(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 August 2012 (16.08.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/109398 A1

(51) International Patent Classification:
C07D 417/12 (2006.01) *A61K 31/4706* (2006.01)
C07D 417/14 (2006.01) *A61K 31/506* (2006.01)
A61K 31/427 (2006.01) *A61P 31/14* (2006.01)
A61K 31/4436 (2006.01)

(21) International Application Number:
PCT/US2012/024389

(22) International Filing Date:
9 February 2012 (09.02.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/441,563 10 February 2011 (10.02.2011) US

(71) Applicant *(for all designated States except US)*: **IDENIX PHARMACEUTICALS, INC.** [US/US]; 60 Hampshire Street, Cambridge, MA 02139 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PARSY, Christophe Claude** [FR/FR]; 6 Rue des Cedres, 34830 Jacou (FR). **ALEXANDRE, Francois-Rene** [FR/FR]; 200 Avenue Major Flandre, L'Occitanie Bat 4, 34090 Montpellier (FR). **CONVARD, Thierry** [FR/FR]; 7 avenue de Bel Air, 69580 Sathona -Cam (FR). **SURLERAUX, Dominique** [BE/BE]; Rue de la Scaillee 13, 1440 Wauthier-Braine (BE).

(74) Agents: **RIEGER, Dale L.** et al.; Jones Day, 222 East 41st Street, New York, NY 10017-6702 (US).

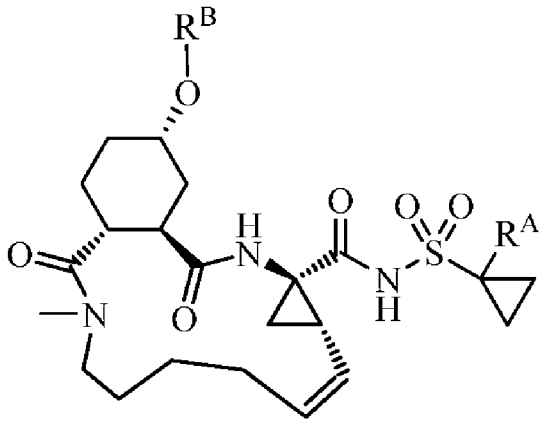
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: MACROCYCLIC SERINE PROTEASE INHIBITORS, PHARMACEUTICAL COMPOSITIONS THEREOF, AND THEIR USE FOR TREATING HCV INFECTIONS

(57) Abstract: Provided herein are macrocyclic serine protease inhibitor compounds, for example, of Formula I, and pharmaceutical compositions and processes of preparation thereof. Also provided are methods of their use for the treatment of an HCV infection in a host in need thereof.



(I)

WO 2012/109398 A1

Published:

— *with international search report (Art. 21(3))*

MACROCYCLIC SERINE PROTEASE INHIBITORS, PHARMACEUTICAL COMPOSITIONS THEREOF, AND THEIR USE FOR TREATING HCV INFECTIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 61/441,563, filed Februry 10, 2011; the disclosure of which is incorporated herein by reference in its entirety.

FIELD

[0002] Provided herein are macrocyclic serine protease inhibitor compounds, and pharmaceutical compositions and processes of preparation thereof. Also provided are methods of their use for the treatment of an HCV infection in a host in need thereof.

BACKGROUND

[0003] Hepatitis C virus (HCV) is known to cause at least 80% of posttransfusion hepatitis and a substantial proportion of sporadic acute hepatitis (Kuo *et al.*, *Science* **1989**, *244*, 362-364; Thomas, *Curr. Top. Microbiol. Immunol.* **2000**, 25-41). Preliminary evidence also implicates HCV in many cases of "idiopathic" chronic hepatitis, "cryptogenic" cirrhosis, and probably hepatocellular carcinoma unrelated to other hepatitis viruses, such as hepatitis B virus (Di Besceglie *et al.*, *Scientific American* **1999**, *October*, 80-85; Boyer *et al.*, *J. Hepatol.* **2000**, *32*, 98-112).

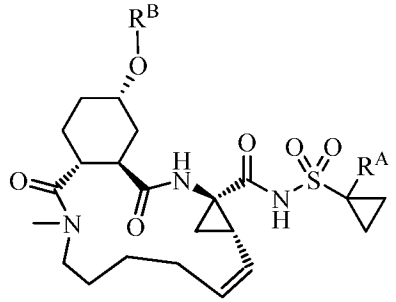
[0004] HCV is an enveloped virus containing a positive-sense single-stranded RNA genome of approximately 9.4 kb (Kato *et al.*, *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 9524-9528; Kato, *Acta Medica Okayama*, **2001**, *55*, 133-159). The viral genome consists of a 5' untranslated region (UTR), a long open reading frame encoding a polyprotein precursor of approximately 3011 amino acids, and a short 3' UTR. The 5' UTR is the most highly conserved part of the HCV genome and is important for the initiation and control of polyprotein translation. Translation of the HCV genome is initiated by a cap-independent mechanism known as an internal ribosome entry. This mechanism involves the binding of ribosomes to an RNA sequence known as the internal ribosome entry site (IRES). An RNA pseudoknot structure has recently been determined to be an essential structural element of the

HCV IRES. Viral structural proteins include a nucleocapsid core protein (C) and two envelope glycoproteins, E1 and E2. HCV also encodes two proteinases, a zinc-dependent metalloproteinase encoded by the NS2-NS3 region and a serine proteinase encoded in the NS3 region. These proteinases are required for cleavage of specific regions of the precursor polyprotein into mature peptides. The carboxyl half of nonstructural protein 5, NS5B, contains the RNA-dependent RNA polymerase. The function of the remaining nonstructural proteins, NS4A and NS4B, and that of NS5A (the amino-terminal half of nonstructural protein 5) remain unknown.

[0005] Presently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in about 40% of patients (Poynard *et al.*, *Lancet* **1998**, *352*, 1426-1432). Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy. However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load (Manns et al, *Lancet* **2001**, *358*, 958-965; Fried *et al.*, *N. Engl. J. Med.* **2002**, *347*, 975-982; Hadziyannis *et al.*, *Ann. Intern. Med.* **2004**, *140*, 346-355). Thus, there is a clear and unmet need to develop effective therapeutics for treatment of HCV infection.

SUMMARY OF THE DISCLOSURE

[0006] Provided herein is a compound of Formula I:

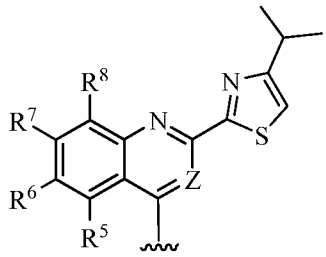


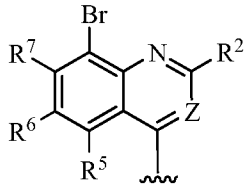
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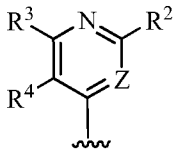
or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein:

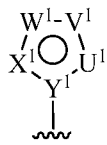
R^A is (i) hydrogen or halogen; or (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; and

R^B is a moiety selected from (Ia), (Ib), (Ic), and (Id):


(Ia)


(Ib)


(Ic)


(Id)

wherein:

each Z is independently CR^1 or N;

U^1, V^1, W^1, and X^1 are each independently O, N, S, CR^9, or NR^9;

Y^1 is C or N;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are each independently (i) hydrogen, halo, cyano, trifluoromethyl, or nitro; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) $–C(O)R^{1a}$, $–C(O)OR^{1a}$, $–C(O)NR^{1b}R^{1c}$, $–C(NR^{1a})NR^{1b}R^{1c}$, $–OR^{1a}$, $–OC(O)R^{1a}$, $–OC(O)OR^{1a}$, $–OC(O)NR^{1b}R^{1c}$, $–OC(=NR^{1a})NR^{1b}R^{1c}$, $–OS(O)R^{1a}$, $–OS(O)_2R^{1a}$, $–OS(O)NR^{1b}R^{1c}$, $–OS(O)_2NR^{1b}R^{1c}$, $–NR^{1b}R^{1c}$, $–NR^{1a}C(O)R^{1d}$, $–NR^{1a}C(O)OR^{1d}$, $–NR^{1a}C(O)NR^{1b}R^{1c}$, $–NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $–NR^{1a}S(O)R^{1d}$, $–NR^{1a}S(O)_2R^{1d}$, $–NR^{1a}S(O)NR^{1b}R^{1c}$, $–NR^{1a}S(O)_2NR^{1b}R^{1c}$, $–P(O)R^{1a}R^{1d}$, $–P(O)(OR^{1a})R^{1d}$, $–P(O)(OR^{1a})(OR^{1d})$, $–SR^{1a}$, $–S(O)R^{1a}$, $–S(O)_2R^{1a}$, $–S(O)NR^{1b}R^{1c}$, or $–S(O)_2NR^{1b}R^{1c}$; and

each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or R^{1a} and R^{1c} together with the C and N atoms to which they are attached form heterocyclyl; or R^{1b} and R^{1c} together with the N atom to which they are attached form heterocyclyl;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q, where each Q is independently selected from (a) oxo, cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; and (c) $–C(O)R^a$, $–C(O)OR^a$, $–C(O)NR^bR^c$, $–C(NR^a)NR^bR^c$, $–OR^a$, $–OC(O)R^a$, $–OC(O)OR^a$, $–OC(O)NR^bR^c$, $–OC(=NR^a)NR^bR^c$, $–OS(O)R^a$, $–OS(O)_2R^a$, $–OS(O)NR^bR^c$, $–OS(O)_2NR^bR^c$, $–NR^bR^c$, $–NR^aC(O)R^d$, $–NR^aC(O)OR^d$, $–NR^aC(O)NR^bR^c$, $–NR^aC(=NR^d)NR^bR^c$, $–NR^aS(O)R^d$, $–NR^aS(O)_2R^d$, $–NR^aS(O)NR^bR^c$, $–NR^aS(O)_2NR^bR^c$, $–P(O)R^aR^d$, $–P(O)(OR^a)R^d$, $–P(O)(OR^a)(OR^d)$, $–SR^a$, $–S(O)R^a$, $–S(O)_2R^a$, $–S(O)NR^bR^c$, and $–S(O)_2NR^bR^c$, wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen; (ii) C_{1-6} alkyl,

C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; or (iii) R^b and R^c together with the N atom to which they are attached form heterocyclyl, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a;

wherein each Q^a is independently selected from the group consisting of (a) oxo, cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^fR^g$, $-C(NR^e)NR^fR^g$, $-OR^e$, $-OC(O)R^e$, $-OC(O)OR^e$, $-OC(O)NR^fR^g$, $-OC(=NR^e)NR^fR^g$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^fR^g$, $-OS(O)_2NR^fR^g$, $-NR^fR^g$, $-NR^eC(O)R^h$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^fR^g$, $-NR^eC(=NR^h)NR^fR^g$, $-NR^eS(O)R^h$, $-NR^eS(O)_2R^h$, $-NR^eS(O)NR^fR^g$, $-NR^eS(O)_2NR^fR^g$, $-P(O)R^eR^h$, $-P(O)(OR^e)R^h$, $-P(O)(OR^e)(OR^h)$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^fR^g$, and $-S(O)_2NR^fR^g$; wherein each R^e, R^f, R^g, and R^h is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heterocyclyl.

