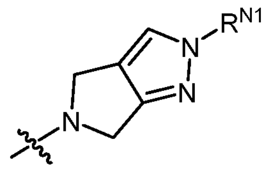
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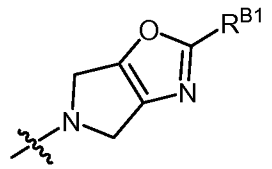
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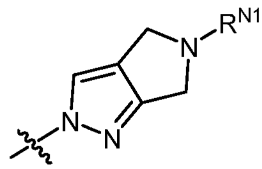
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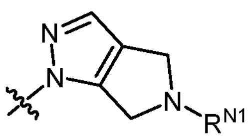
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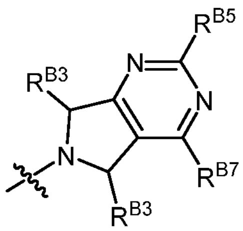
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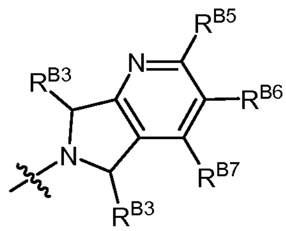
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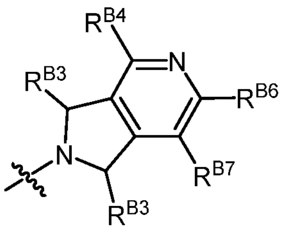
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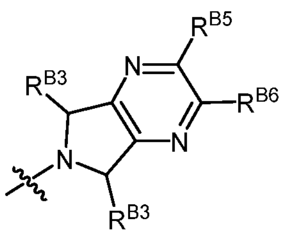
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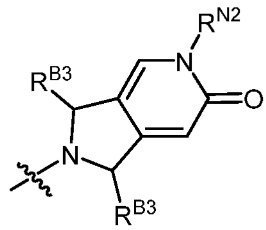
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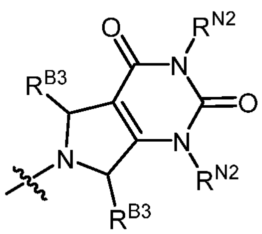
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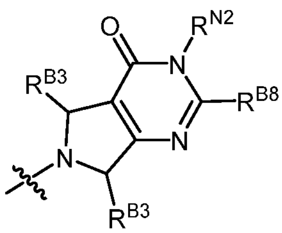
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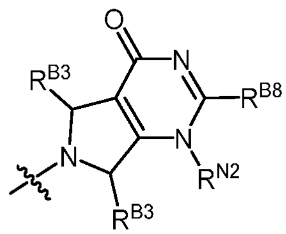
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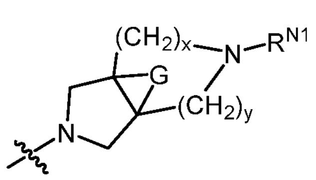

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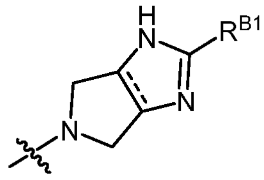

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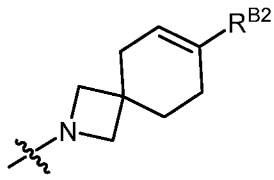

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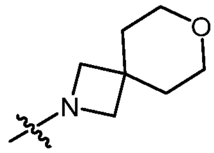

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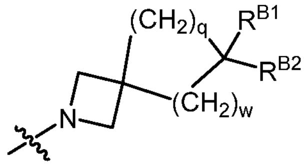

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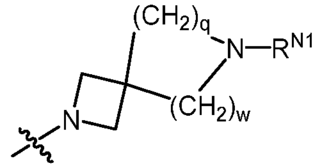

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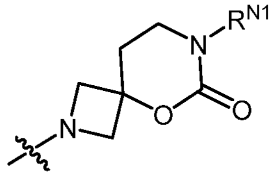

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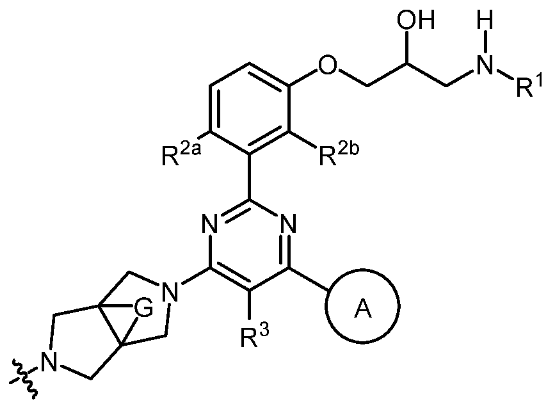


(xxix)

wherein:

q is 1, 2, or 3 and w is 1; or q is 2 and w is 0 or 2;

x is 1 and y is 1 or 2;

n is 0, 1, or 2;

L_1 is –NH–, substituted or unsubstituted C_2alkylene, substituted or unsubstituted C_2alkenylene, or substituted or unsubstituted C_2alkynylene;

R^{N1} is substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted 4- to 6-membered heterocyclyl, -C(=O)R^{N1A}, -C(=O)N(R^{N1A})(R^{N1B}), -C(=O)OR^{N1A}, or -S(O)$_2$$R^{N1A}$; wherein:

R^{N1A} is substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_{3-6} carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl;

R^{N1B} is hydrogen, substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_{3-6} carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl; or

R^{N1A} and R^{N1B} are joined to form a substituted or unsubstituted 4- to 6-membered heterocyclyl; or

each instance of R^{N2} and R^{B8} is independently substituted or unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl, or R^{N2} and R^{B8} are joined to form a substituted or unsubstituted 5- to 6-membered ring;

R^{B1} is substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, halogen, -CN, -OR^{B1B}, -SR^{B1B}, -$N(R^{B1A})(R^{B1B})$, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted 4- to 6-membered heterocyclyl, -$C(=O)R^{B1A}$, -$C(=O)N(R^{B1A})(R^{B1B})$, -$C(=O)OR^{B1A}$, -$S(O)_2R^{B1A}$, -$OC(=O)R^{B1A}$, -$OC(=O)N(R^{B1A})(R^{B1B})$, -$OC(=O)OR^{B1A}$, -$NR^{BIB}C(=O)R^{B1A}$, -$NR^{BIB}C(=O)N(R^{B1A})(R^{B1B})$, or -$NR^{BIB}C(=O)OR^{B1A}$;

wherein:

R^{B1A} is substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_{3-6} carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl; and

R^{B1B} is hydrogen, substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_{3-6} carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl; or

R^{B1A} and R^{B1B} are joined to form a substituted or unsubstituted 4- to 6-membered heterocyclyl;

R^{B2} is hydrogen, halogen, -OR^{B2A}, substituted or unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl, wherein R^{B2A} is substituted or unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl; or

R^{B1} and R^{B2} are joined to form a substituted or unsubstituted 4- to 6-membered heterocyclyl;

each instance of R^{B3} is independently hydrogen, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl, provided at least one instance of R^{B3} is hydrogen;

each instance of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is independently hydrogen, substituted or unsubstituted C_{1-3}alkyl, C_{1-3}haloalkyl, halogen, -CN, -OR^{B4B}, -SR^{B4B}, -$N(R^{B4A})(R^{B4B})$, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted 4- to 6-membered heterocyclyl, -$C(=O)R^{B4A}$, -$C(=O)N(R^{B4A})(R^{B4B})$, -

C(=O)OR^{B4A}, -S(O)$_2$R^{B4A}, -OC(=O)R^{B4A}, -OC(=O)N(R^{B4A})(R^{B4B}), -OC(=O)OR^{B4A}, -NR^{B4B}C(=O)R^{B4A}, -NR^{B4B}C(=O)N(R^{B4A})(R^{B4B}), or -NR^{B4B}C(=O)OR^{B4A};

wherein:

R^{B4A} is substituted or unsubstituted C$_{1-3}$alkyl, C$_{1-3}$haloalkyl, substituted or unsubstituted C$_{3-6}$ carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl; and

R^{B4B} is hydrogen, substituted or unsubstituted C$_{1-3}$alkyl, C$_{1-3}$haloalkyl, substituted or unsubstituted C$_{3-6}$ carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl; or

R^{B4A} and R^{B4B} are joined to form a substituted or unsubstituted 4- to 6-membered heterocyclyl;

and

wherein ==== represents a single or double bond; and

further wherein  represents a single or double bond or G is –CH$_2$–;

wherein each instance of substituted independently refers to substitution with 1, 2, or 3 R^{C1} groups, as valency permits,

and wherein:

each instance of R^{C1} is independently unsubstituted C$_{1-3}$alkyl, C$_{1-3}$haloalkyl, halogen, -CN, -OR^{C1B}, -SR^{C1B}, -N(R^{C1A})(R^{C1B}), -C(=O)R^{C1A}, -C(=O)N(R^{C1A})(R^{C1B}), -C(=O)OR^{C1A}, -S(O)$_2$R^{C1A}, -OC(=O)R^{C1A}, -OC(=O)N(R^{C1A})(R^{C1B}), -OC(=O)OR^{C1A}, -NR^{CIB}C(=O)R^{C1A}, -NR^{CIB}C(=O)N(R^{C1A})(R^{C1B}), or -NR^{CIB}C(=O)OR^{C1A};

wherein:

R^{C1A} is unsubstituted C$_{1-3}$alkyl, C$_{1-3}$haloalkyl, C$_{3-6}$carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups; or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups; and

R^{C1B} is hydrogen, unsubstituted C$_{1-3}$alkyl, C$_{1-3}$haloalkyl, C$_{3-6}$carbocylyl unsubstituted or substituted with 1 or 2 R^{D1} groups, or 4-6 membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups; or

R^{C1A} and R^{C1B} are joined to form an 4- to 6- membered heterocyclyl unsubstituted or substituted with 1 or 2 R^{D1} groups; and

wherein:

each instance of R^{D1} is independently halogen, -CN, -OR^{D1A}, unsubstituted C$_{1-3}$alkyl, or C$_{1-3}$haloalkyl, wherein R^{D1A} is hydrogen, unsubstituted C$_{1-3}$alkyl, or C$_{1-3}$haloalkyl.

2. The compound of claim 1, wherein R^1 is $-CH_3$.

3. The compound of claim 1, wherein R^1 is hydrogen.

4. The compound of claim 1, wherein R^1 is $-CHO$.

5. The compound of any one of claims 1-4, wherein R^{2a} is halogen and R^{2b} is hydrogen.

6. The compound of claim 5, wherein R^{2a} is $-F$ or $-Cl$.

7. The compound of any one of claims 1-4, wherein R^{2a} is C_{1-3}haloalkyl and R^{2b} is hydrogen.

8. The compound of claim 7, wherein R^{2a} is $-CF_3$.

9. The compound of any one of claims 1-4, wherein R^{2a} is halogen and R^{2b} is halogen.

10. The compound of claim 9, wherein R^{2a} is $-Cl$ and R^{2b} is $-Cl$.

11. The compound of any one of claims 1-4, wherein each of R^{2a} and R^{2b} is hydrogen.

12. The compound of any one of claims 1-11, wherein R^3 is $-CH_3$.

13. The compound of any one of claims 1-11, wherein R^3 is $-Cl$ or $-F$.

14. The compound of claim 1, wherein each of R^{2a} is $-Cl$ and R^3 is $-Cl$.

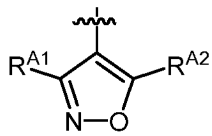
15. The compound of claim 1, wherein R^{2a} is $-F$ and R^3 is $-F$.

16. The compound of claim 1, wherein R^{2a} is $-Cl$ and R^3 is $-CH_3$.

17. The compound of claim 1, wherein R^{2a} is $-F$ and R^3 is $-CH_3$.

18. The compound of claim 1, wherein R^{2a} is $-CF_3$ and R^3 is $-CH_3$.

19. The compound of any one of claims 1 to 18, wherein Ring A is of formula (A-i):

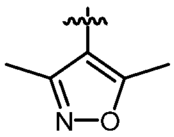
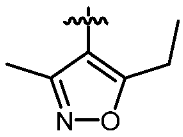
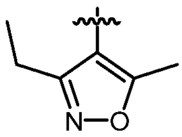
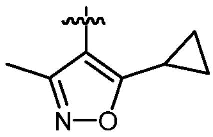
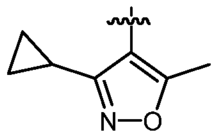


(A-i).

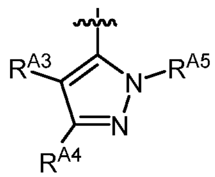
20. The compound of claim 19, wherein at least one of R^{A1} and R^{A2} is $-CH_3$ or $-CH_2CH_3$.

21. The compound of claim 19, wherein at least one of R^{A1} and R^{A2} is unsubstituted cyclopropyl.

22. The compound of claim 19, wherein Ring A is:

 ,  ,  ,  , or  .

23. The compound of any one of claims 1-18, wherein Ring A is of formula (A-ii):



(A-ii).

24. The compound of claim 23, wherein at least one of R^{A3} and R^{A4} is halogen or $-CN$.

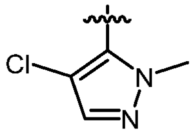
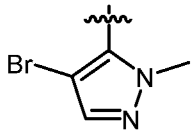
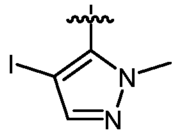
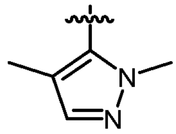
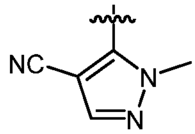
25. The compound of claim 23 or 24, wherein R^{A5} is $-CH_3$ or $-CH_2CH_3$.

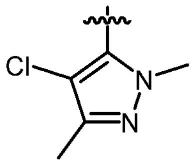
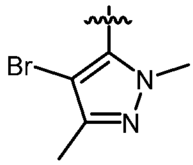
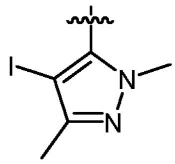
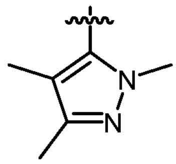
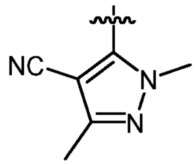
26. The compound of claim 23, wherein R^{A4} is hydrogen.