[0007] Also provided herein are pharmaceutical compositions comprising a compound disclosed herein, *e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more pharmaceutically acceptable excipients or carriers.

[0008] Further provided herein is a method for treating or preventing an HCV infection in a subject, which comprises administering to the subject a therapeutically effective amount of a compound disclosed herein, *e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0009] Additionally provided herein is a method for treating, preventing, or ameliorating one or more symptoms of a liver disease or disorder associated with an HCV infection in a subject, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, *e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0010] Provided herein is a method for inhibiting replication of a virus in a host, which comprises administering to the host a therapeutically effective amount of a compound

disclosed herein, *e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0011] Provided herein is a method for inhibiting the activity of a serine protease, which comprises contacting the serine protease with a compound disclosed herein, *e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

DETAILED DESCRIPTION

[0012] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below.

[0013] Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0014] The term "subject" refers to an animal, including, but not limited to, a primate (*e.g.*, human), cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human subject, in one embodiment, a human.

[0015] The term "host" refers to a unicellular or multicellular organism in which a virus can replicate, including, but not limited to, a cell, cell line, and animal, such as a human.

[0016] The terms "treat," "treating," and "treatment" are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or alleviating or eradicating the cause(s) of the disorder, disease, or condition itself.

[0017] The terms "prevent," "preventing," and "prevention" are meant to include a method of delaying and/or precluding the onset of a disorder, disease, or condition, and/or its attendant symptoms; barring a subject from acquiring a disorder, disease, or condition; or reducing a subject's risk of acquiring a disorder, disease, or condition.

[0018] The term "therapeutically effective amount" are meant to include the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disorder, disease, or condition being treated. The term "therapeutically effective amount" also refers to the amount of a compound that is sufficient to elicit the biological or medical response of a biological molecule (*e.g.*, a protein, enzyme, RNA, or DNA), cell, tissue, system, animal, or human, which is being sought by a researcher, veterinarian, medical doctor, or clinician.

[0019] The term "IC_{50}" or "EC_{50}" refers an amount, concentration, or dosage of a compound that is required for 50% inhibition of a maximal response in an assay that measures such response.

[0020] The term "CC_{50}" refers an amount, concentration, or dosage of a compound that results in 50% reduction of the viability of a host. In certain embodiments, the CC_{50} of a compound is the amount, concentration, or dosage of the compound that is required to reduce the viability of cells treated with the compound by 50%, in comparison with cells untreated with the compound.

[0021] The term "pharmaceutically acceptable carrier," "pharmaceutically acceptable excipient," "physiologically acceptable carrier," or "physiologically acceptable excipient" refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. In one embodiment, each component is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, Remington: The Science and Practice of Pharmacy*, 21st ed.; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients*, 6th ed.; Rowe *et al.*, Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives*, 3rd ed.; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation*, 2nd ed.; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

[0022] The term "about" or "approximately" means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on

how the value is measured or determined. In certain embodiments, the term "about" or "approximately" means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term "about" or "approximately" means within 50%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

[0023] The terms "active ingredient" and "active substance" refer to a compound, which is administered, alone or in combination with one or more pharmaceutically acceptable excipients, to a subject for treating, preventing, or ameliorating one or more symptoms of a condition, disorder, or disease. As used herein, "active ingredient" and "active substance" may be an optically active isomer or an isotopic variant of a compound described herein.

[0024] The terms "drug," "therapeutic agent," and "chemotherapeutic agent" refer to a compound, or a pharmaceutical composition thereof, which is administered to a subject for treating, preventing, or ameliorating one or more symptoms of a condition, disorder, or disease.

[0025] The term "alkyl" refers to a linear or branched saturated monovalent hydrocarbon radical, wherein the alkyl may optionally be substituted with one or more substituents Q as described herein. For example, C_{1-6} alkyl refers to a linear saturated monovalent hydrocarbon radical of 1 to 6 carbon atoms or a branched saturated monovalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkyl is a linear saturated monovalent hydrocarbon radical that has 1 to 20 (C_{1-20}), 1 to 15 (C_{1-15}), 1 to 10 (C_{1-10}), or 1 to 6 (C_{1-6}) carbon atoms, or branched saturated monovalent hydrocarbon radical of 3 to 20 (C_{3-20}), 3 to 15 (C_{3-15}), 3 to 10 (C_{3-10}), or 3 to 6 (C_{3-6}) carbon atoms. As used herein, linear C_{1-6} and branched C_{3-6} alkyl groups are also referred as "lower alkyl." Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl (including all isomeric forms), *n*-propyl, isopropyl, butyl (including all isomeric forms), *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl, pentyl (including all isomeric forms), and hexyl (including all isomeric forms).

[0026] The term "alkenyl" refers to a linear or branched monovalent hydrocarbon radical, which contains one or more, in one embodiment, one to five, in another embodiment, one, carbon-carbon double bond(s). The alkenyl may be optionally substituted with one or more substituents Q as described herein. The term "alkenyl" embraces radicals having a "*cis*" or "*trans*" configuration or a mixture thereof, or alternatively, a "Z" or "E" configuration or a mixture thereof, as appreciated by those of ordinary skill in the art. For

example, C_{2-6} alkenyl refers to a linear unsaturated monovalent hydrocarbon radical of 2 to 6 carbon atoms or a branched unsaturated monovalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkenyl is a linear monovalent hydrocarbon radical of 2 to 20 (C_{2-20}), 2 to 15 (C_{2-15}), 2 to 10 (C_{2-10}), or 2 to 6 (C_{2-6}) carbon atoms, or a branched monovalent hydrocarbon radical of 3 to 20 (C_{3-20}), 3 to 15 (C_{3-15}), 3 to 10 (C_{3-10}), or 3 to 6 (C_{3-6}) carbon atoms. Examples of alkenyl groups include, but are not limited to, ethenyl, propen-1-yl, propen-2-yl, allyl, butenyl, and 4-methylbutenyl.

[0027] The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical, which contains one or more, in one embodiment, one to five, in another embodiment, one, carbon-carbon triple bond(s). The alkynyl may be optionally substituted with one or more substituents Q as described herein. For example, C_{2-6} alkynyl refers to a linear unsaturated monovalent hydrocarbon radical of 2 to 6 carbon atoms or a branched unsaturated monovalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkynyl is a linear monovalent hydrocarbon radical of 2 to 20 (C_{2-20}), 2 to 15 (C_{2-15}), 2 to 10 (C_{2-10}), or 2 to 6 (C_{2-6}) carbon atoms, or a branched monovalent hydrocarbon radical of 3 to 20 (C_{3-20}), 3 to 15 (C_{3-15}), 3 to 10 (C_{3-10}), or 3 to 6 (C_{3-6}) carbon atoms. Examples of alkynyl groups include, but are not limited to, ethynyl (–C≡CH), propynyl (including all isomeric forms, *e.g.*, 1-propynyl (–C≡CCH_3) and propargyl (–CH_2C≡CH)), butynyl (including all isomeric forms, *e.g.*, 1-butyn-1-yl and 2-butyn-1-yl), pentynyl (including all isomeric forms, *e.g.*, 1-pentyn-1-yl and 1-methyl-2-butyn-1-yl), and hexynyl (including all isomeric forms, *e.g.*, 1-hexyn-1-yl).

[0028] The term "cycloalkyl" refers to a cyclic monovalent hydrocarbon radical, which may be optionally substituted with one or more substituents Q as described herein. In one embodiment, cycloalkyl groups may be saturated or unsaturated but non-aromatic, and/or spiro, and/or non-spiro, and/or bridged, and/or non-bridged, and/or fused bicyclic groups. In certain embodiments, the cycloalkyl has from 3 to 20 (C_{3-20}), from 3 to 15 (C_{3-15}), from 3 to 10 (C_{3-10}), or from 3 to 7 (C_{3-7}) carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cycloheptenyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, decalinyl, and adamantyl.

[0029] The term "aryl" refers to a monovalent monocyclic aromatic group and/or monovalent polycyclic aromatic group that contain at least one aromatic carbon ring. In

certain embodiments, the aryl has from 6 to 20 (C_{6-20}), from 6 to 15 (C_{6-15}), or from 6 to 10 (C_{6-10}) ring atoms. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, fluorenyl, azulenyl, anthryl, phenanthryl, pyrenyl, biphenyl, and terphenyl. Aryl also refers to bicyclic or tricyclic carbon rings, where one of the rings is aromatic and the others of which may be saturated, partially unsaturated, or aromatic, for example, dihydronaphthyl, indenyl, indanyl, or tetrahydronaphthyl (tetralinyl). In certain embodiments, the aryl may be optionally substituted with one or more substituents Q as described herein.

[0030] The term "aralkyl" or "arylalkyl" refers to a monovalent alkyl group substituted with one or more aryl groups. In certain embodiments, the aralkyl has from 7 to 30 (C_{7-30}), from 7 to 20 (C_{7-20}), or from 7 to 16 (C_{7-16}) carbon atoms. Examples of aralkyl groups include, but are not limited to, benzyl, 2-phenylethyl, and 3-phenylpropyl. In certain embodiments, the aralkyl are optionally substituted with one or more substituents Q as described herein.

[0031] The term "heteroaryl" refers to a monovalent monocyclic aromatic group or monovalent polycyclic aromatic group that contain at least one aromatic ring, wherein at least one aromatic ring contains one or more heteroatoms independently selected from O, S, N, and P in the ring. Heteroaryl groups are bonded to the rest of a molecule through the aromatic ring. Each ring of a heteroaryl group can contain one or two O atoms, one or two S atoms, one to four N atoms, and/or one or two P atoms, provided that the total number of heteroatoms in each ring is four or less and each ring contains at least one carbon atom. In certain embodiments, the heteroaryl has from 5 to 20, from 5 to 15, or from 5 to 10 ring atoms. Examples of monocyclic heteroaryl groups include, but are not limited to, furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, tetrazolyl, triazinyl, and triazolyl. Examples of bicyclic heteroaryl groups include, but are not limited to, benzofuranyl, benzimidazolyl, benzoisoxazolyl, benzopyranyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzotriazolyl, benzoxazolyl, furopyridyl, imidazopyridinyl, imidazothiazolyl, indolizinyl, indolyl, indazolyl, isobenzofuranyl, isobenzothienyl, isoindolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxazolopyridinyl, phthalazinyl, pteridinyl, purinyl, pyridopyridyl, pyrrolopyridyl, quinolinyl, quinoxalinyl, quinazolinyl, thiadiazolopyrimidyl, and thienopyridyl. Examples of tricyclic heteroaryl groups include, but are not limited to, acridinyl, benzindolyl, carbazolyl, dibenzofuranyl, perimidinyl, phenanthrolinyl,

phenanthridinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxazinyl, and xanthenyl. In certain embodiments, the heteroaryl may also be optionally substituted with one or more substituents Q as described herein.

[0032] The term "heterocyclyl" or "heterocyclic" refers to a monovalent monocyclic non-aromatic ring system or monovalent polycyclic ring system that contains at least one non-aromatic ring, wherein one or more of the non-aromatic ring atoms are heteroatoms independently selected from O, S, N, and P; and the remaining ring atoms are carbon atoms. In certain embodiments, the heterocyclyl or heterocyclic group has from 3 to 20, from 3 to 15, from 3 to 10, from 3 to 8, from 4 to 7, or from 5 to 6 ring atoms. Heterocyclyl groups are bonded to the rest of a molecule through the non-aromatic ring. In certain embodiments, the heterocyclyl is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may be spiro, fused, or bridged, and in which nitrogen or sulfur atoms may be optionally oxidized, nitrogen atoms may be optionally quaternized, and some rings may be partially or fully saturated, or aromatic. The heterocyclyl may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Examples of such heterocyclic groups include, but are not limited to, azepinyl, benzodioxanyl, benzodioxolyl, benzofuranonyl, benzopyranonyl, benzopyranyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, benzothiopyranyl, benzoxazinyl, β-carbolinyl, chromanyl, chromonyl, cinnolinyl, coumarinyl, decahydroisoquinolinyl, dihydrobenzisothiazinyl, dihydrobenzisoxazinyl, dihydrofuryl, dihydroisoindolyl, dihydropyranyl, dihydropyrazolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dioxolanyl, 1,4-dithianyl, furanonyl, imidazolidinyl, imidazolinyl, indolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isochromanyl, isocoumarinyl, isoindolinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, oxazolidinonyl, oxazolidinyl, oxiranyl, piperazinyl, piperidinyl, 4-piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydropyranyl, tetrahydrothienyl, thiamorpholinyl, thiazolidinyl, tetrahydroquinolinyl, and 1,3,5-trithianyl. In certain embodiments, the heterocyclyl may also be optionally substituted with one or more substituents Q as described herein.

[0033] The term "halogen", "halide" or "halo" refers to fluorine, chlorine, bromine, and/or iodine.

[0034] The term "optionally substituted" is intended to mean that a group or

substituent, such as an alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, or heterocyclyl group, may be substituted with one or more substituents Q, each of which is independently selected from, *e.g.*, (a) oxo (=O), halo, cyano (–CN), and nitro ($–NO_2$); (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; and (c) $–C(O)R^a$, $–C(O)OR^a$, $–C(O)NR^bR^c$, $–C(NR^a)NR^bR^c$, $–OR^a$, $–OC(O)R^a$, $–OC(O)OR^a$, $–OC(O)NR^bR^c$, $–OC(=NR^a)NR^bR^c$, $–OS(O)R^a$, $–OS(O)_2R^a$, $–OS(O)NR^bR^c$, $–OS(O)_2NR^bR^c$, $–NR^bR^c$, $–NR^aC(O)R^d$, $–NR^aC(O)OR^d$, $–NR^aC(O)NR^bR^c$, $–NR^aC(=NR^d)NR^bR^c$, $–NR^aS(O)R^d$, $–NR^aS(O)_2R^d$, $–NR^aS(O)NR^bR^c$, $–NR^aS(O)_2NR^bR^c$, $–P(O)R^aR^d$, $–P(O)(OR^a)R^d$, $–P(O)(OR^a)(OR^d)$, $–SR^a$, $–S(O)R^a$, $–S(O)_2R^a$, $–S(O)NR^bR^c$, and $–S(O)_2NR^bR^c$, wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; or (iii) R^b and R^c together with the N atom to which they are attached form heteroaryl or heterocyclyl, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a. As used herein, all groups that can be substituted are "optionally substituted," unless otherwise specified.

[0035] In one embodiment, each Q^a is independently selected from the group consisting of (a) oxo, cyano, halo, and nitro; and (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) $–C(O)R^e$, $–C(O)OR^e$, $–C(O)NR^fR^g$, $–C(NR^e)NR^fR^g$, $–OR^e$, $–OC(O)R^e$, $–OC(O)OR^e$, $–OC(O)NR^fR^g$, $–OC(=NR^e)NR^fR^g$, $–OS(O)R^e$, $–OS(O)_2R^e$, $–OS(O)NR^fR^g$, $–OS(O)_2NR^fR^g$, $–NR^fR^g$, $–NR^eC(O)R^h$, $–NR^eC(O)OR^h$, $–NR^eC(O)NR^fR^g$, $–NR^eC(=NR^h)NR^fR^g$, $–NR^eS(O)R^h$, $–NR^eS(O)_2R^h$, $–NR^eS(O)NR^fR^g$, $–NR^eS(O)_2NR^fR^g$, $–P(O)R^eR^h$, $–P(O)(OR^e)R^h$, $–P(O)(OR^e)(OR^h)$, $–SR^e$, $–S(O)R^e$, $–S(O)_2R^e$, $–S(O)NR^fR^g$, and $–S(O)_2NR^fR^g$; wherein each R^e, R^f, R^g, and R^h is independently (i) hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (ii) R^f and R^g together with the N atom to which they are attached form heteroaryl or heterocyclyl.

[0036] The terms "optically active" and "enantiomerically active" refer to a collection of molecules, which has an enantiomeric excess of no less than about 50%, no less than about 70%, no less than about 80%, no less than about 90%, no less than about 91%, no less than

about 92%, no less than about 93%, no less than about 94%, no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%. In certain embodiments, the compound comprises about 95% or more of one enantiomer and about 5% or less of the other enantiomer based on the total weight of the racemate in question.

[0037] In describing an optically active compound, the prefixes R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The (+) and (-) are used to denote the optical rotation of the compound, that is, the direction in which a plane of polarized light is rotated by the optically active compound. The (-) prefix indicates that the compound is levorotatory, that is, the compound rotates the plane of polarized light to the left or counterclockwise. The (+) prefix indicates that the compound is dextrorotatory, that is, the compound rotates the plane of polarized light to the right or clockwise. However, the sign of optical rotation, (+) and (-), is not related to the absolute configuration of the molecule, R and S.

[0038] The term "isotopic variant" refers to a compound that contains an unnatural proportion of an isotope at one or more of the atoms that constitute such compounds. In certain embodiments, an "isotopic variant" of a compound contains unnatural proportions of one or more isotopes, including, but not limited to, hydrogen (^{1}H), deuterium (^{2}H), tritium (^{3}H), carbon-11 (^{11}C), carbon-12 (^{12}C), carbon-13 (^{13}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), oxygen-14 (^{14}O), oxygen-15 (^{15}O), oxygen-16 (^{16}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), fluorine-17 (^{17}F), fluorine-18 (^{18}F), phosphorus-31 (^{31}P), phosphorus-32 (^{32}P), phosphorus-33 (^{33}P), sulfur-32 (^{32}S), sulfur-33 (^{33}S), sulfur-34 (^{34}S), sulfur-35 (^{35}S), sulfur-36 (^{36}S), chlorine-35 (^{35}Cl), chlorine-36 (^{36}Cl), chlorine-37 (^{37}Cl), bromine-79 (^{79}Br), bromine-81 (^{81}Br), iodine-123 (^{123}I), iodine-125 (^{125}I), iodine-127 (^{127}I), iodine-129 (^{129}I), and iodine-131 (^{131}I). In certain embodiments, an "isotopic variant" of a compound is in a stable form, that is, non-radioactive. In certain embodiments, an "isotopic variant" of a compound contains unnatural proportions of one or more isotopes, including, but not limited to, hydrogen (^{1}H), deuterium (^{2}H), carbon-12 (^{12}C), carbon-13 (^{13}C), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), oxygen-16 (^{16}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), fluorine-17 (^{17}F), phosphorus-31 (^{31}P), sulfur-32 (^{32}S), sulfur-33 (^{33}S), sulfur-34 (^{34}S), sulfur-36 (^{36}S), chlorine-35 (^{35}Cl), chlorine-37 (^{37}Cl), bromine-79 (^{79}Br), bromine-81 (^{81}Br), and iodine-127 (^{127}I). In certain embodiments, an "isotopic variant" of a compound is in an unstable form,

that is, radioactive. In certain embodiments, an "isotopic variant" of a compound contains unnatural proportions of one or more isotopes, including, but not limited to, tritium (^{3}H), carbon-11 (^{11}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), oxygen-14 (^{14}O), oxygen-15 (^{15}O), fluorine-18 (^{18}F), phosphorus-32 (^{32}P), phosphorus-33 (^{33}P), sulfur-35 (^{35}S), chlorine-36 (^{36}Cl), iodine-123 (^{123}I), iodine-125 (^{125}I), iodine-129 (^{129}I), and iodine-131 (^{131}I). It will be understood that, in a compound as provided herein, any hydrogen can be ^{2}H, as example, or any carbon can be ^{13}C, as example, or any nitrogen can be ^{15}N, as example, and any oxygen can be ^{18}O, as example, where feasible according to the judgment of one of skill. In certain embodiments, an "isotopic variant" of a compound contains unnatural proportions of deuterium.