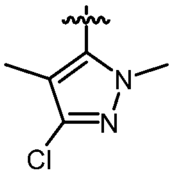
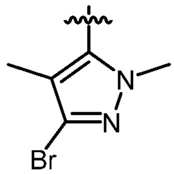
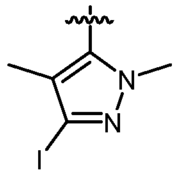
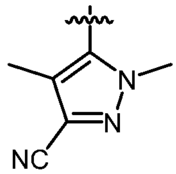
27. The compound of claim 23, wherein R^{A3} is unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl and R^{A4} is halogen or $-CN$.

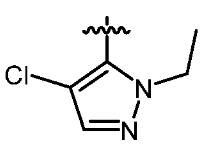
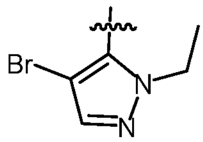
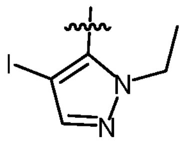
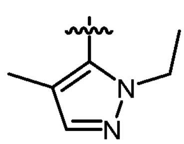
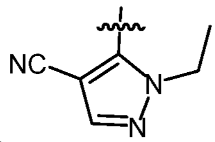
28. The compound of claim 23, wherein R^{A4} is unsubstituted C_{1-3}alkyl or C_{1-3}haloalkyl and R^{A3} is halogen or $-CN$.

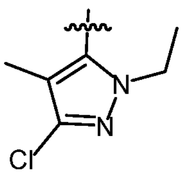
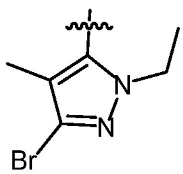
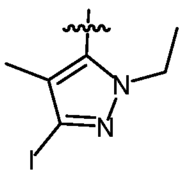
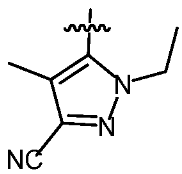
29. The compound of claim 23, wherein Ring A is:

, , , , ,

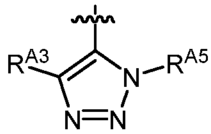
, , , , ,

, , , ,

, , , , ,

, , , or .

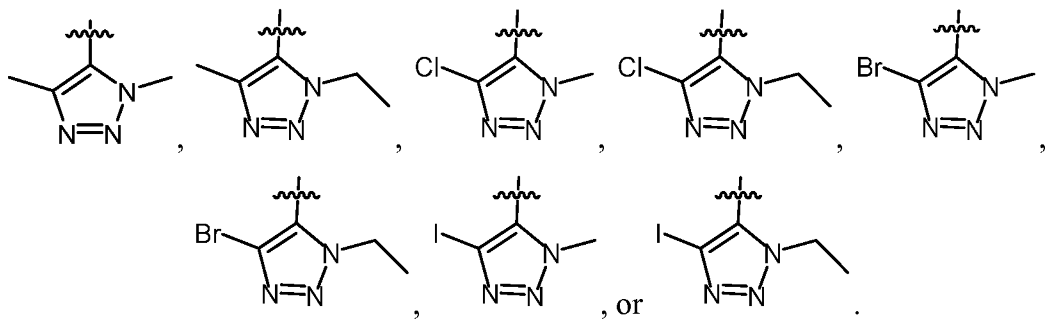
30. The compound of any one of claims 1-18, wherein Ring A is of formula (A-ii):

 (A-iii).

31. The compound of claim 30, wherein R^{A5} is $-CH_3$ or $-CH_2CH_3$.

32. The compound of claim 30, wherein R^{A3} is halogen, unsubstituted C_{1-3}alkyl, or C_{1-3}haloalkyl.

33. The compound of claim 30, wherein Ring A is:



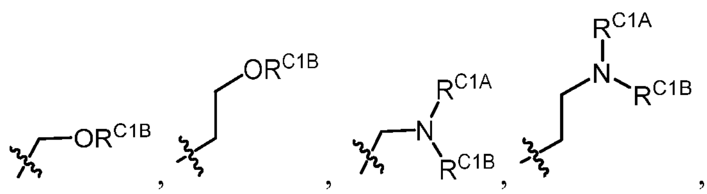
34. The compound of any one of the proceeding claims, wherein each instance of unsubstituted $C_{1\text{-}3}$alkyl is independently $–CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$.

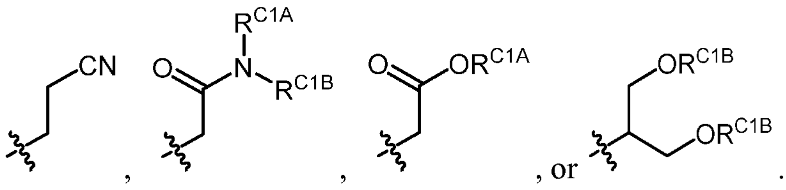
35. The compound of any one of the proceeding claims, wherein each instance of $C_{1\text{-}3}$haloalkyl is independently $–CF_3$, $–CCl_3$, $–CFCl_2$, $–CF_2Cl$, $–CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$, $–CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$, $–CF_2CF_2CF_3$, $–CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$.

36. The compound of any one of the proceeding claims, wherein each instance of substituted $C_{1\text{-}3}$alkyl is independently $C_{1\text{-}3}$alkyl substituted with 1, 2, or 3 R^{C1} groups, as valency permits, selected from the group consisting of halogen, -CN, $-OR^{C1B}$, $-SR^{C1B}$, $-N(R^{C1A})(R^{C1B})$, $-C(=O)R^{C1A}$, $-C(=O)N(R^{C1A})(R^{C1B})$, $-C(=O)OR^{C1A}$, $-S(O)_2R^{C1A}$, $-OC(=O)R^{C1A}$, $-OC(=O)N(R^{C1A})(R^{C1B})$, $-OC(=O)OR^{C1A}$, $-NR^{CIB}C(=O)R^{B1A}$, $-NR^{CIB}C(=O)N(R^{C1A})(R^{C1BB})$, and $-NR^{CIB}C(=O)OR^{C1A}$.

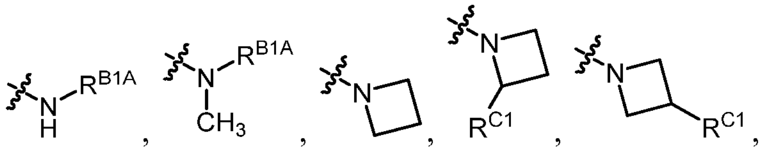
37. The compound of claim 36, wherein each instance of substituted $C_{1\text{-}3}$alkyl is independently $C_{1\text{-}3}$alkyl substituted with 1 or 2 R^{C1} groups selected from the group consisting of -CN, $-OR^{C1B}$, $-N(R^{C1A})(R^{C1B})$, $-C(=O)N(R^{C1A})(R^{C1B})$, and $-C(=O)OR^{C1A}$.

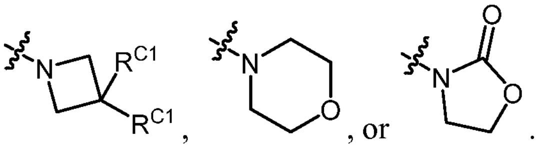
38. The compound of claim 37, wherein each instance of substituted $C_{1\text{-}3}$alkyl is independently:



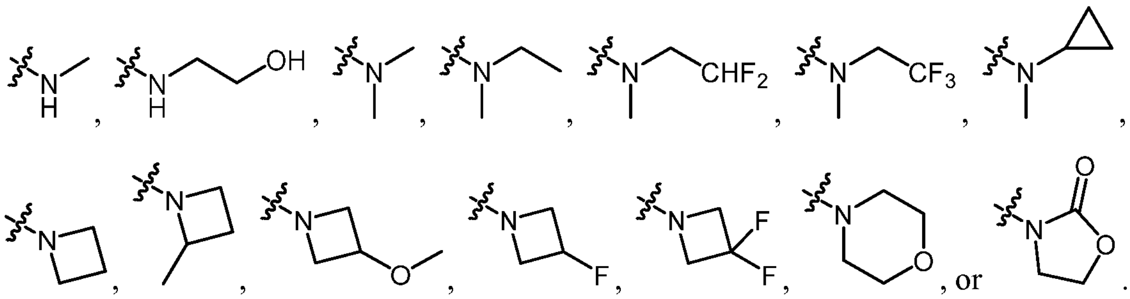


39. The compound of any one of the preceding claims, wherein each instance of -$N(R^{B1A})(R^{B1B})$ is independently:

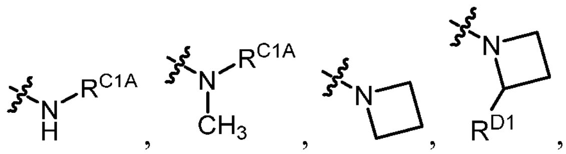


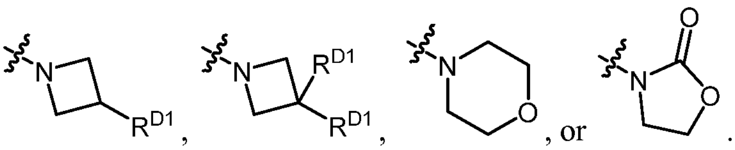


40. The compound of claim 39, wherein each instance of - $N(R^{B1A})(R^{B1B})$ is independently:

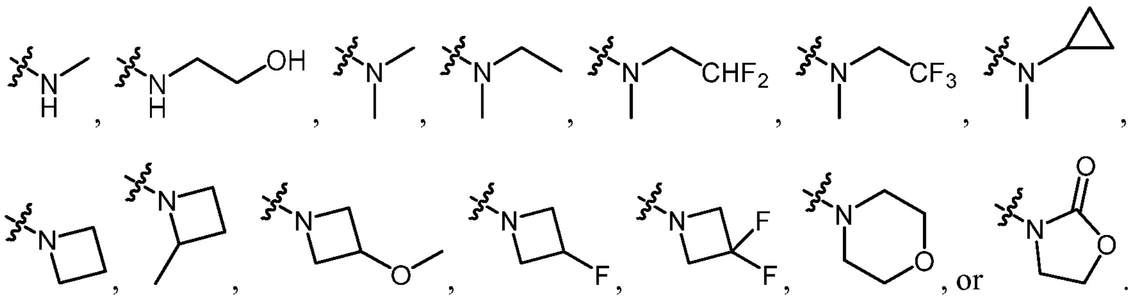


41. The compound of any one of the preceding claims, wherein each instance of -$N(R^{C1A})(R^{C1B})$ is independently:





42. The compound of claim 41, wherein each instance of - $N(R^{C1A})(R^{C1B})$ is independently:

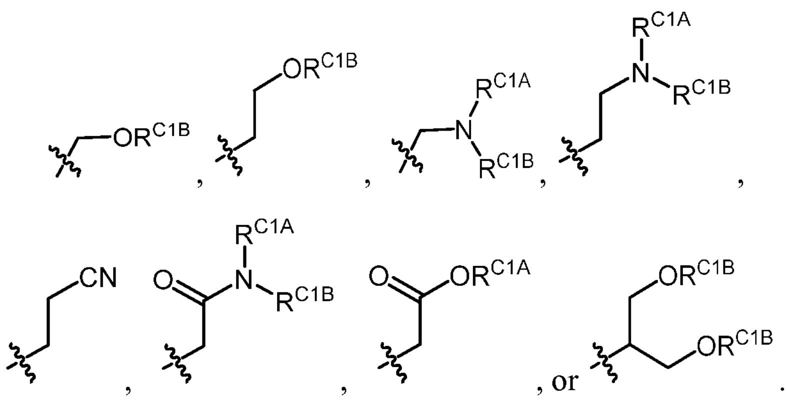


43. The compound of any one of the preceding claims wherein Ring B is of formula (iii), (v), (vi), (vii), (viii), (ix), (x), (xii), (xiii), (xxii), (xxvii), or (xxviii), and further wherein each instance of R^{N1} is independently substituted or unsubstituted $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$haloalkyl, substituted or unsubstituted C_3 carbocyclyl, $-C(=O)R^{N1A}$, $-C(=O)OR^{N1A}$, $-S(O)_2R^{N1A}$, $-C(=O)N(R^{N1A})(R^{N1B})$, substituted or unsubstituted 4- membered heterocyclyl, substituted or unsubstituted 5- membered heterocyclyl, or substituted or unsubstituted 6-membered heterocyclyl.

44. The compound of claim 43, wherein at least one instance of R^{N1} is an unsubstituted $C_{1\text{-}3}$alkyl of formula $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$.

45. The compound of claim 43, wherein at least one instance of R^{N1} is $C_{1\text{-}3}$haloalkyl of formula $-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$, $-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$, $-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$.

46. The compound of claim 43, wherein at least one instance of R^{N1} is substituted $C_{1\text{-}3}$alkyl of formula:



47. The compound of claim 43, wherein at least one instance of R^{N1} is substituted or unsubstituted C_3 carbocyclyl.

48. The compound of claim 47, wherein at least one instance of R^{N1} is


.

49. The compound of claim 43, wherein at least one instance of R^{N1} is substituted or unsubstituted 4- to 6-membered heterocyclyl comprising one oxygen ring heteroatom.

50. The compound of claim 49, wherein at least one instance of R^{N1} is: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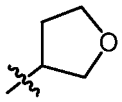
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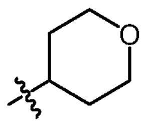
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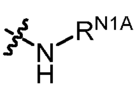
51. The compound of claim 43, wherein at least one instance of R^{N1} is -C(=O)R^{N1A}, -C(=O)OR^{N1A}, or -S(O)$_2R^{N1A}$, wherein R^{N1A} is –CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH(CH_3)_2$, –CF_3, –CCl_3, –$CFCl_2$, –CF_2Cl, –CH_2F, -CHF_2, -CH_2Cl, $CHCl_2$, –CF_2CF_3, -CH_2CF_3, -CH_2CHF_2, -CH_2CH_2F, -CH_2CCl_3, -CH_2CHCl_2, -CH_2CH_2Cl, –$CF_2CF_2CF_3$, –$CH_2CF_2CF_3$, -$CH_2CH_2CF_3$, -$CH_2CH_2CHF_2$, - $CH_2CH_2CH_2F$, - $CH_2CH_2CCl_3$, - $CH_2CH_2CHCl_2$, -$CH_2CH_2CH_2Cl$, -$CH(CH_3)CHF_2$, -$CH(CH_3)CF_3$.