[0039] The term "solvate" refers to a complex or aggregate formed by one or more molecules of a solute, *e.g.*, a compound provided herein, and one or more molecules of a solvent, which present in a stoichiometric or non-stoichiometric amount. Suitable solvents include, but are not limited to, water, methanol, ethanol, *n*-propanol, isopropanol, and acetic acid. In certain embodiments, the solvent is pharmaceutically acceptable. In one embodiment, the complex or aggregate is in a crystalline form. In another embodiment, the complex or aggregate is in a noncrystalline form. Where the solvent is water, the solvate is a hydrate. Examples of hydrates include, but are not limited to, a hemihydrate, monohydrate, dihydrate, trihydrate, tetrahydrate, and pentahydrate.

[0040] The phrase "an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof" has the same meaning as the phrase "an isotopic variant of the compound referenced therein; or a pharmaceutically acceptable salt, solvate, or prodrug of the compound referenced therein, or a pharmaceutically acceptable salt, solvate, or prodrug of an isotopic variant of the compound referenced therein."

Compounds

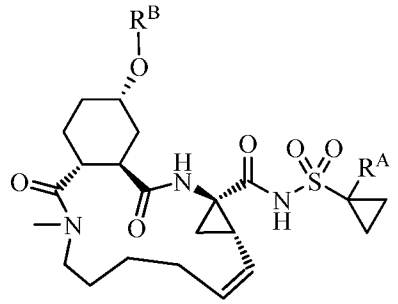
[0041] HCV has a single positive-stranded RNA genome having about 9.6 kb in length that encodes a large polyprotein having about 3010 amino acids. This precursor polyprotein is then processed into a range of structural proteins, including core protein, C, and envelope glycoproteins, E1 and E2; and non-structural proteins, including NS2, NS3, NS4A, NS4B, NS5A, and NS5B, by host signal peptidases and two viral proteases, NS2-3 and NS3. The NS3 protein contains a trypsin-like serine protease domain at its N-terminus,

while its C-terminal domain has helicase activity. Because of its vital role in viral replication, HCV NS3 serine protease has been actively pursued as a drug target for developing a new anti-HCV therapy.

[0042] Inhibitors of HCV NS3 protease that have been reported include linear and cyclic peptides and peptide mimetics, and non-peptide molecules (Llinàs-Brunet *et al.*, *Bioorg. Med. Chem. Lett.* **1998**, *8,* 1713-1718; Steinkühler *et al.*, *Biochemistry* **1998**, *37*, 8899-8905; U.S. Pat. Nos.: 5,538,865; 5,990,276; 6,143,715; 6,265,380; 6,323,180; 6,329,379; 6,410,531; 6,420,380; 6,534,523; 6,608,027; 6,642,204; 6,653,295; 6,727,366; 6,838,475; 6,846,802; 6,867,185; 6,869,964; 6,872,805; 6,878,722; 6,908,901; 6,911,428; 6,995,174; 7,012,066; 7,041,698; 7,091,184; 7,169,760; 7,176,208; 7,208,600; and 7,491,794; U.S. Pat. Appl. Publ. Nos.: 2002/0016294, 2002/0016442; 2002/0032175; 2002/0037998; 2004/0229777; 2005/0090450; 2005/0153877; 2005/176648; 2006/0046956; 2007/0021330; 2007/0021351; 2007/0049536; 2007/0054842; 2007/0060510; 2007/0060565; 2007/0072809; 2007/0078081; 2007/0078122; 2007/0093414; 2007/0093430; 2007/0099825; 2007/0099929; 2007/0105781, 2008/0152622, 2009/0035271, 2009/0035272, 2009/0111969, 2009/0111982, 2009/0123425, 2009/0130059, 2009/148407, 2009/0156800, 2009/0169510, 2009/0175822, and 2009/0180981; and International Pat. Appl. Publ. Nos.: WO 98/17679; WO 98/22496; WO 99/07734; WO 00/09543; WO 00/59929; WO 02/08187; WO 02/08251; WO 02/08256; WO 02/08198; WO 02/48116; WO 02/48157; WO 02/48172; WO 02/60926; WO 03/53349; WO 03/64416; WO 03/64455; WO 03/64456; WO 03/66103; WO 03/99274; WO 03/99316; WO 2004/032827; WO 2004/043339; WO 2005/037214; WO 2005/037860; WO 2006/000085; WO 2006/119061; WO 2006/122188; WO 2007/001406; WO 2007/014925; WO 2007/014926; WO 2007/015824, WO 2007/056120, WO 2008/019289, WO 2008/021960, WO 2008/022006, WO 2008/086161, WO 2009/053828, WO 2009/058856, WO 2009/073713, WO 2009/073780, WO 2009/080542, WO 2009/082701, WO 2009/082697, and WO 2009/085978). However, citation of any reference herein is not an admission that such reference is prior art to the present disclosure.

[0043] Provided herein are compounds which are useful for the treatment of HCV infection, which, in one embodiment, can have activity as HCV serine protease inhibitors. Also provided herein are pharmaceutical compositions that comprise the compounds, methods of manufacture of the compounds, and methods of use of the compounds for the treatment of HCV infection in a subject in need of treatment.

[0044] In one embodiment, provided herein is a compound of Formula I:

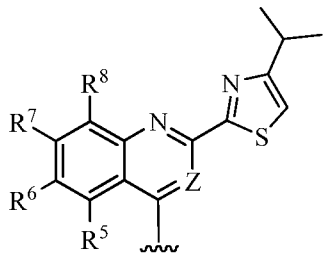


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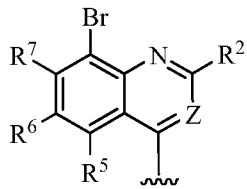
or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein:

R^A is (i) hydrogen or halogen; or (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; and

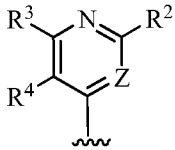
R^B is a moiety selected from (Ia), (Ib), (Ic), and (Id):



(Ia)



(Ib)



(Ic)



(Id)

wherein:

each Z is independently CR^1 or N;

U^1, V^1, W^1, and X^1 are each independently O, N, S, CR^9, or NR^9;

Y^1 is C or N;

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are each independently (i) hydrogen, halo, cyano, trifluoromethyl, or nitro; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-P(O)R^{1a}R^{1d}$, $-P(O)(OR^{1a})R^{1d}$, $-P(O)(OR^{1a})(OR^{1d})$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; and

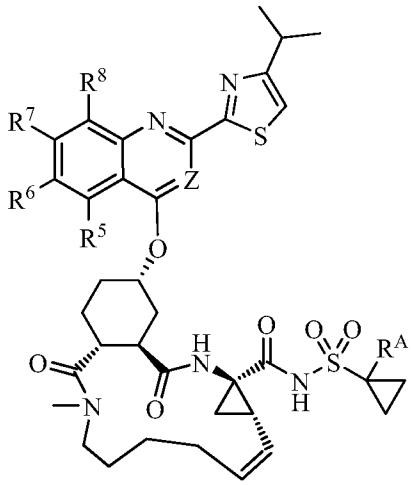
each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or

R^{1a} and R^{1c} together with the C and N atoms to which they are attached form heterocyclyl; or R^{1b} and R^{1c} together with the N atom to which they are attached form heterocyclyl;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q, where each Q is independently selected from (a) oxo, cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; and (c) $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^bR^c$, $-C(NR^a)NR^bR^c$, $-OR^a$, $-OC(O)R^a$, $-OC(O)OR^a$, $-OC(O)NR^bR^c$, $-OC(=NR^a)NR^bR^c$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-OS(O)NR^bR^c$, $-OS(O)_2NR^bR^c$, $-NR^bR^c$, $-NR^aC(O)R^d$, $-NR^aC(O)OR^d$, $-NR^aC(O)NR^bR^c$, $-NR^aC(=NR^d)NR^bR^c$, $-NR^aS(O)R^d$, $-NR^aS(O)_2R^d$, $-NR^aS(O)NR^bR^c$, $-NR^aS(O)_2NR^bR^c$, $-P(O)R^aR^d$, $-P(O)(OR^a)R^d$, $-P(O)(OR^a)(OR^d)$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^bR^c$, and $-S(O)_2NR^bR^c$, wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; or (iii) R^b and R^c together with the N atom to which they are attached form heterocyclyl, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a;

wherein each Q^a is independently selected from the group consisting of (a) oxo, cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^fR^g$, $-C(NR^e)NR^fR^g$, $-OR^e$, $-OC(O)R^e$, $-OC(O)OR^e$, $-OC(O)NR^fR^g$, $-OC(=NR^e)NR^fR^g$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^fR^g$, $-OS(O)_2NR^fR^g$, $-NR^fR^g$, $-NR^eC(O)R^h$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^fR^g$, $-NR^eC(=NR^h)NR^fR^g$, $-NR^eS(O)R^h$, $-NR^eS(O)_2R^h$, $-NR^eS(O)NR^fR^g$, $-NR^eS(O)_2NR^fR^g$, $-P(O)R^eR^h$, $-P(O)(OR^e)R^h$, $-P(O)(OR^e)(OR^h)$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^fR^g$, and $-S(O)_2NR^fR^g$; wherein each R^e, R^f, R^g, and R^h is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heterocyclyl.

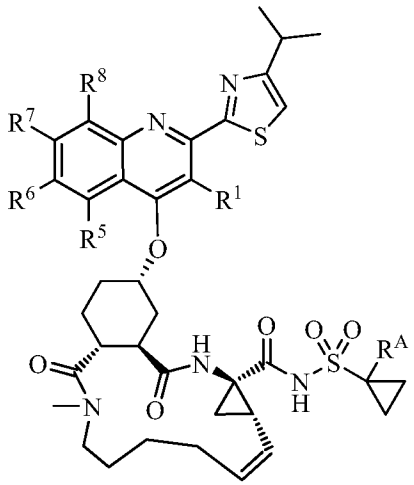
[0045] In another embodiment, provided herein is a compound of Formula IA:



(IA)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^5, R^6, R^7, R^8, and Z are each as defined herein.