52. The compound of claim 43, wherein at least one instance of R^{N1} is -C(=O)N(R^{N1A})(R^{N1B}), wherein N(R^{N1A})(R^{N1B}) is:



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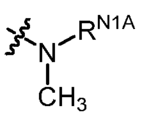

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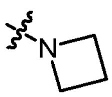

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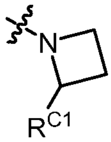

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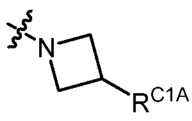

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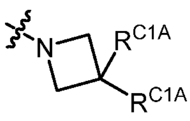

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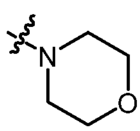

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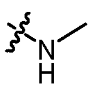
53. The compound of claim 52, wherein at least one instance of R^{N1} is -C(=O)N(R^{N1A})(R^{N1B}), wherein -N(R^{N1A})(R^{N1B}) is:



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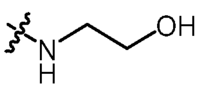

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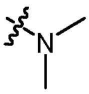

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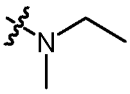

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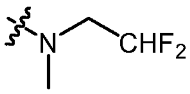

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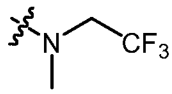

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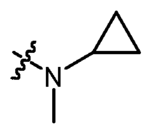

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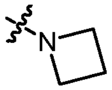
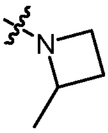
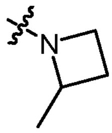
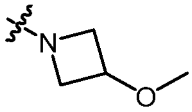
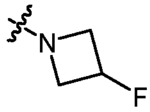
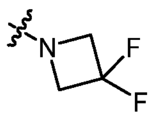
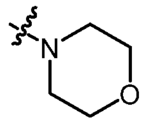
, , , , , , or .

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54. The compound of any one of the preceding claims,

wherein:

R^{B1} is unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, C_{1-3} alkyl substituted with -OR^{C1B}, C_{1-3} alkyl substituted with -$N(R^{C1A})(R^{C1B})$, C_{1-3}alkyl substituted with –CN, C_{1-3} alkyl substituted with -$C(=O)N(R^{C1A})(R^{C1B})$, C_{1-3} alkyl substituted with -$C(=O)OR^{C1A}$, -$C(=O)N(R^{B1A})(R^{B1B})$, -$OC(=O)OR^{B1A}$, -$N(R^{B1A})(R^{B1B})$, -OR^{B1B}, -SR^{B1B}, -$S(O)_2R^{B1A}$, -F, -Cl, –CN, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl;

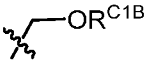
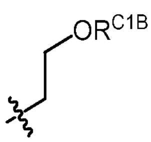
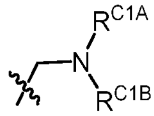
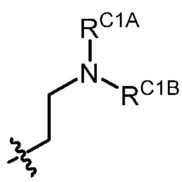
or

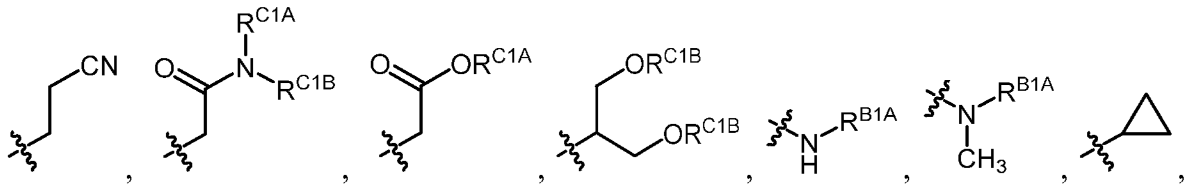
at least one instance of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, C_{1-3} alkyl substituted with -OR^{C1B}, C_{1-3} alkyl substituted with -$N(R^{C1A})(R^{C1B})$, C_{1-3}alkyl substituted with –CN, C_{1-3} alkyl substituted with -$C(=O)N(R^{C1A})(R^{C1B})$, C_{1-3} alkyl substituted with -$C(=O)OR^{C1A}$, -$C(=O)N(R^{B4A})(R^{B4B})$, -$OC(=O)OR^{B4A}$, -$N(R^{B4A})(R^{B4B})$, -OR^{B4B}, -SR^{B4B}, -$S(O)_2R^{B4A}$, -F, -Cl, –CN, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4- to 6-membered heterocyclyl

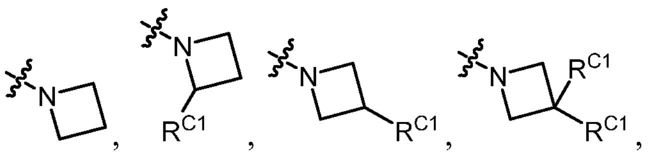
55. The compound of claim 54,

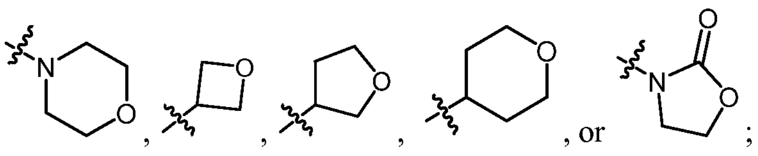
wherein:

R^{B1} is $–CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $–CF_3$, $–CCl_3$, $–CFCl_2$, $–CF_2Cl$, $–CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$, $–CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$, $–CF_2CF_2CF_3$, $–CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $- CH_2CH_2CCl_3$, $- CH_2CH_2CHCl_2$, $- CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, $-CH(CH_3)CF_3$,

, , , ,

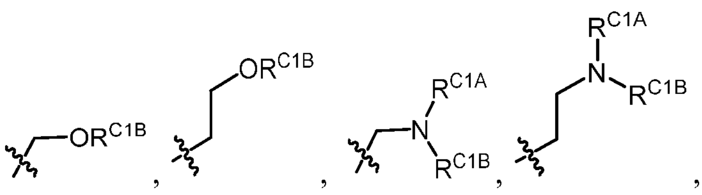


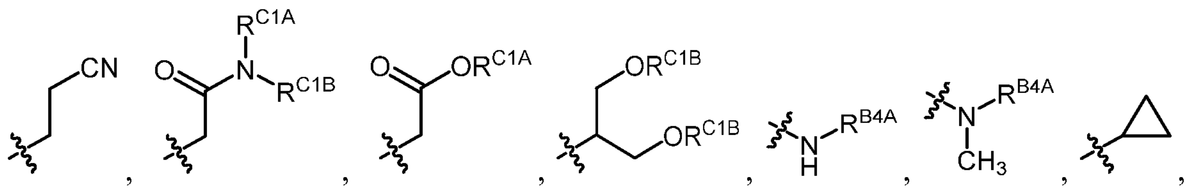


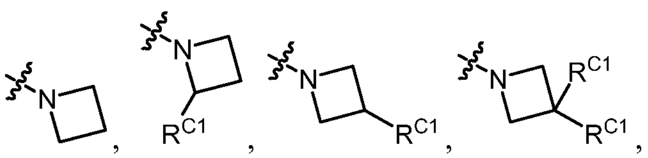


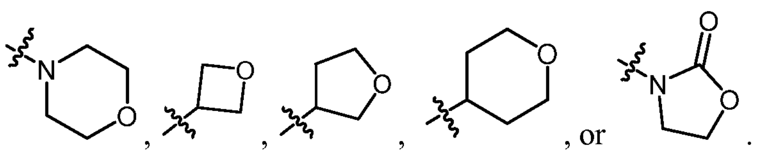
or

at least one instance of R^{B4}, R^{B5}, R^{B6}, and R^{B7} is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, $-CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$, $-CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$, $-CF_2CF_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CCl_3$, $-CH_2CH_2CHCl_2$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, $-CH(CH_3)CF_3$,









56. The compound of any one of the preceding claims, wherein R^{B2} is hydrogen, $-OR^{B2A}$, $-F$, unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, or C_{1-3} alkyl substituted with $-OR^{C1B}$.

57. The compound of any one of the preceding claims, wherein R^{B3} is hydrogen or $–CH_3$, provided at least one instance of R^{B3} is hydrogen.

58. The compound of any one of the preceding claims, wherein each instance of R^{B8} and R^{N2} is independently $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $–CF_3$, $–CCl_3$, $–CFCl_2$, $–CF_2Cl$, $–CH_2F$, $-CHF_2$, $-CH_2Cl$, $CHCl_2$, $–CF_2CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CCl_3$, $-CH_2CHCl_2$, $-CH_2CH_2Cl$, $–CF_2CF_2CF_3$, $–CH_2CF_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CHF_2$, $- CH_2CH_2CH_2F$, $- CH_2CH_2CCl_3$, $- CH_2CH_2CHCl_2$, $- CH_2CH_2CH_2Cl$, $-CH(CH_3)CHF_2$, or $-CH(CH_3)CF_3$; or R^{N2} and R^{B8} are joined to form an unsubstituted 5-membered ring; or R^{N2} and R^{B8} are joined to form an unsubstituted 5-membered ring.

59. The compound of any one of the preceding claims wherein Ring B is of formula (i), (ii), or (xxvi), further wherein:

a. R^{B1} is $-N(R^{B1A})(R^{B1B})$, $-OR^{B1B}$, $-SR^{B1B}$, $-S(O)_2R^{B1A}$, -F, -Cl, –CN, $-OC(=O)OR^{B1A}$, $-C(=O)N(R^{B1A})(R^{B1B})$, and R^{B2} is hydrogen; or
b. R^{B1} is -F and R^{B2} is –F; or
c. R^{B1} is $-OR^{B1B}$, $-C(=O)N(R^{B1A})(R^{B1B})$, –CN , or C_{1-3} alkyl substituted with $-OR^{C1B}$, C_{1-3} alkyl substituted with $-N(R^{C1A})(R^{C1B})$, and R^{B2} is substituted or unsubstituted C_{1-3} alkyl or C_{1-3}haloalkyl; or
d. R^{B1} is $-OR^{B1B}$ and R^{B2} is $-OR^{B2A}$, and each instance of R^{B1B} and R^{B2A} is independently substituted or unsubstituted C_{1-3} alkyl or C_{1-3}haloalkyl; or
e. R^{B1} is $-OR^{B1B}$ and R^{B2} is $-OR^{B2A}$, and R^{B1B} and R^{B2A} are joined to form a substituted or unsubstituted 5- to 6- membered heterocyclyl.

60. The compound of any one of the preceding claims, wherein Ring B is of formula (xiv), further wherein:

a. each instance of R^{B5} and R^{B7} is hydrogen; or
b. each instance of R^{B5} and R^{B7} is independently $-OR^{B4B}$; or
c. R^{B5} is $-N(R^{B4A})(R^{B4B})$, $-OR^{B4B}$, $-SR^{B4B}$, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl; and R^{B7} is hydrogen; or

d. R^{B5} is hydrogen and R^{B7} is -N(R^{B4A})(R^{B4B}), -OR^{B4B}, -SR^{B4B}, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, or substituted or unsubstituted C_3 carbocyclyl.

61. The compound of any one of the preceding claims, wherein Ring B is of formula (xv), further wherein:

a. each instance of R^{B5}, R^{B6}, and R^{B7} is hydrogen; or

b. $R^{B5}$is -N(R^{B4A})(R^{B4B}), -OR^{B4B}, -SR^{B4B}, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B6} and R^{B7} are hydrogen; or

c. $R^{B6}$is -N(R^{B4A})(R^{B4B}), -OR^{B4B}, -SR^{B4B}, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B5} and R^{B7} are hydrogen; or

d. $R^{B7}$is -N(R^{B4A})(R^{B4B}), -OR^{B4B}, -SR^{B4B}, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B5} and R^{B6} are hydrogen.

62. The compound of any one of the preceding claims, wherein Ring B is of formula (xvi), further wherein:

a. $R^{B4}$is -N(R^{B4A})(R^{B4B}), -OR^{B4B}, -SR^{B4B}, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B6} and R^{B7} are hydrogen; or

b. $R^{B6}$is -N(R^{B4A})(R^{B4B}), -OR^{B4B}, -SR^{B4B}, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B5} and R^{B7} are hydrogen; or

c. $R^{B7}$is -N(R^{B4A})(R^{B4B}), -OR^{B4B}, -SR^{B4B}, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B5} and R^{B6} are hydrogen; or

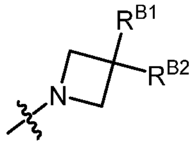
d. $R^{B4}$and $R^{B6}$are-N(R^{B4A})(R^{B4B}), -OR^{B4B}, -SR^{B4B}, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B7} is hydrogen.

63. The compound of any one of the preceding claims, wherein Ring B is of formula (xvii), further wherein:

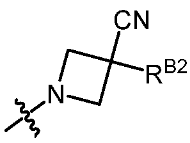
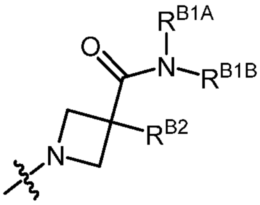
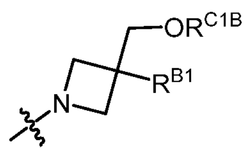
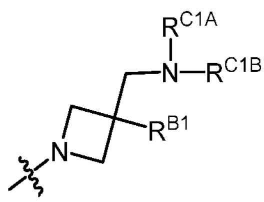
a. $R^{B5}$is -N(R^{B4A})(R^{B4B}), -OR^{B4B}, -SR^{B4B}, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B6} is hydrogen; or

b. $R^{B6}$is -N(R^{B4A})(R^{B4B}), -OR^{B4B}, -SR^{B4B}, halogen, substituted or unsubstituted C_{1-3} alkyl, C_{1-3}haloalkyl, substituted or unsubstituted C_3 carbocyclyl, or substituted or unsubstituted 4-6 membered heterocyclyl, and R^{B5} is hydrogen.

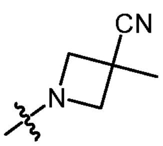
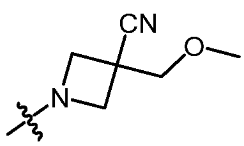
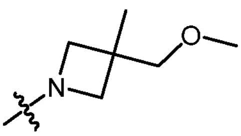
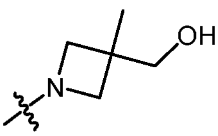
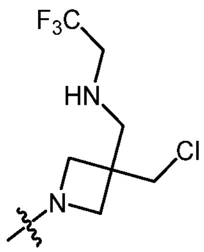
64. The compound of any one of claims 1-58, wherein Ring B is of formula:

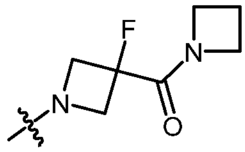
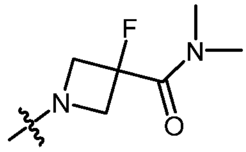
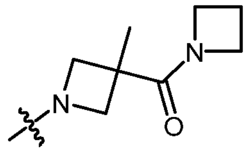
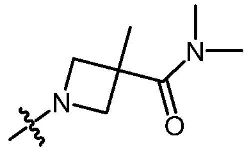

(i).

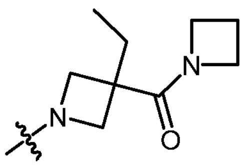
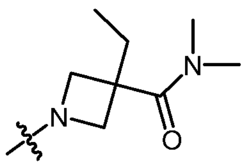
65. The compound of claim 64, wherein Ring B is of formula:


,

,

, or

.

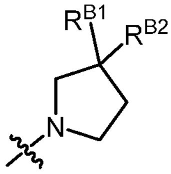
66. The compound of claim 65, wherein Ring B is of formula:


,

,

,

,

,

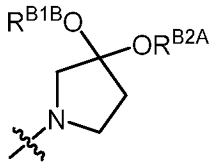
, , , ,

, or .

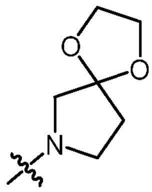
67. The compound of any one of claims 1-58, wherein Ring B is of formula:

 (ii).

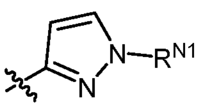
68. The compound of claim 67, wherein Ring B is of formula:

.

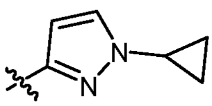
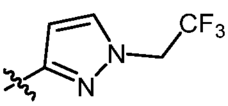
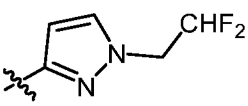
69. The compound of claim 68, wherein Ring B is of formula:

.

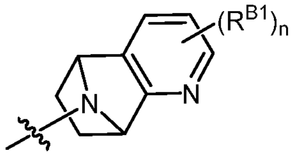
70. The compound of any one of claims 1-58, wherein Ring B is of formula:

 (iii).

71. The compound of claim 70, wherein Ring B is of formula:

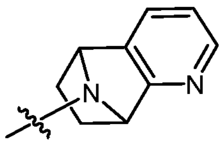
, , or .

72. The compound of any one of claims 1-58, wherein Ring B is of formula:



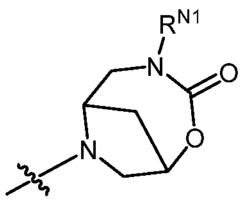
(iv).

73. The compound of claim 72, wherein Ring B is of formula:



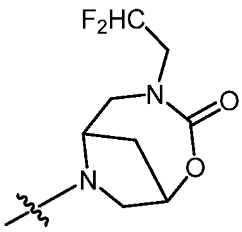
.

74. The compound of any one of claims 1-58, wherein Ring B is of formula:



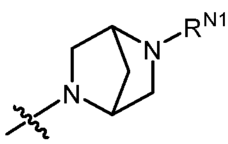
(v).

75. The compound of claim 74, wherein Ring B is of formula:



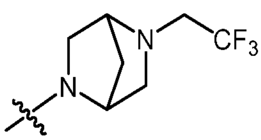
.

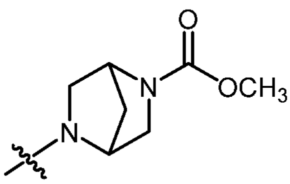
76. The compound of any one of claims 1-58, wherein Ring B is of formula:

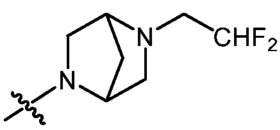


(vi).

77. The compound of claim 76, wherein Ring B is of formula:

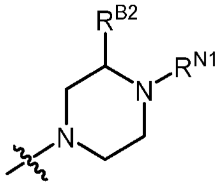


, 

, or 

.

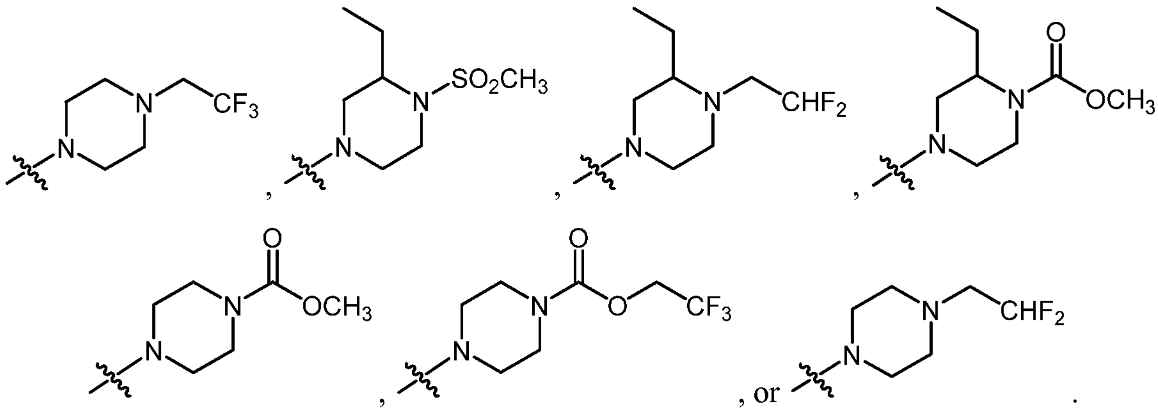
78. The compound of any one of claims 1-58, wherein Ring B is of formula:



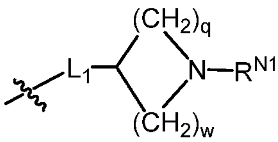
(vii).

79. The compound of claim 78, wherein R^{B2} is hydrogen or $-CH_3CH_3$.

80. The compound of claim 79, wherein Ring B is of formula:



81. The compound of any one of claims 1-58, wherein Ring B is of formula:

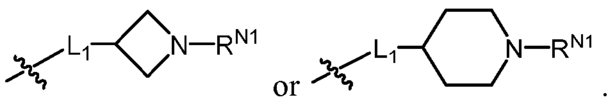


(viii).

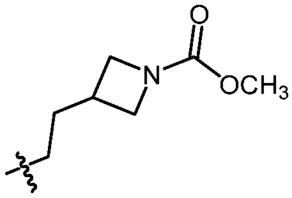
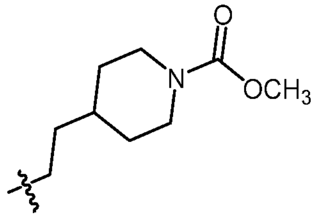
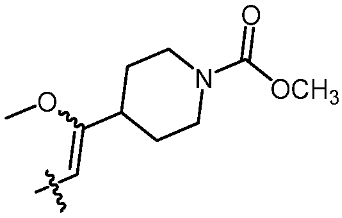
82. The compound of claim 81 , wherein q is 1, 2, or 3 and w is 1.

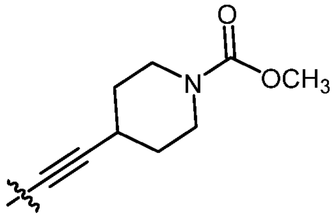
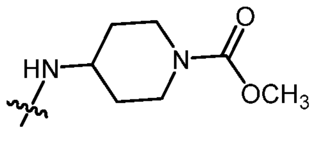
83. The compound of claim 81, wherein q is 2 and w is 0 or 2.

84. The compound of claim 81, wherein Ring B is of formula:

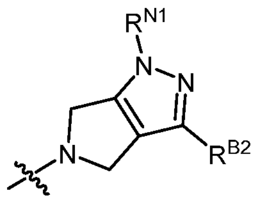


85. The compound of claim 84, wherein Ring B is of formula:

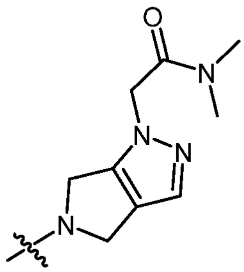
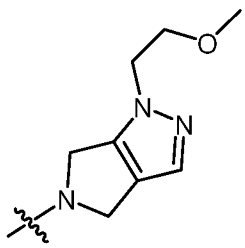
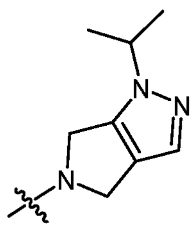
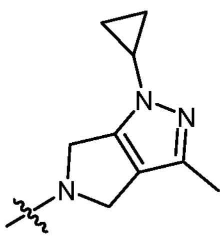
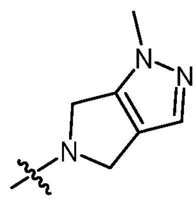
, , ,

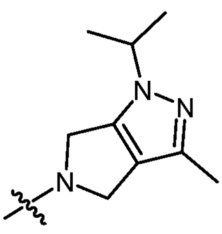
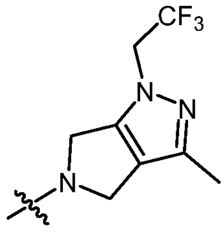
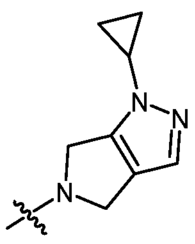
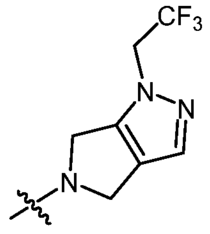
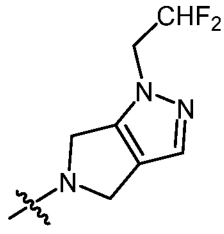
, or .

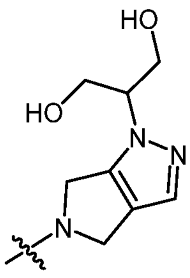
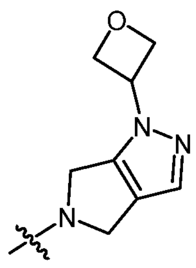
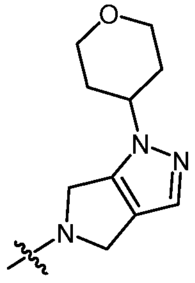
86. The compound of any one of claims 1-58, wherein Ring B is of formula:

 (ix).

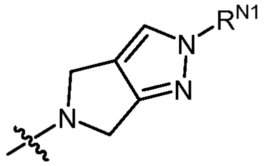
87. The compound of claim 86, wherein Ring B is of formula:

, , , , ,

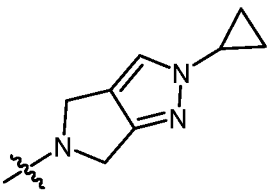
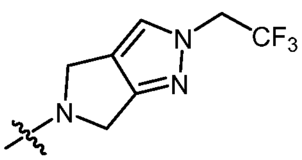
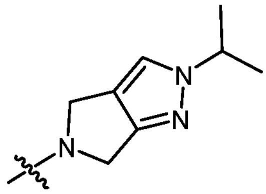
, , , , ,

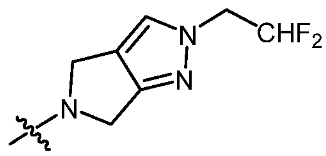
, , or .

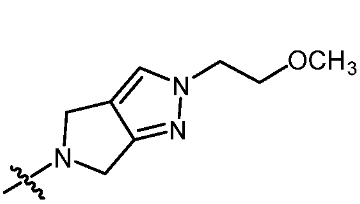
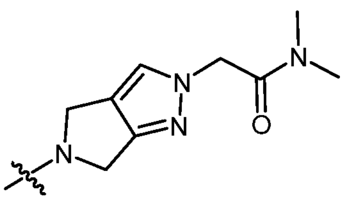
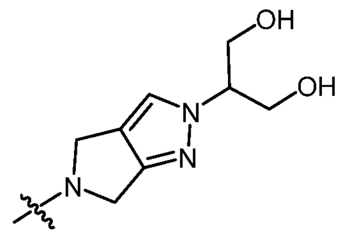
88. The compound of any one of claims 1-58, wherein Ring B is of formula:

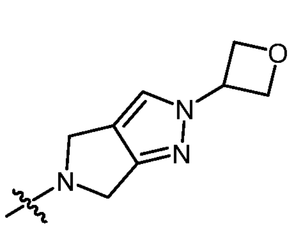
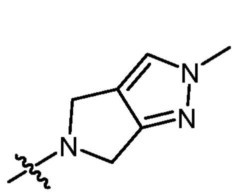
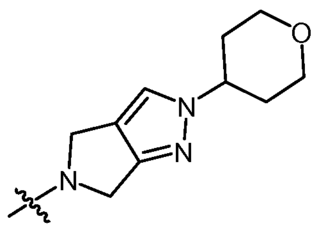
 (x).

89. The compound of claim 88, wherein Ring B is of formula:

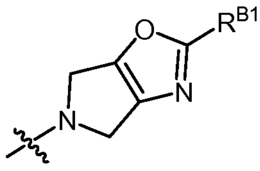
, , ,

,

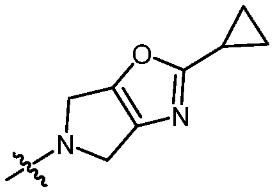
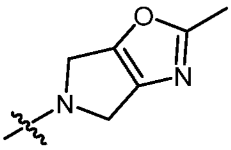
, , ,

, , or .

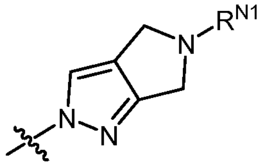
90. The compound of any one of claims 1-58, wherein Ring B is of formula:


(xi).