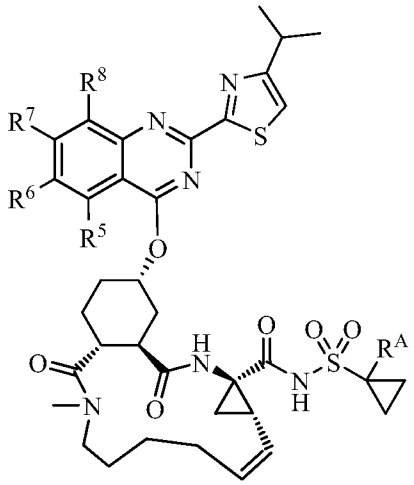
[0046] In one embodiment, provided herein is a compound of Formula IIA:



(IIA)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^1, R^5, R^6, R^7, and R^8 are each as defined herein.

[0047] In another embodiment, provided herein is a compound of Formula IIIA:

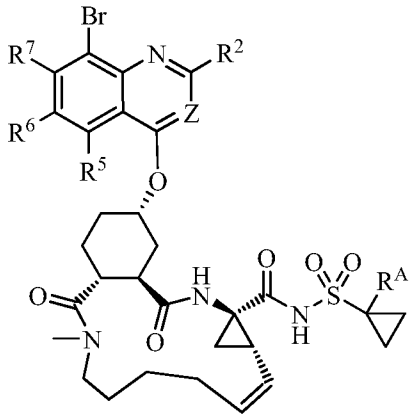


(IIIA)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^5, R^6, R^7, and R^8 are each as defined herein.

[0048] In Formula I, IA, IIA, or IIIA, in certain embodiments, R^A is hydrogen or methyl; in certain embodiments, R^1 is hydrogen; in certain embodiments, R^5 is hydrogen; in certain embodiments, R^6 is hydrogen; in certain embodiments, R^1, R^5, and R^6 are all hydrogen; in certain embodiments, R^7 is $-OR^{1a}$, where R^{1a} is as defined herein; in certain embodiments, R^7 is $-O-C_{1-6}$ alkyl, where the alkyl is optionally substituted with one or more substituents Q; in certain embodiments, R^7 is methoxy; in certain embodiments, R^8 is C_{1-6} alkyl, where the alkyl is optionally substituted with one or more substituents Q; and in certain embodiments, R^8 is methyl.

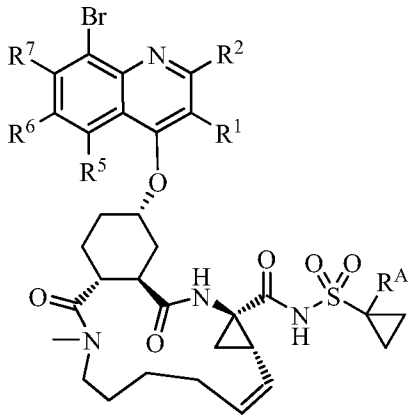
[0049] In yet another embodiment, provided herein is a compound of Formula IB:



(IB)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^2, R^5, R^6, R^7, and Z are each as defined herein.

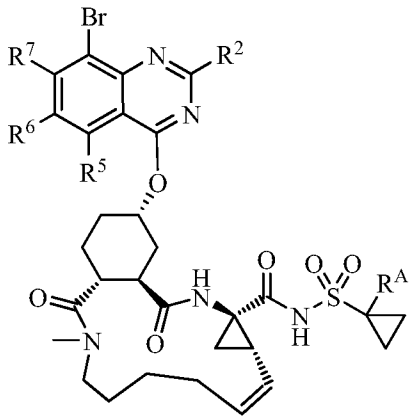
[0050] In one embodiment, provided herein is a compound of Formula IIB:



(IIB)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^1, R^2, R^5, R^6, and R^7 are each as defined herein.

[0051] In another embodiment, provided herein is a compound of Formula IIIB:



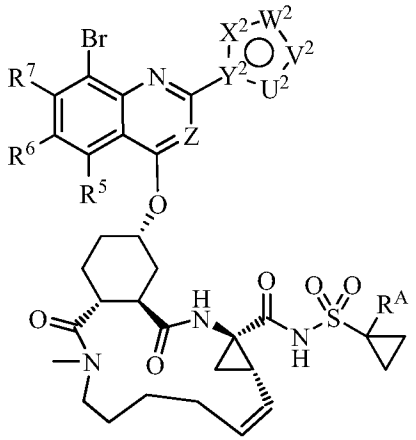
(IIIB)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^2, R^5, R^6, and R^7 are each as defined herein.

[0052] In Formula I, IB, IIB, or IIIB, in certain embodiments, R^A is hydrogen or methyl; in certain embodiments, R^1 is hydrogen; in certain embodiments, R^2 is heteroaryl, optionally substituted with one or more substituents Q; in certain embodiments, R^2 is 5-membered heteroaryl, optionally substituted with one or more substituents Q; in certain embodiments, R^2 is thiazolyl, optionally substituted with one or more substituents Q; in certain embodiments, R^5 is hydrogen; in certain embodiments, R^6 is hydrogen; in certain embodiments, R^1, R^5, and R^6 are all hydrogen; in certain embodiments, R^7 is $-OR^{1a}$, where R^{1a} is as defined herein; in certain embodiments, R^7 is $-O-C_{1-6}$ alkyl, where the alkyl is optionally substituted with one or more substituents Q; and in certain embodiments, R^7 is

methoxy.

[0053] In yet another embodiment, provided herein is a compound of Formula IVB:



(IVB)

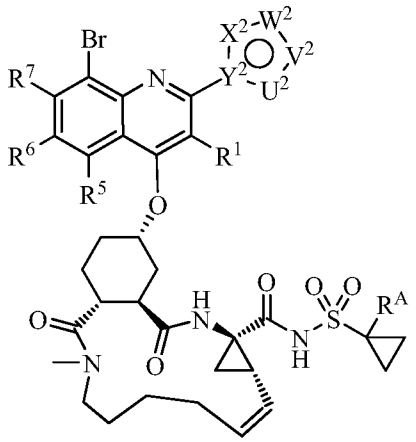
or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein:

U^2, V^2, W^2, and X^2 are each independently O, N, S, CR^9, or NR^9;

Y^2 is C or N; and

R^A, R^5, R^6, R^7, R^9, and Z are each as defined herein.

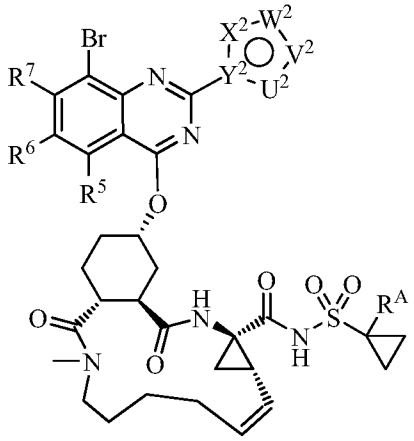
[0054] In one embodiment, provided herein is a compound of Formula VB:



(VB)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^1, R^5, R^6, R^7, U^2, V^2, W^2, X^2, and Y^2 are each as defined herein.

[0055] In another embodiment, provided herein is a compound of Formula VIB:

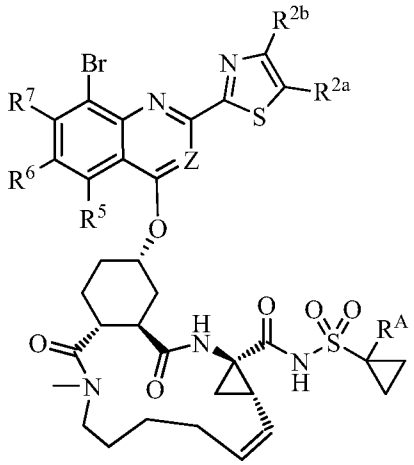


(VIB)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^5, R^6, R^7, U^2, V^2, W^2, X^2, and Y^2 are each as defined herein.

[0056] In Formula IVB, VB, or VIB, in certain embodiments, R^A is hydrogen or methyl; in certain embodiments, R^1 is hydrogen; in certain embodiments, R^5 is hydrogen; in certain embodiments, R^6 is hydrogen; in certain embodiments, R^1, R^5, and R^6 are all hydrogen; in certain embodiments, R^7 is $-OR^{1a}$, where R^{1a} is as defined herein; in certain embodiments, R^7 is $-O-C_{1-6}$ alkyl, where the alkyl is optionally substituted with one or more substituents Q; and in certain embodiments, R^7 is methoxy.

[0057] In yet another embodiment, provided herein is a compound of Formula VIIB:



(VIIB)

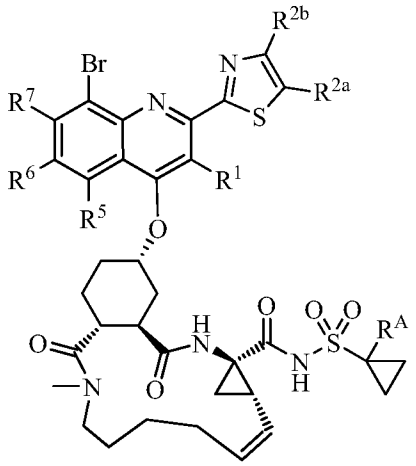
or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein:

R^{2a} and R^{2b} are each independently (i) hydrogen, halo, cyano, trifluoromethyl, or nitro; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl,

heteroaryl, or heterocyclyl, each optionally substituted with one or more substituents Q; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-P(O)R^{1a}R^{1d}$, $-P(O)(OR^{1a})R^{1d}$, $-P(O)(OR^{1a})(OR^{1d})$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; and

R^A, R^5, R^6, R^7, R^{1a}, R^{1b}, R^{1c}, R^{1d}, and Z are each as defined herein.

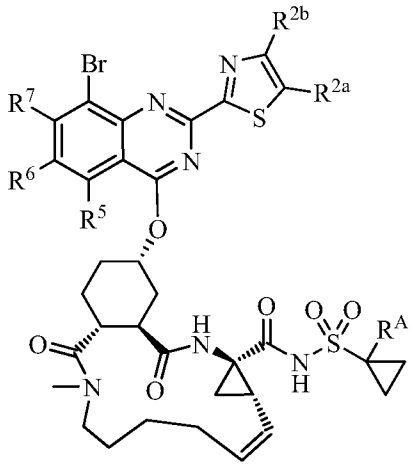
[0058] In one embodiment, provided herein is a compound of Formula VIIIB:



(VIIIB)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^1, R^5, R^6, R^7, R^{2a}, and R^{2b} are each as defined herein.