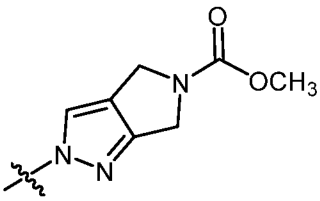
91. The compound of claim 90, wherein Ring B is of formula:


or

.

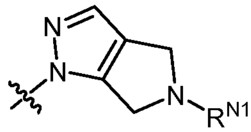
92. The compound of any one of claims 1-58, wherein Ring B is of formula:


(xii).

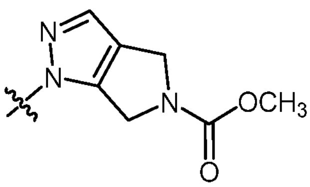
93. The compound of claim 92, wherein Ring B is of formula:


.

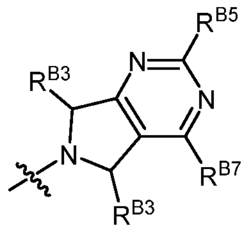
94. The compound of any one of claims 1-58, wherein Ring B is of formula:


(xiii).

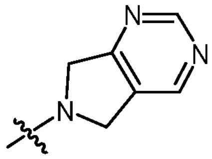
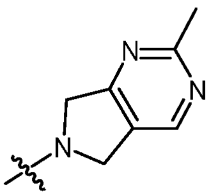
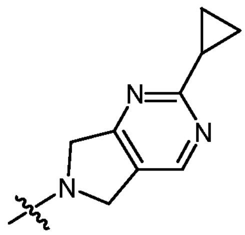
95. The compound of claim 94, wherein Ring B is of formula:

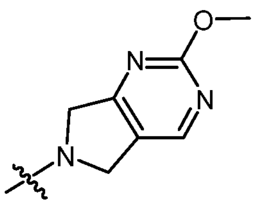
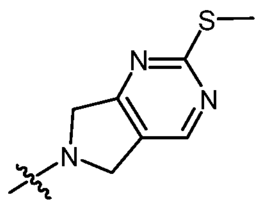

.

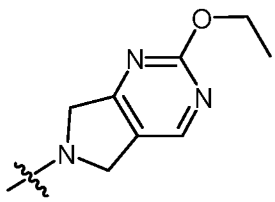
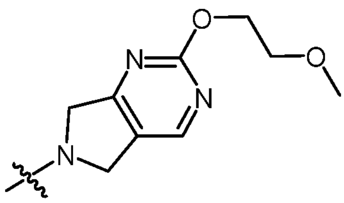
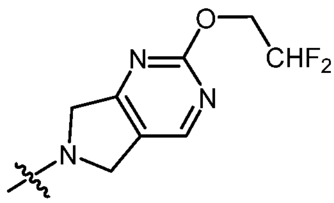
96. The compound of any one of claims 1-58, wherein Ring B is of formula:

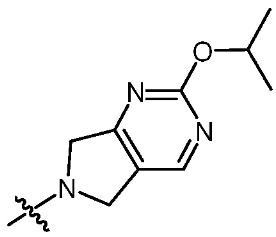
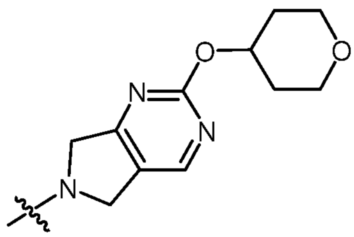
 (xiv).

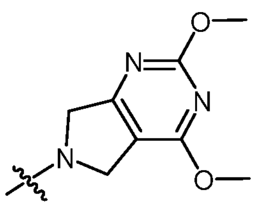
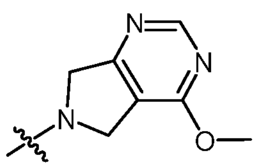
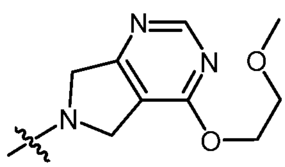
97. The compound of claim 96, wherein Ring B is of formula:

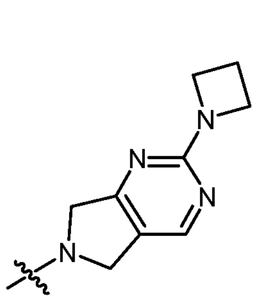
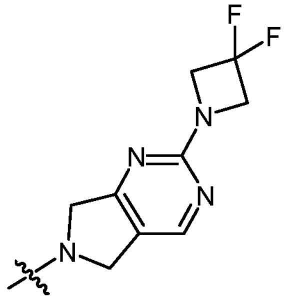
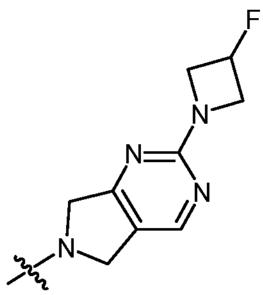
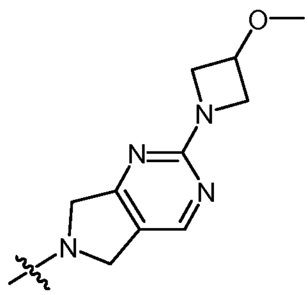
, , ,

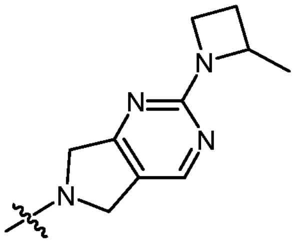
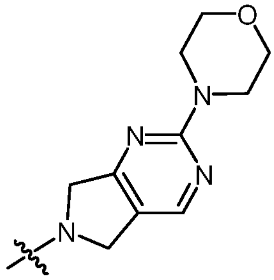
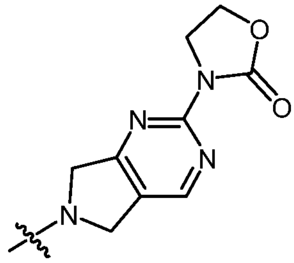
, ,

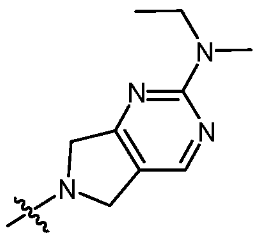
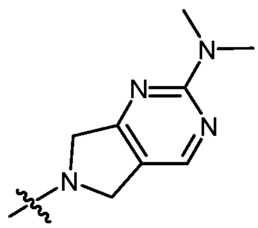
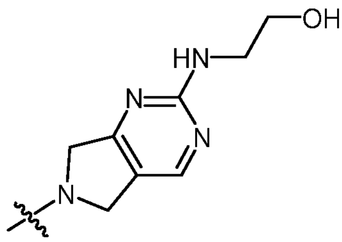
, , ,

, ,

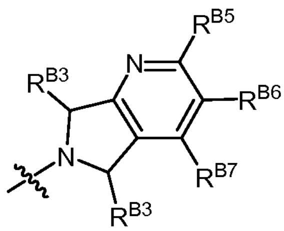
, , ,

, , , ,

, , ,

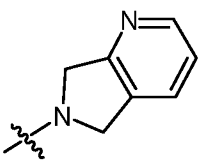
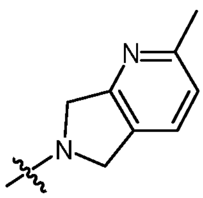
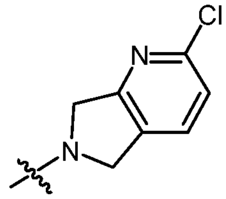
, , or .

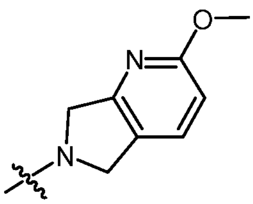
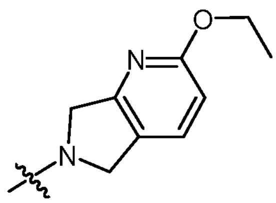
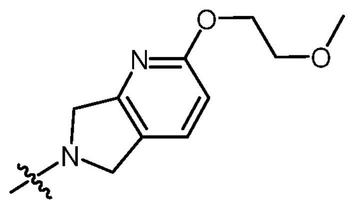
98. The compound of any one of claims 1-58, wherein Ring B is of formula:

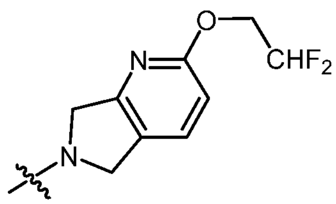
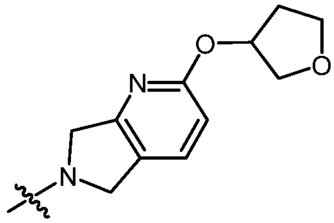


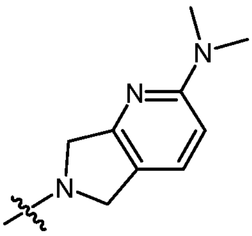
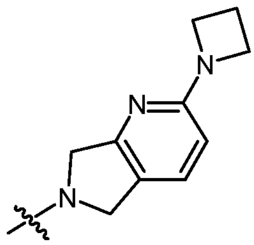
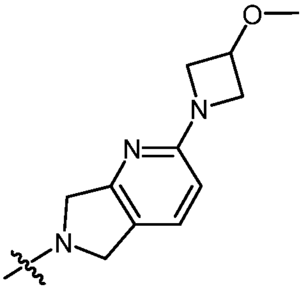
(xv).

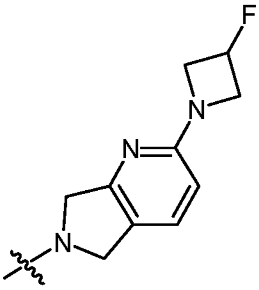
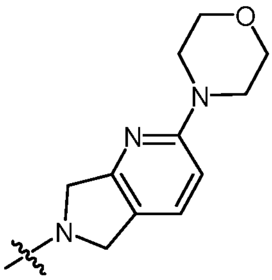
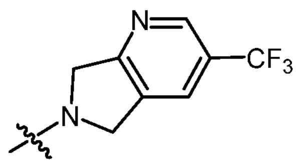
99. The compound of claim 98, wherein Ring B is of formula:

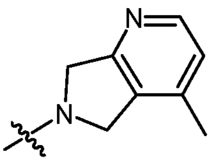
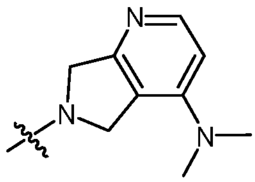
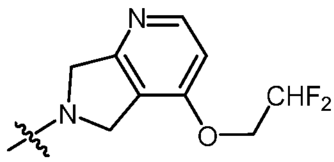
, , ,

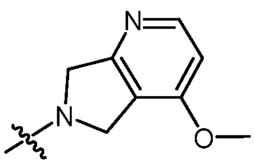
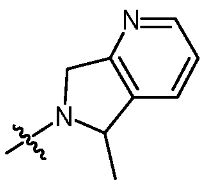
, , ,

, ,

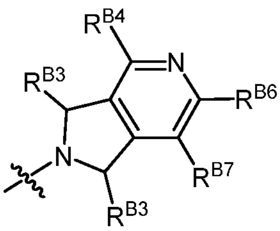
, , ,

, , ,

, , ,

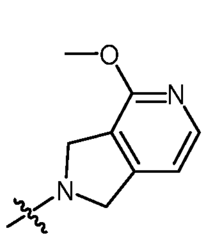
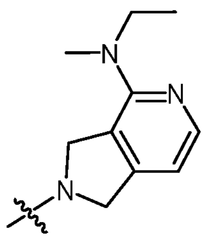
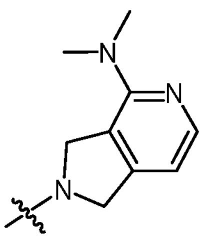
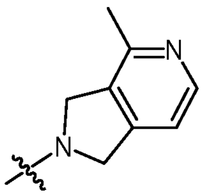
, or .

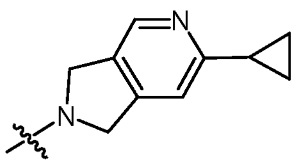
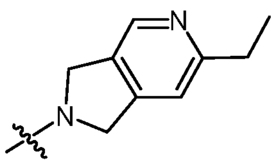
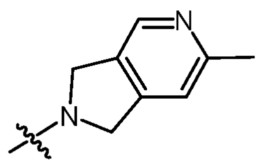
100. The compound of any one of claims 1-58, wherein Ring B is of formula:

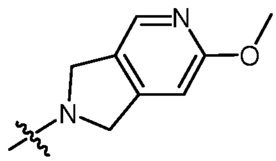
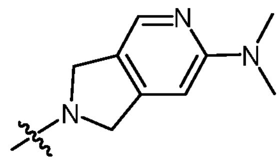


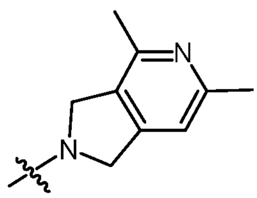
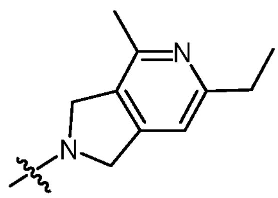
(xvi).

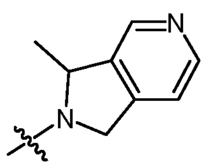
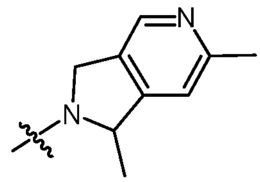
101. The compound of claim 100, wherein Ring B is of formula:

, , , ,

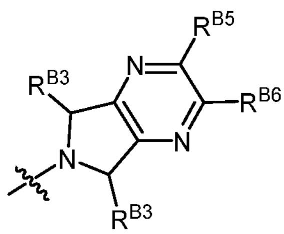
, , ,

, ,

, ,

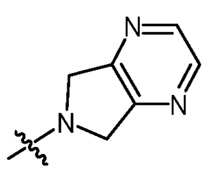
, or .

102. The compound of any one of claims 1-58, wherein Ring B is of formula:



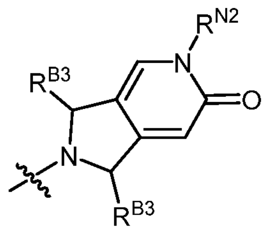
(xvii).