[0059] In another embodiment, provided herein is a compound of Formula IXB:

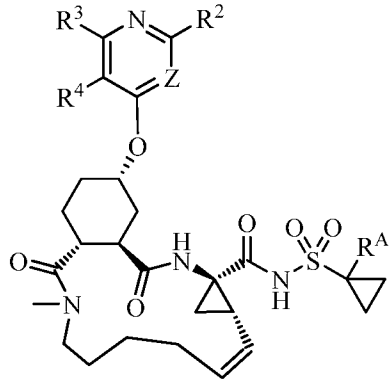


(IXB)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^5, R^6, R^7, R^{2a}, and R^{2b} are each as defined herein.

[0060] In Formula VIIB, VIIIB, or IXB, in certain embodiments, R^A is hydrogen or methyl; in certain embodiments, R^1 is hydrogen; in certain embodiments, R^5 is hydrogen; in certain embodiments, R^6 is hydrogen; in certain embodiments, R^1, R^5, and R^6 are all hydrogen; in certain embodiments, R^7 is $-OR^{1a}$, where R^{1a} is as defined herein; in certain embodiments, R^7 is $-O-C_{1-6}$ alkyl, where the alkyl is optionally substituted with one or more substituents Q; in certain embodiments, R^7 is methoxy; in certain embodiments, R^{2a} is hydrogen; in certain embodiments, R^{2b} is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each optionally substituted with one or more substituents Q; in certain embodiments, R^{2b} is C_{1-6} alkyl, optionally substituted with one or more substituents Q; in certain embodiments, R^{2b} is C_{2-6} alkynyl, optionally substituted with one or more substituents Q; and in certain embodiments, R^{2b} is trfluoromethyl or ethynyl.

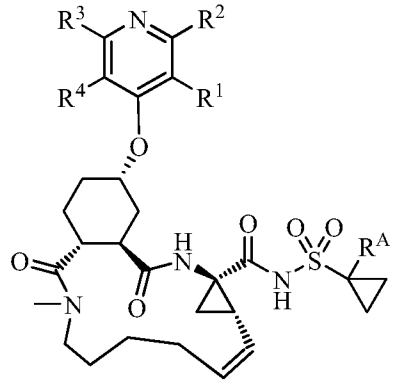
[0061] In yet another embodiment, provided herein is a compound of Formula IC:



(IC)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^2, R^3, R^4, and Z are each as defined herein.

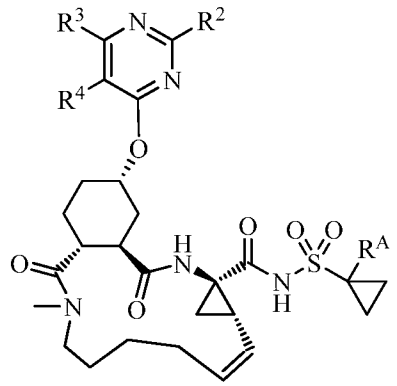
[0062] In one embodiment, provided herein is a compound of Formula IIC:



(IIC)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^1, R^2, R^3, and R^4 are each as defined herein.

[0063] In another embodiment, provided herein is a compound of Formula IIIC:



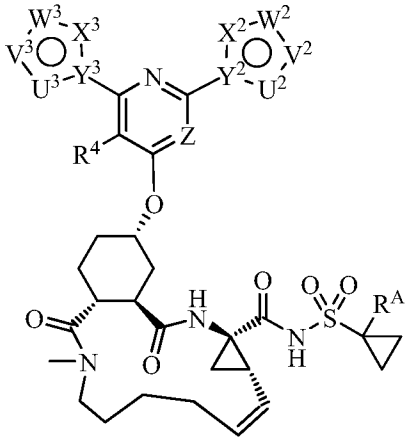
(IIIC)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^2, R^3, and R^4 are each as defined herein.

[0064] In Formula IC, IIC, or IIIC, in certain embodiments, R^A is hydrogen or methyl; in certain embodiments, R^1 is hydrogen; in certain embodiments, R^4 is hydrogen; in certain embodiments, R^2 is heteroaryl, optionally substituted with one or more substituents Q; in certain embodiments, R^2 is monocyclic heteroaryl, optionally substituted with one or more substituents Q; in certain embodiments, R^2 is 5-membered heteroaryl, optionally substituted with one or more substituents Q; in certain embodiments, R^2 is thiazolyl, optionally substituted with one or more substituents Q; in certain embodiments, R^3 is heteroaryl, optionally substituted with one or more substituents Q; in certain embodiments, R^3 is monocyclic heteroaryl, optionally substituted with one or more substituents Q; in certain embodiments, R^3 is 5-membered heteroaryl, optionally substituted with one or more substituents Q; in certain embodiments, R^3 is thiazolyl, optionally substituted with one or

more substituents Q; and in certain R^1 and R^4 are hydrogen, and R^2 and R^3 are each independently 5-membered heteroaryl, optionally substituted with one or more substituents Q.

[0065] In yet another embodiment, provided herein is a compound of Formula IVC:



(IVC)

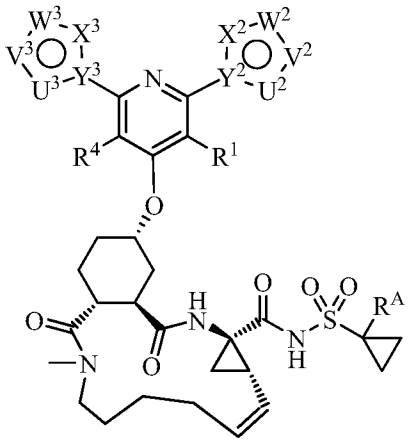
or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein:

U^3, V^3, W^3, and X^3 are each independently O, S, N, CR^9, or NR^9;

each Y^3 is independently C or N; and

R^A, R^4, R^9, Z, U^2, V^2, W^2, X^2, and Y^2 are each as defined herein.

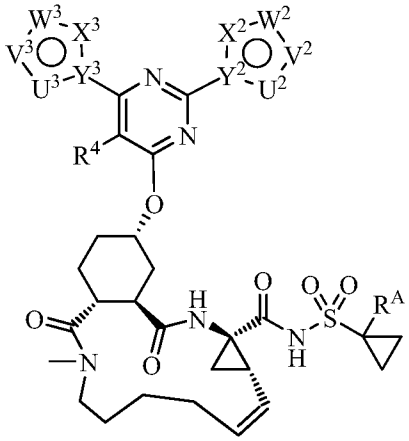
[0066] In one embodiment, provided herein is a compound of Formula VC:



(VC)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^1, R^4, U^2, V^2, W^2, X^2, Y^2, U^3, V^3, W^3, X^3, and Y^3 are each as defined herein.

[0067] In another embodiment, provided herein is a compound of Formula VIC:

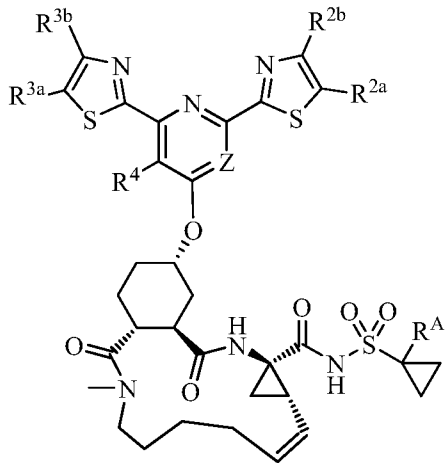


(VIC)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^4, U^2, V^2, W^2, X^2, Y^2, U^3, V^3, W^3, X^3, and Y^3 are each as defined herein.

[0068] In Formula IVC, VC, or VIC, in certain embodiments, R^A is hydrogen or methyl; in certain embodiments, R^1 is hydrogen; and in certain embodiments, R^4 is hydrogen.

[0069] In yet another embodiment, provided herein is a compound of Formula VIIB:



(VIIB)

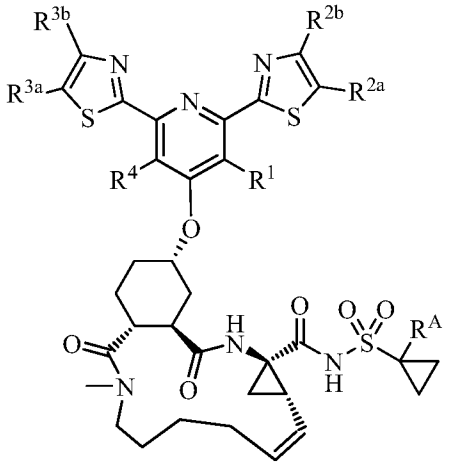
or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein:

R^{3a} and R^{3b} are each independently (i) hydrogen, halo, cyano, trifluoromethyl, or nitro; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more substituents Q; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$,

$-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-P(O)R^{1a}R^{1d}$, $-P(O)(OR^{1a})R^{1d}$, $-P(O)(OR^{1a})(OR^{1d})$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; and

R^A, R^4, R^{1a}, R^{1b}, R^{1c}, R^{1d}, and Z are each as defined herein.

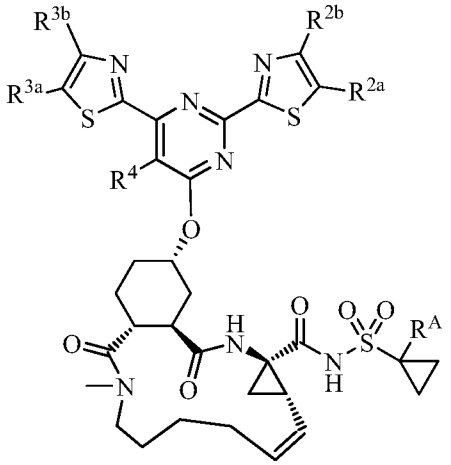
[0070] In one embodiment, provided herein is a compound of Formula VIIIC:



(VIIIC)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^1, R^4, R^{2a}, R^{2b}, R^{3a}, and R^{3b} are each as defined herein.

[0071] In another embodiment, provided herein is a compound of Formula IXC:



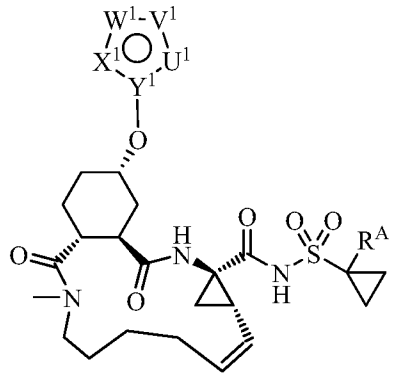
(IXC)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, R^4, R^{2a}, R^{2b}, R^{3a}, and R^{3b} are each as defined herein.

[0072] In Formula VIIC, VIIIC, or IXC, in certain embodiments, R^A is hydrogen or

methyl; in certain embodiments, R^1 is hydrogen; in certain embodiments, R^4 is hydrogen; in certain embodiments, R^{2a} is hydrogen; in certain embodiments, R^{2b} is C_{1-6} alkyl, optionally substituted with one or more substituents Q; in certain embodiments, R^{2b} is methyl or isopropyl, each optionally substituted with one or more substituents Q; in certain embodiments, R^{2b} is methyl, trifluoromethyl, or isopropyl; in certain embodiments, R^{3a} is hydrogen; in certain embodiments, R^{3b} is C_{1-6} alkyl, optionally substituted with one or more substituents Q; in certain embodiments, R^{3b} is methyl or isopropyl, each optionally substituted with one or more substituents Q; in certain embodiments, R^{3b} is methyl, trifluoromethyl, or isopropyl; and in certain embodiments, R^1, R^4, R^{2a}, and R^{3a} are hydrogen, and R^{2b} and R^{3b} are each independently methyl, trifluoromethyl, or isopropyl.

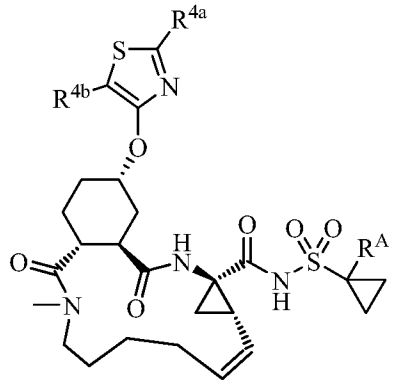
[0073] In yet another embodiment, provided herein is a compound of Formula ID:



(ID)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^A, U^1, V^1, W^1, X^1, and Y^1 are each as defined herein.

[0074] In still another embodiment, provided herein is a compound of Formula IID:



(IID)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein:

R^{4a} and R^{4b} are each independently (i) hydrogen, halo, cyano, trifluoromethyl, or nitro; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-P(O)R^{1a}R^{1d}$, $-P(O)(OR^{1a})R^{1d}$, $-P(O)(OR^{1a})(OR^{1d})$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; and

R^A, R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each as defined herein.

[0075] In Formula VIIC, VIIIC, or IXC, in certain embodiments, R^A is hydrogen or methyl; in certain embodiments, R^{4a} is C_{6-14} aryl, optionally substituted with one or more substituents Q; in certain embodiments, R^{4a} is phenyl, optionally substituted with one or more substituents Q; in certain embodiments, R^{4b} is C_{6-14} aryl, optionally substituted with one or more substituents Q; in certain embodiments, in certain embodiments, R^{4b} is phenyl, optionally substituted with one or more substituents Q; in certain embodiments, R^{4a} and R^{4b} are each indpendently C_{6-14} aryl, optionally substituted with one or more substituents Q; and in certain embodiments, R^{4a} and R^{4b} are each indpendently phenyl, optionally substituted with one or more substituents Q.

[0076] The groups, R^A, R^B, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, U^1, V^1, W^1, X^1, Y^1, U^2, V^2, W^2, X^2, Y^2, U^3, V^3, W^3, X^3, Y^3, and Z in formulae described herein, including Formulae I, IA to IIIA, IB to IXB, IC to IXC, ID, and IID,are further defined herein. All combinations of the embodiments provided herein for such groups are within the scope of this disclosure.

[0077] In certain embodiments, R^A is hydrogen. In certain embodiments, R^A is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^A is methyl. In certain embodiments, R^A is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^A is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^A is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^A is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^A is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^A is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments,

R^A is heterocyclyl, optionally substituted with one or more substituents Q.

[0078] In certain embodiments, R^B is monocyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^B is 6-membered heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^B is pyridinyl or pyrimidinyl, optionally substituted with one or more substituents Q.

[0079] In certain embodiments, R^B is pyridinyl, optionally substituted with one or more substituents Q. In certain embodiments, R^B is pyridinyl, optionally substituted with one or more substituents Q. In certain embodiments, R^B is pyridinyl, substituted with two substituents Q. In certain embodiments, R^B is pyridinyl, substituted with two substituents Q, each independently selected from C_{6-14} aryl or heteroaryl, wherein the aryl and heteroaryl are each independently optionally substituted with one or more substituents Q. In certain embodiments, R^B is pyridinyl, substituted with two heteroaryl, wherein each heteroaryl is independently optionally substituted with one or more substituents Q. In certain embodiments, R^B is pyridinyl, optionally substituted with one or more substituents, each of which is independently selected from fluoro, methoxy, phenoxy, dimethylamino, phenyl, furanyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, pyrazolyl, and morpholinyl, each of which is further optionally substituted with one or more substituents, each of which is independently selected from fluoro, chloro, cyano, methoxy, methyl, ethyl, isopropyl, trifluoromethyl, ethynyl, phenyl, benzyl, and pyrrolidinyl.

[0080] In certain embodiments, R^B is pyridinyl, optionally substituted with one or more substituents, each of which is independently selected from fluoro, methoxy, phenoxy, dimethylamino, phenyl, fluorophenyl, chlorophenyl, methoxyphenyl, furanyl, thienyl, cyanothienyl, methoxythienyl, methylthienyl, dimethylthienyl, (trifluoromethyl)thienyl, phenylthienyl, thiazolyl, methylthiazolyl, trifluoromethylthiazolyl, isopropylthiazolyl, dimethylthiazolyl, ethynylthiazolyl, pyrrolidinyl-thiazolyl, methyl-1*H*-pyrazolyl, ethyl-1*H*-pyrazolyl, trifluoromethyl-pyrazolyl, methyl-(trifluoromethyl)-1*H*-pyrazolyl, benzyl-1*H*-pyrazolyl, trimethyl-1*H*-pyrazolyl, methyl-1*H*-imidazolyl, phenyl-oxazolyl, dimethylisoxazolyl, and morpholinyl.

[0081] In certain embodiments, R^B is pyridinyl, optionally substituted with one or more substituents, each of which is independently selected from fluoro, methoxy, phenoxy, dimethylamino, phenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-methoxyphenyl,

furan-2-yl, thien-2-yl, 4-cyanothien-2-yl, 5-methoxythien-2-yl, 3-methoxy-thien-2-yl, 3-methylthien-2-yl, 5-methylthien-2-yl, 3,5-dimethylthien-2-yl, 5-(trifluoromethyl)-thien-2-yl, 5-phenylthien-2-yl, thien-3-yl, 2-methylthien-3-yl, 4-methyl-thien-3-yl, 2,5-dimethylthien-3-yl, 2-cyano-thien-3-yl, thiazol-2-yl, 4-methyl-thiazol-2-yl, 4-isopropylthiazol-2-yl, 4-trifluoromethyl-thiazol-2-yl, 4-ethynyl-thiazol-2-yl, 5-methyl-thiazol-2-yl, 4,5-dimethylthiazol-2-yl, 2-(pyrrolidin-1-yl)thiazol-4-yl, thiazol-5-yl, 2,4-dimethylthiazol-5-yl, thiazol-4-yl, 2-methoxythiazol-4-yl, 3-trifluoromethyl-pyrazol-1-yl, 1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl, 1-methyl-1*H*-pyrazol-4-yl, 1-ethyl-1*H*-pyrazol-4-yl, 1-benzyl-1*H*-pyrazol-4-yl, 1,3,5-trimethyl-1*H*-pyrazol-4-yl, 1-methyl-1*H*-imidazol-2-yl, 1-methyl-1*H*-imidazol-5-yl, 2-phenyloxazol-5-yl, 3,5-dimethylisoxazol-4-yl, and morpholin-4-yl.

[0082] In certain embodiments, R^B is 5-fluoropyridin-2-yl, 2-dimethylaminopyridin-5-yl, 2-(4-fluorophenyl)-6-(4-isopropylthiazol-2-yl)pyridin-4-yl, 2-(4-trifluoromethyl-thiazol-2-yl)-6-(4-(trifluoromethyl)thiazol-2-yl)pyridin-4-yl, 2-(4-ethynyl-thiazol-2-yl)-6-(4-(trifluoromethyl)thiazol-2-yl) pyridin-4-yl, or 2-(morpholin-4-yl)pyridin-5-yl. In certain embodiments, R^A is 5-fluoro-pyridin-2-yl. Further examples of pyridinyl groups and their syntheses can be found, *e.g.*, in U.S. Pat. No. 7,491,794; and U.S. Pat. Appl. Publ. Nos.: 2009/0111982 and 2009/0169510; the disclosure of each of which is incorporated herein by reference in its entirety.

[0083] In certain embodiments, R^B is pyrimidinyl, optionally substituted with one or more substituents Q. In certain embodiments, R^B is pyrimidinyl, optionally substituted with one or more substituents Q. In certain embodiments, R^B is pyrimidinyl, substituted with two substituents Q. In certain embodiments, R^B is pyrimidinyl, substituted with two substituents Q, each independently selected from C_{6-14} aryl or heteroaryl, wherein the aryl and heteroaryl are each independently optionally substituted with one or more substituents Q. In certain embodiments, R^B is pyrimidinyl, substituted with two heteroaryl, wherein each heteroaryl is independently optionally substituted with one or more substituents Q.