103. The compound of claim 102, wherein Ring B is of formula:



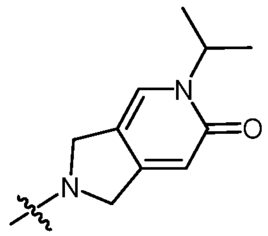
.

104. The compound of any one of claims 1-58, wherein Ring B is of formula:



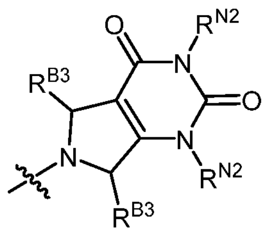
(xviii).

105. The compound of claim 104, wherein Ring B is of formula:



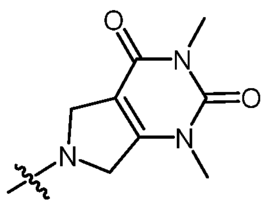
.

106. The compound of any one of claims 1-58, wherein Ring B is of formula:

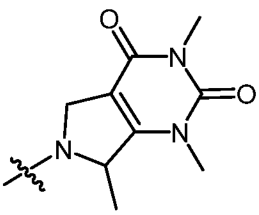


(xix).

107. The compound of claim 106, wherein Ring B is of formula:

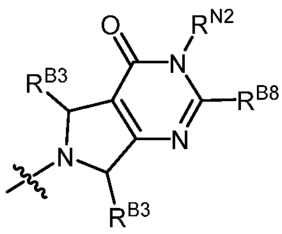


or



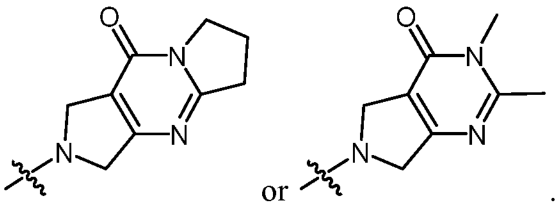
.

108. The compound of any one of claims 1-58, wherein Ring B is of formula:

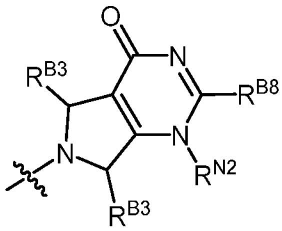


(xx).

109. The compound of claim 108, wherein Ring B is of formula:

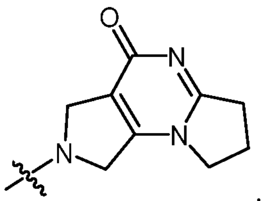


110. The compound of any one of claims 1-58, wherein Ring B is of formula:

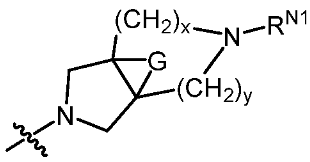


(xxi).

111. The compound of claim 110, wherein Ring B is of formula:



112. The compound of any one of claims 1-58, wherein Ring B is of formula:

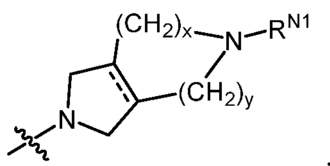


(xxii).

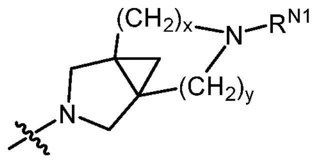
113. The compound of claim 112, wherein x is 1 and y is 1.

114. The compound of claim 112 , wherein x is 1 and y is 2.

115. The compound of claim 112, wherein Ring B is of formula:

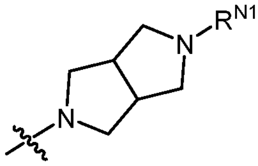
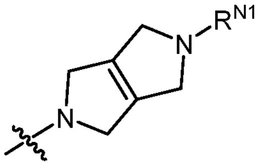
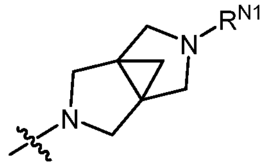


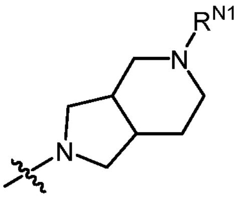
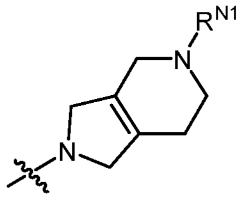
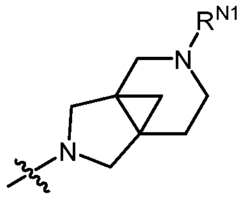
116. The compound of claim 112, wherein Ring B is of formula:



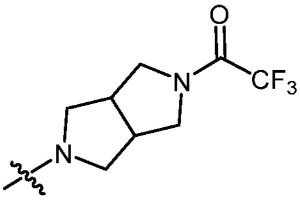
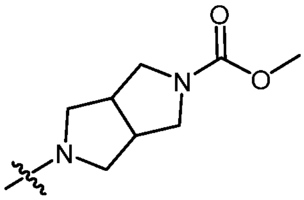
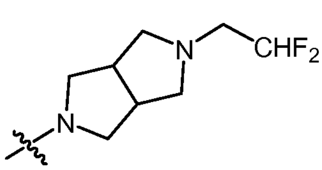
.

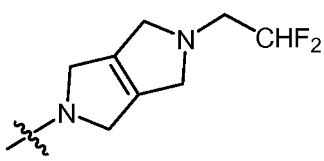
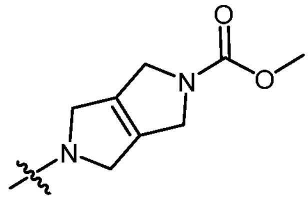
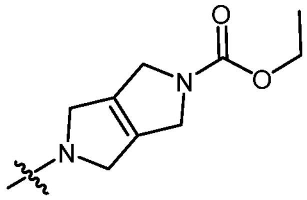
117. The compound of claim 112, wherein Ring B is of formula:

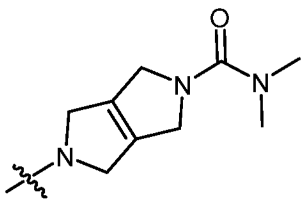
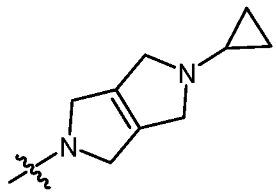
, , ,

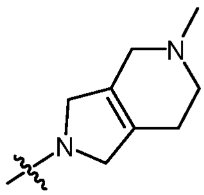
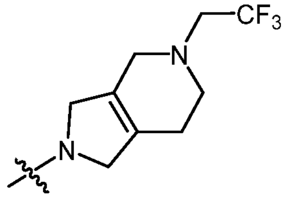
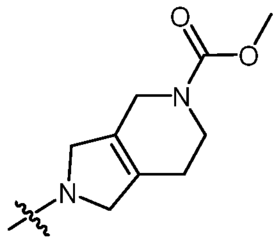
, , or .

118. The compound of claim 112, wherein Ring B is of formula:

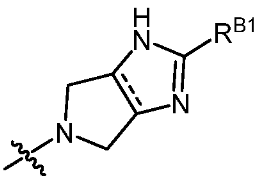
, , ,

, , ,

, ,

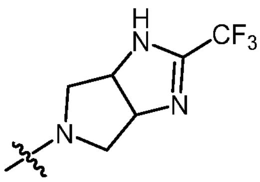
, , or .

119. The compound of any one of claims 1-58, wherein Ring B is of formula:

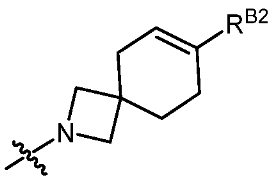


(xxiii).

120. The compound of claim 119, wherein Ring B is of formula:

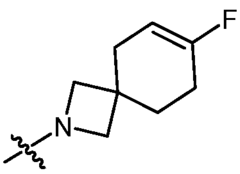
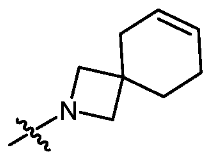
.

121. The compound of any one of claims 1-58, wherein Ring B is of formula:

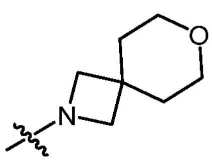


(xxiv).

122. The compound of claim 121, wherein Ring B is of formula:

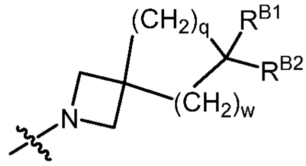
 or .

123. The compound of any one of claims 1-58, wherein Ring B is of formula:



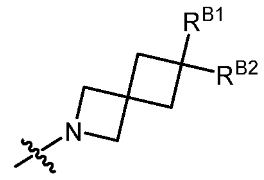
(xxv).

124. The compound of any one of claims 1-58, wherein Ring B is of formula:

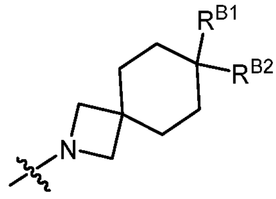


(xxvi).

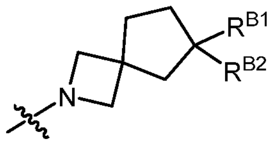
125. The compound of claim 124, wherein Ring B is of formula:



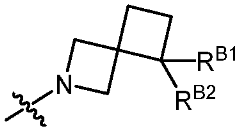
,



,

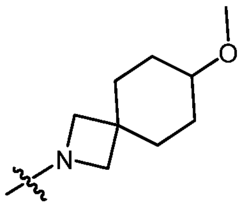


, or

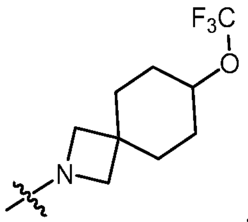


.

126. The compound of claim 124, wherein Ring B is of formula:



,



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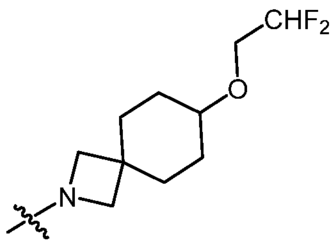

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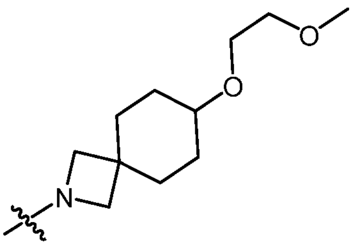

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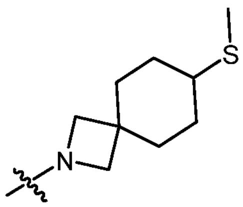

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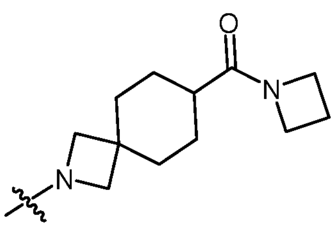

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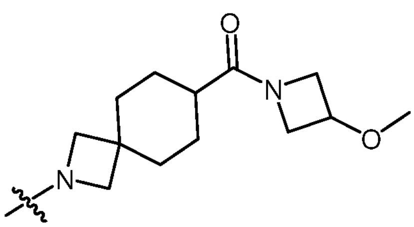

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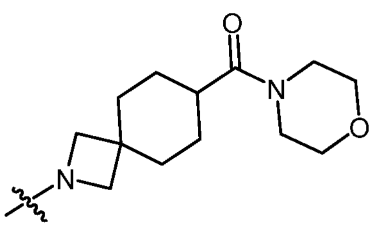

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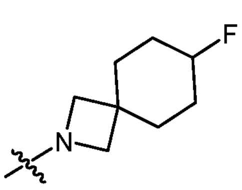
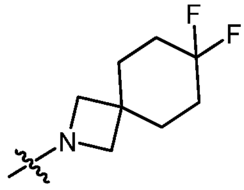
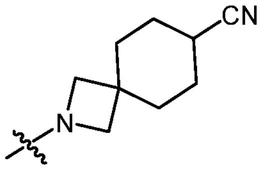
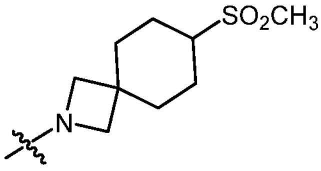
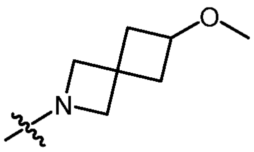
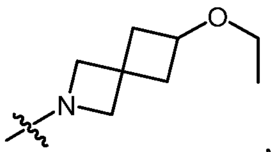
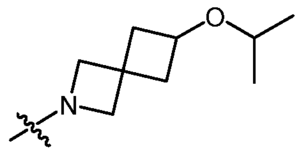
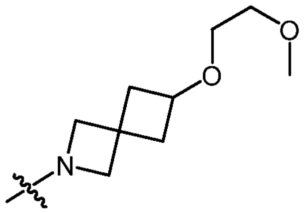
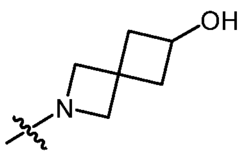
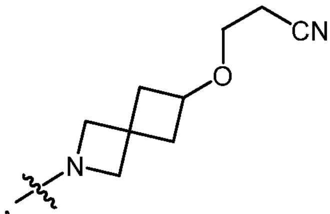
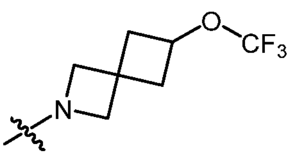
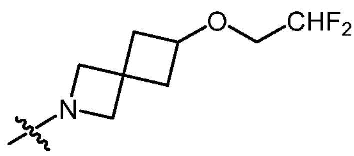
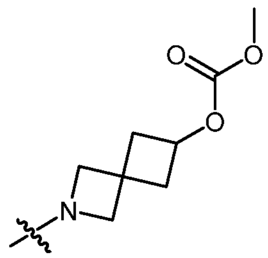
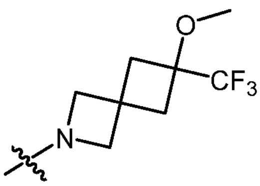
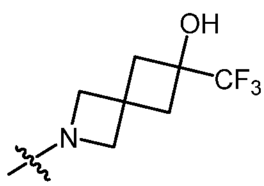
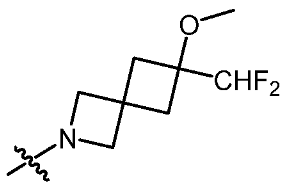
, , , or .

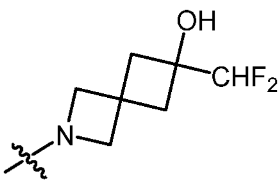
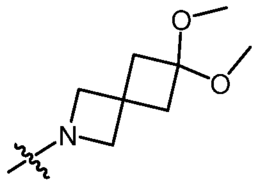
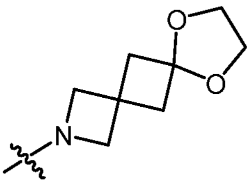
127. The compound of claim 124, wherein Ring B is of formula:

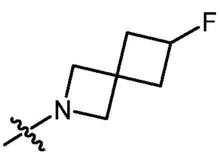
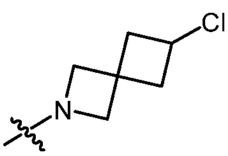
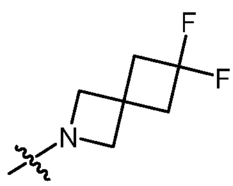
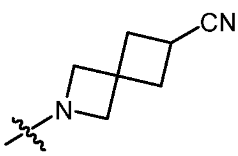
, , ,

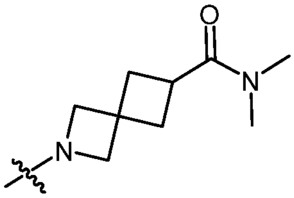
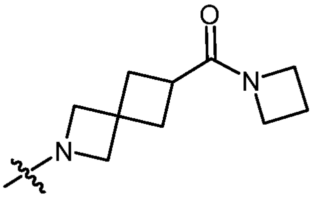
, , ,

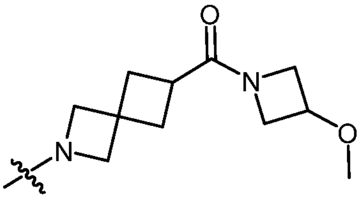
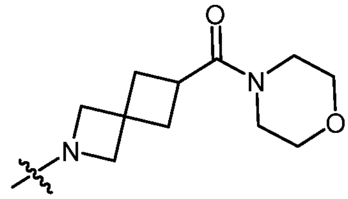
, , ,

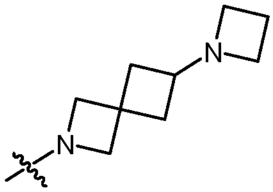
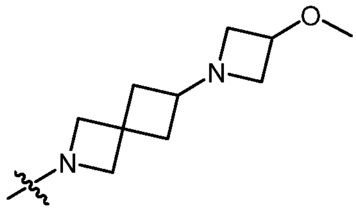
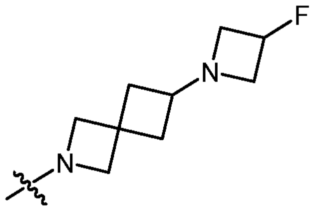
, , ,

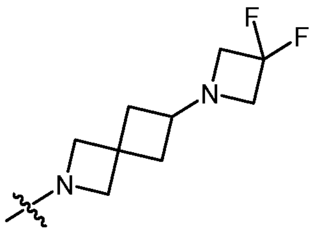
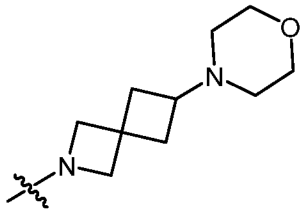
, , ,

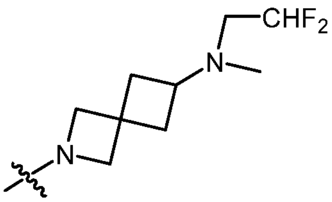
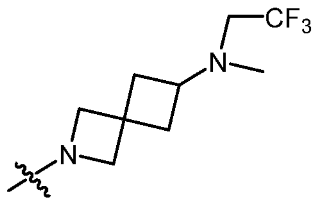
, , , ,

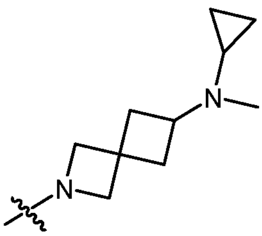
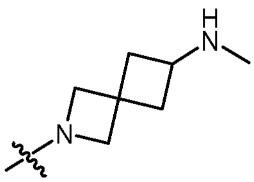
, ,

, ,

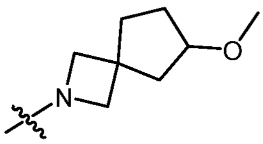
, , ,

, ,

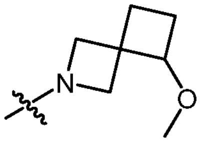
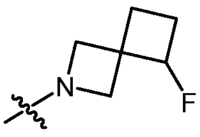
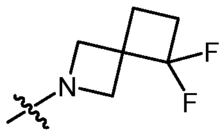
, ,

, or .

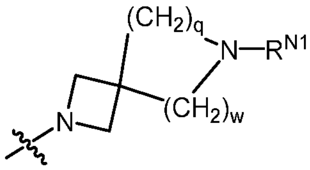
128. The compound of claim 124, wherein Ring B is of formula:

.

129. The compound of claim 124, wherein Ring B is of formula:

, , or .

130. The compound of any one of claims 1-58, wherein Ring B is of formula:

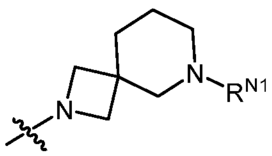
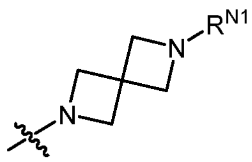
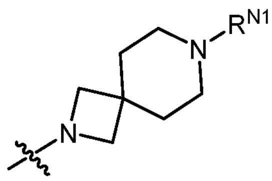


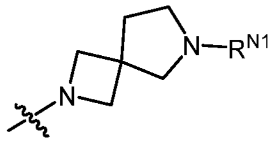
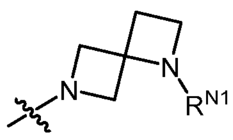
(xxvii).

131. The compound of claim 130 , wherein q is 1, 2, or 3 and w is 1.

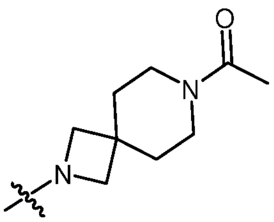
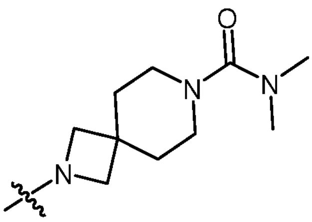
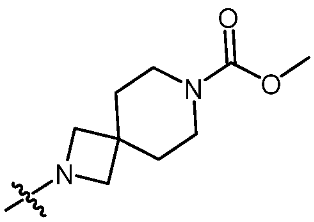
132. The compound of claim 130, wherein q is 2 and w is 0 or 2.

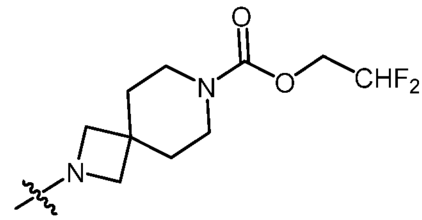
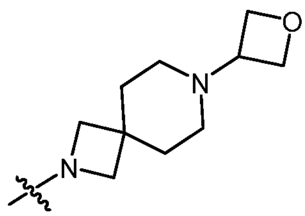
133. The compound of claim 130, wherein Ring B is of formula:

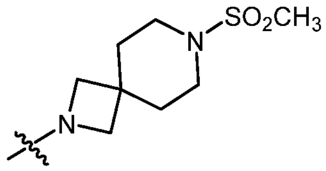
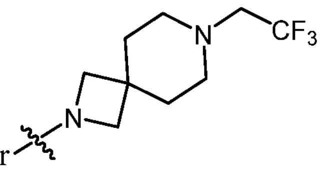
, , ,

, or .

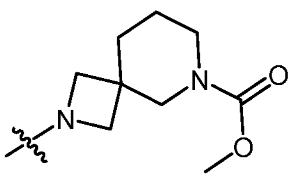
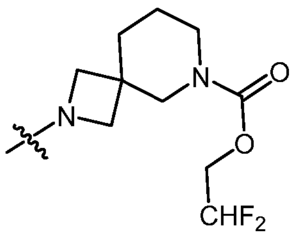
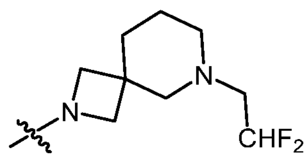
134. The compound of claim 130, wherein Ring B is of formula:

 , ,

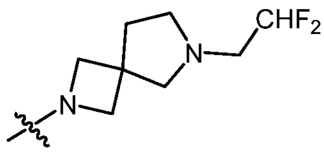
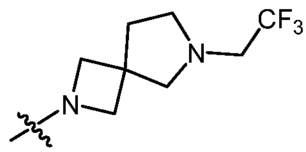
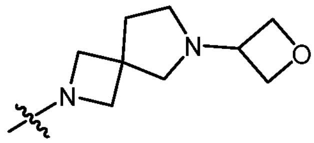
, ,

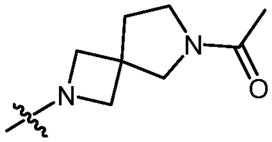
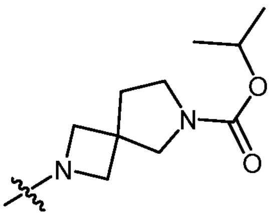
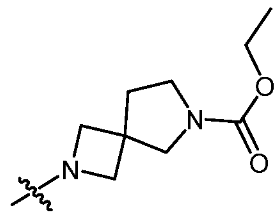
, or .

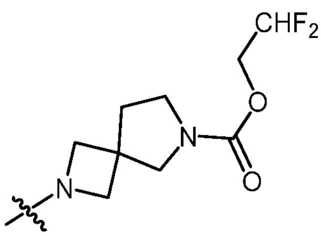
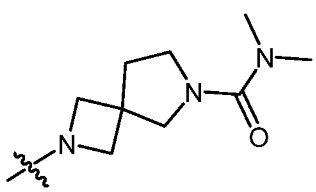
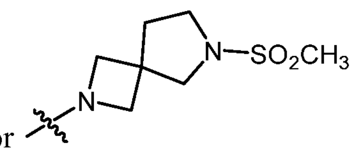
135. The compound of claim 130, wherein Ring B is of formula:

, , or .

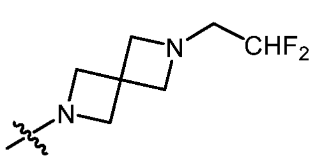
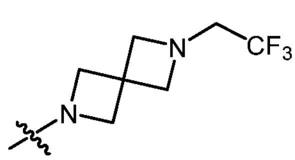
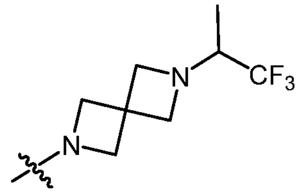
136. The compound of claim 130, wherein Ring B is of formula:

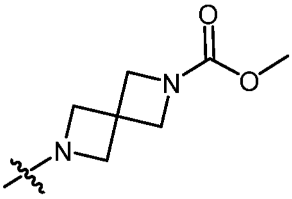
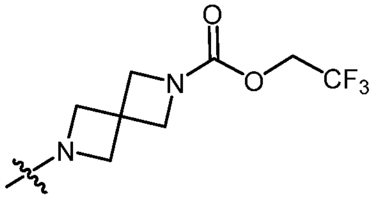
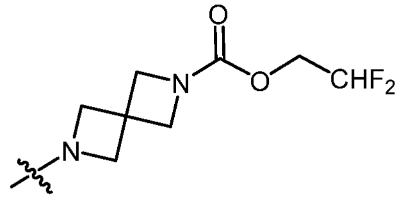
, , ,

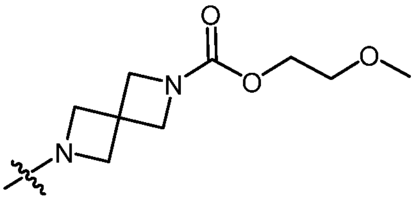
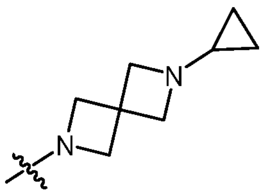
, , ,

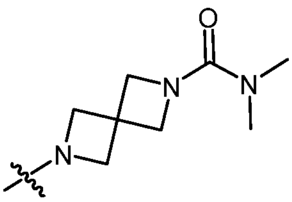
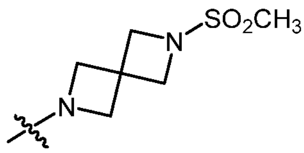
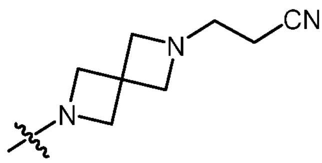
, , or .

137. The compound of claim 130, wherein Ring B is of formula:

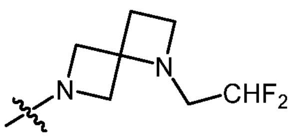
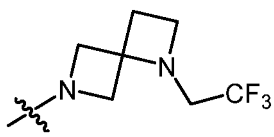
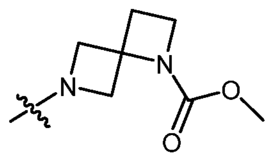
, , ,

. , ,

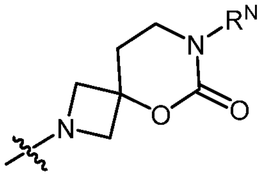
, ,

, , or .

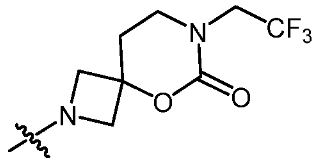
138. The compound of claim 130, wherein Ring B is of formula:

, , or .

139. The compound of any one of claims 1-58, wherein Ring B is of formula:

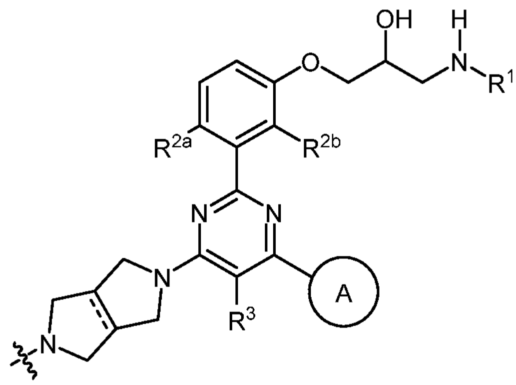
 (xxviii).

140. The compound of claim 139, wherein Ring B is of formula:



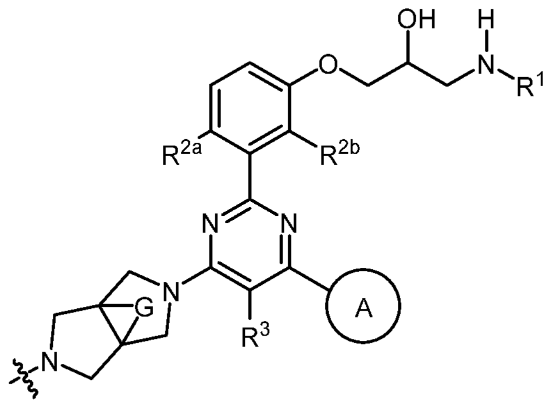
.

141. The compound of any one of claims 1-58, wherein Ring B is of formula:



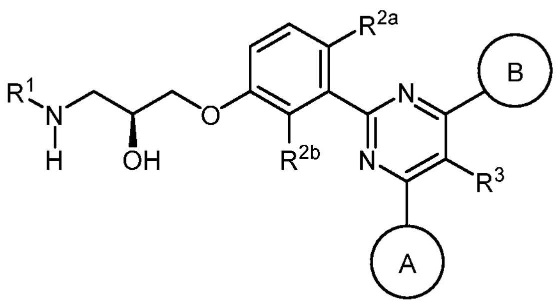
(xxix).

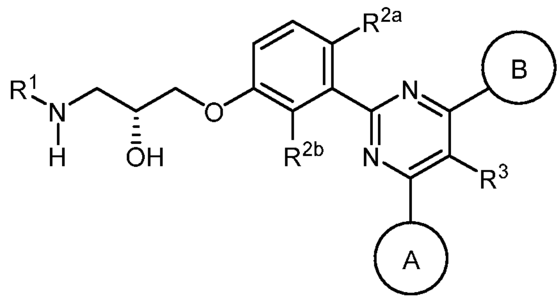
142. The compound of claim 141, wherein Ring B is of formula:



.

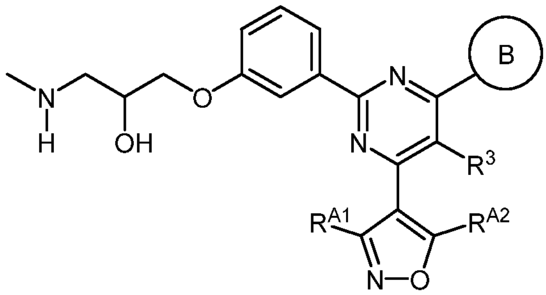
143. The compound of any one of claims 1-142, wherein the compound is of Formula:



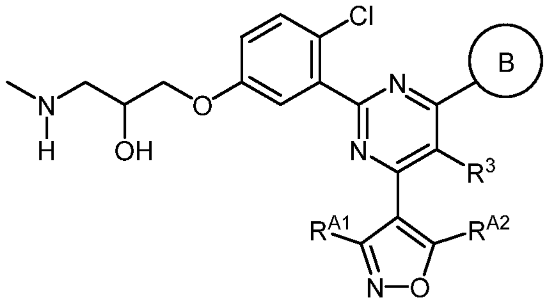


or a pharmaceutically acceptable salt thereof.

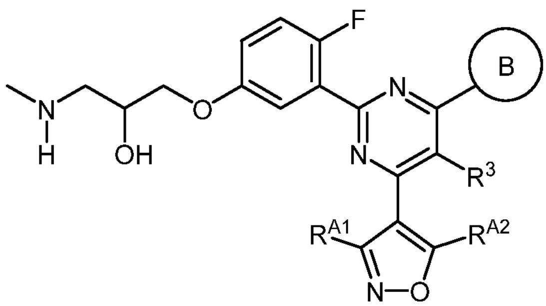
144. The compound of any one of claims 1-142, wherein the compound is of Formula:



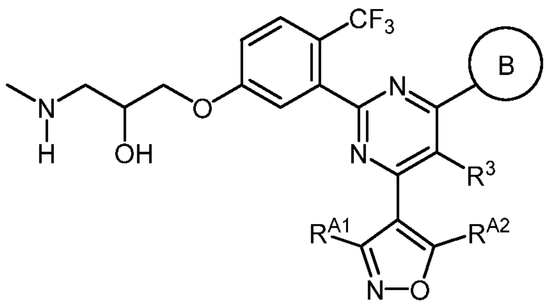
,



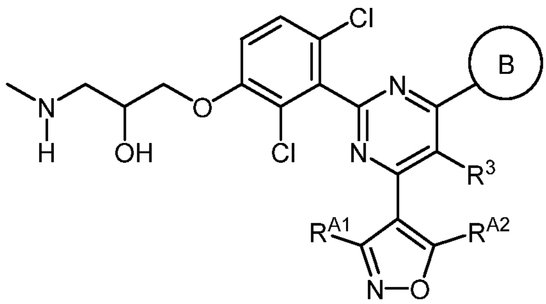
,



,



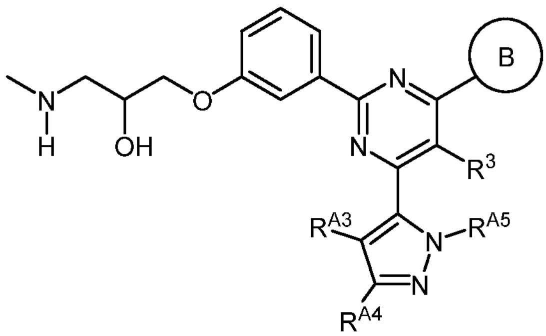
,



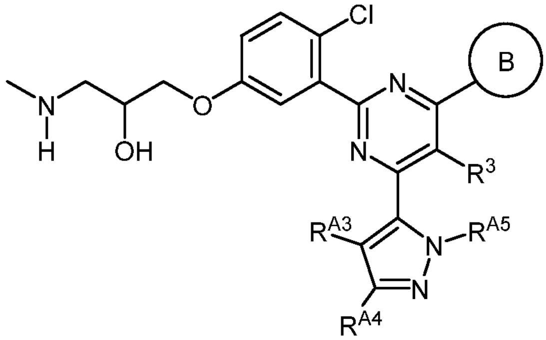
,

or a pharmaceutically acceptable salt thereof.

145. The compound of any one of claims 1-142, wherein the compound is of Formula:



,



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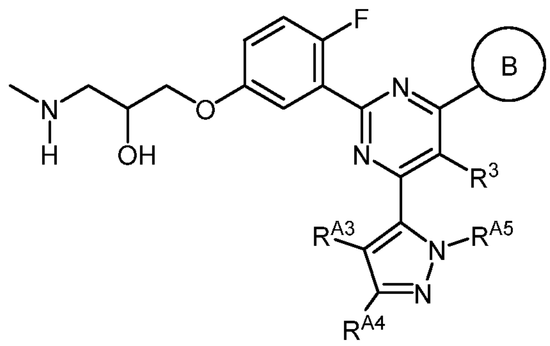

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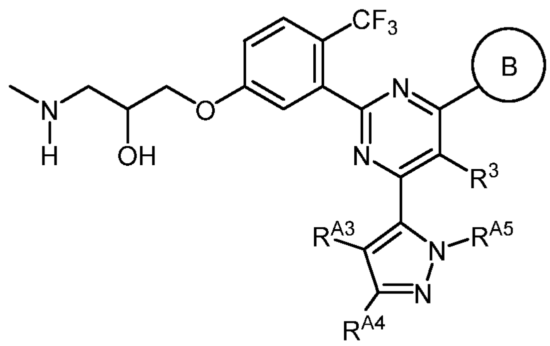
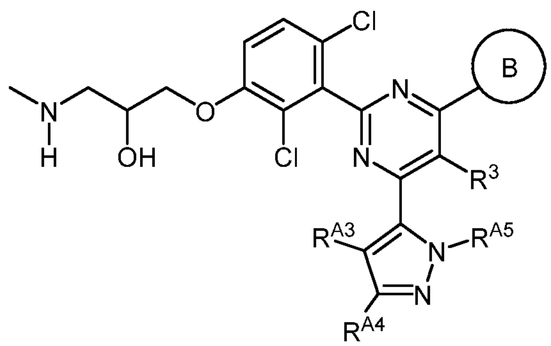
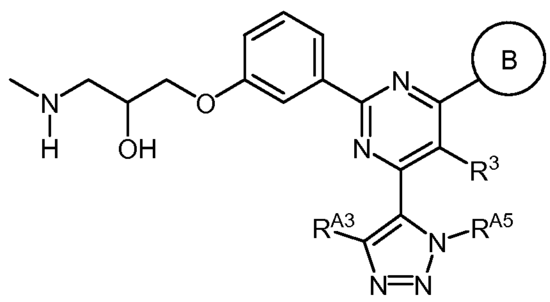


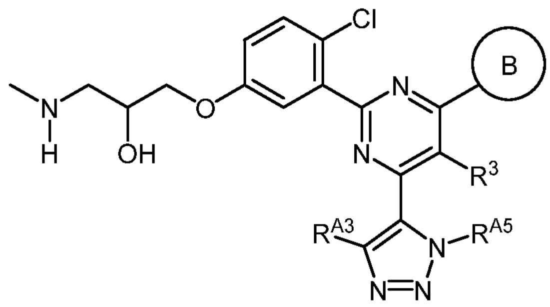
,



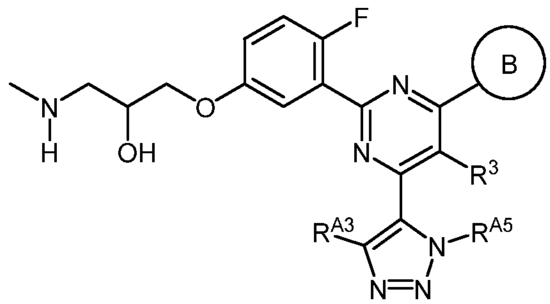
146. The compound of any one of claims 1-142, wherein the compound is of Formula:



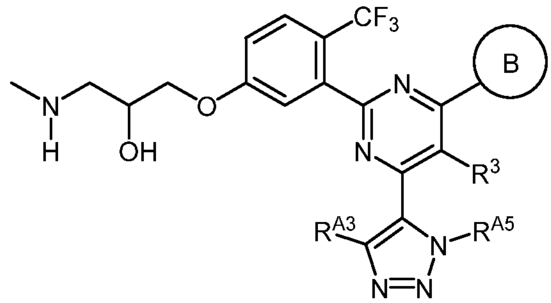
,



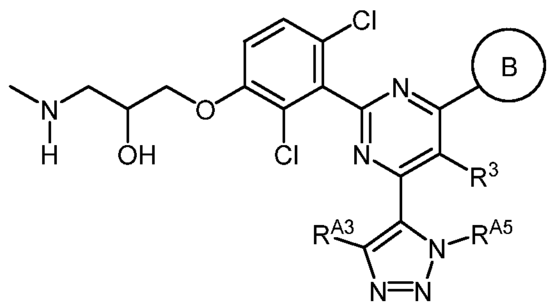
,



,



,



,

or a pharmaceutically acceptable salt thereof.

147. The compound of any one of claims 1-146, wherein the compound is selected from the group consisting of compounds depicted in Table 1 and pharmaceutically acceptable salts thereof.

148. A pharmaceutical composition comprising a compound of any one of claims 1-146 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

149. A kit or packaged pharmaceutical comprising a compound of any any one of claims 1-146 or a pharmaceutically acceptable salt thereof, and instructions for use thereof.

150. A method of treating a CARM1–mediated disorder, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-146, or a pharmaceutically acceptable salt thereof.

151. The method of claim 150, wherein the disorder is a proliferative disorder.

152. The method of claim 151, wherein the proliferative disorder is cancer.

153. The method of claim 152, wherein the cancer is associated with E2F1 upregulation.

154. The method of claim 152, wherein the cancer is associated with aberrant CARM1 activity.

155. The method of claim 152, wherein the cancer is breast cancer, prostate cancer, or colorectal cancer.

156. The method of claim 152, wherein the cancer is ERα-dependent breast cancer.

157. The method of claim 152, wherein the cancer is castration-resistant prostate cancer.

158. The method of claim 152, wherein the cancer is colorectal cancer associated with dysregulated WNT/β-catenin signaling.

159. The method of claim 150, wherein the disorder is a metabolic disorder.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/50712

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 47/10 (2015.01)
CPC - C07C 271/22; C07C 2101/14; A61K 31/27
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)
CPC: C07C 271/22; C07C 2101/14; A61K 31/27
IPC: A01N 47/10 (2015.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/487; 514/485 (See Search Words Below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PATBASE: Full-text = AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO
Google: Scholar/Patents: phenoxy propan-2-ol amine pyrimidine indole indazole morpholino amino methyltransferase thiol phenyl antiproliferative cancer proline dimethyloxazole difluoro pyrazole

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,710,052 B2 (PEASE et al.) 23 March 2004 (23.03.2004) Col 2, ln 47-50; Col 28, ln 17-25;Col 32, ln 15-30,	1-11; 14-18
Y	US 2010/0144722 A1 (ALEXANDER et al.) 10 June 2010 (10.06.2010) para [0252];[0732];[0733];[0854]	1-11; 14-18
Y	US 2014/0228360 A1 (DUNCAN et al.) 14 August 2014 (14.08.2014) para [0011]; [0034];[0035];[0044];[0106];[0190];[0245]	5-10; 14-18

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 November 2015 (12.11.2015)	15 DEC 2015

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/50712

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 12-13; 19-159
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.