[0084] In certain embodiments, R^B is pyrimidinyl, optionally substituted with one or more substituents, each substituent independently selected from $-OR^a$, $-NR^bR^c$, halo, C_{6-14} aryl, heteroaryl, and heterocyclyl; wherein the aryl, heteroaryl, and heterocyclyl are each further optionally substituted with one or more substituents as described herein, and R^a, R^b, and R^c are each as defined herein. In certain embodiments, R^B is pyrimidinyl, optionally

substituted with one or more substituents, each of which is independently selected from fluoro, methoxy, phenoxy, dimethylamino, phenyl, furanyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, pyrazolyl, and morpholinyl, each of which is further optionally substituted with one or more substituents, each of which is independently selected from fluoro, chloro, cyano, methoxy, methyl, ethyl, isopropyl, trifluoromethyl, ethynyl, phenyl, benzyl, and pyrrolidinyl.

[0085] In certain embodiments, R^B is pyrimidinyl, optionally substituted with one or more substituents, each of which is independently selected from fluoro, methoxy, phenoxy, dimethylamino, phenyl, fluorophenyl, chlorophenyl, methoxyphenyl, furanyl, thienyl, cyanothienyl, methoxythienyl, methylthienyl, dimethylthienyl, (trifluoromethyl)thienyl, phenylthienyl, thiazolyl, methylthiazolyl, trifluoromethylthiazolyl, isopropylthiazolyl, dimethylthiazolyl, ethynylthiazolyl, pyrrolidinyl-thiazolyl, methyl-1*H*-pyrazolyl, ethyl-1*H*-pyrazolyl, trifluoromethyl-pyrazolyl, methyl-(trifluoromethyl)-1*H*-pyrazolyl, benzyl-1*H*-pyrazolyl, trimethyl-1*H*-pyrazolyl, methyl-1*H*-imidazolyl, phenyl-oxazolyl, dimethylisoxazolyl, and morpholinyl.

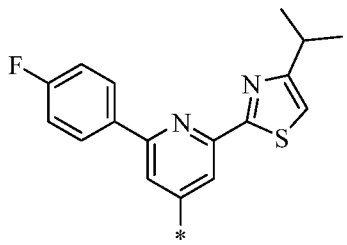
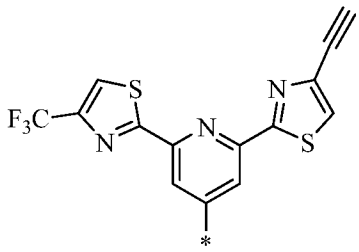
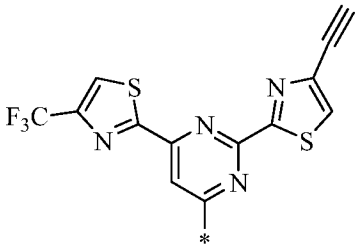
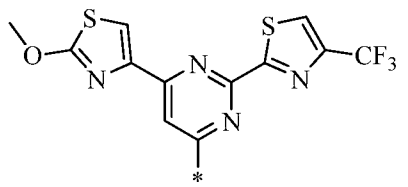
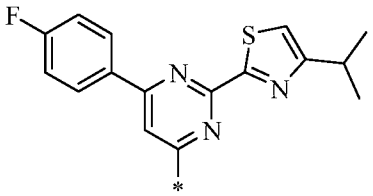
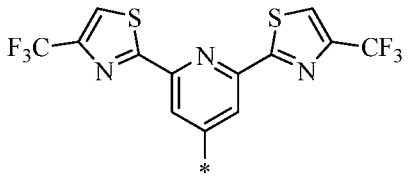
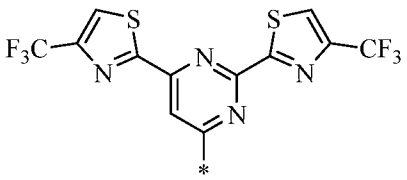
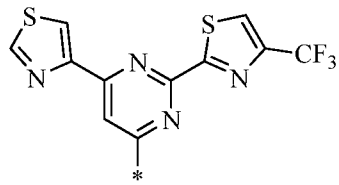
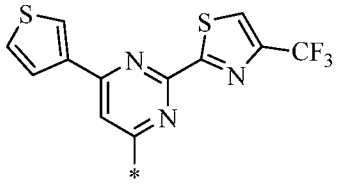
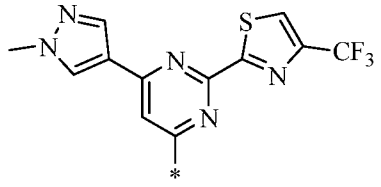
[0086] In certain embodiments, R^B is pyrimidinyl, optionally substituted with one or more substituents, each of which is independently selected from fluoro, methoxy, phenoxy, dimethylamino, phenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-methoxyphenyl, furan-2-yl, thien-2-yl, 3-cyanothien-2-yl, 4-cyanothien-2-yl, 5-methoxythien-2-yl, 3-methoxy-thien-2-yl, 3-methylthien-2-yl, 5-methylthien-2-yl, 3,5-dimethylthien-2-yl, 5-(trifluoromethyl)-thien-2-yl, 5-phenylthien-2-yl, thien-3-yl, 2-methylthien-3-yl, 4-methyl-thien-3-yl, 2,5-dimethylthien-3-yl, 2-cyano-thien-3-yl, thiazol-2-yl, 4-methyl-thiazol-2-yl, 4-isopropylthiazol-2-yl, 4-trifluoromethyl-thiazol-2-yl, 4-ethynyl-thiazol-2-yl, 5-methyl-thiazol-2-yl, 4,5-dimethylthiazol-2-yl, 2-(pyrrolidin-1-yl)thiazol-4-yl, thiazol-5-yl, 2,4-dimethylthiazol-5-yl, thiazol-4-yl, 2-methoxythiazol-4-yl, 3-trifluoromethyl-pyrazol-1-yl, 1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl, 1-methyl-1*H*-pyrazol-4-yl, 1-ethyl-1*H*-pyrazol-4-yl, 1-benzyl-1*H*-pyrazol-4-yl, 1,3,5-trimethyl-1*H*-pyrazol-4-yl, 1-methyl-1*H*-imidazol-2-yl, 1-methyl-1*H*-imidazol-5-yl, 2-phenyloxazol-5-yl, 3,5-dimethylisoxazol-4-yl, and morpholin-4-yl.

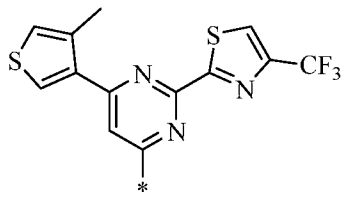
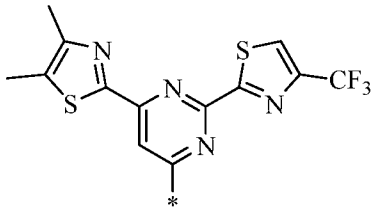
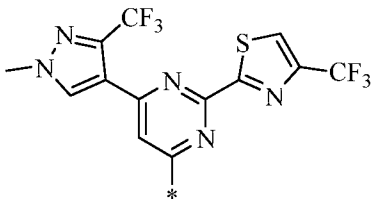
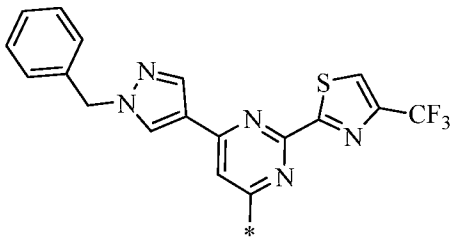
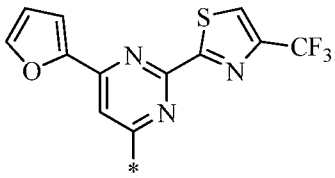
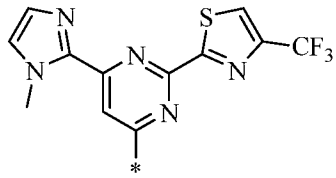
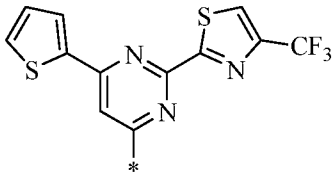
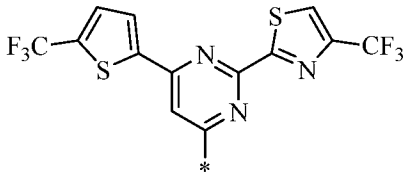
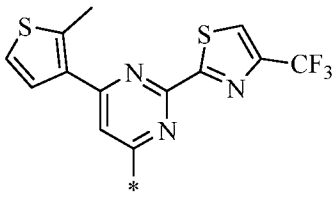
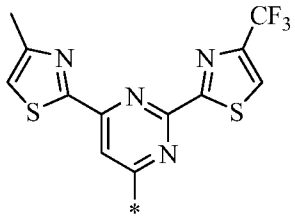
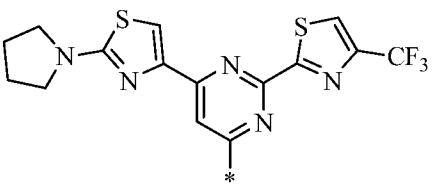
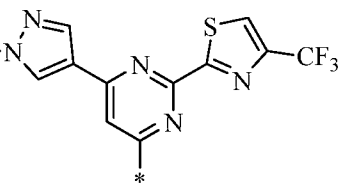
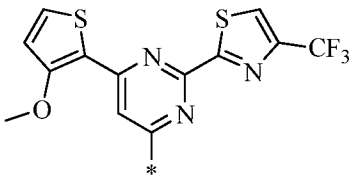
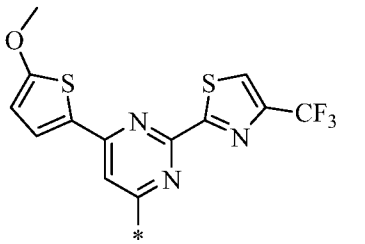
[0087] In certain embodiments, R^B is 6-methoxy-2-(4-isopropylthiazol-2-yl)pyrimidin-4-yl, 5-phenoxy-2-(4-(trifluoromethyl)thiazol-2-yl)pyrimidin-4-yl; 6-phenoxy-2-(4-(trifluoromethyl)thiazol-2-yl)pyrimidin-4-yl; 6-(4-fluorophenyl)-2-(4-isopropylthiazol-

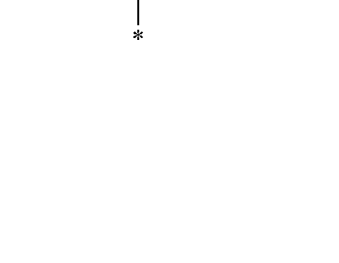
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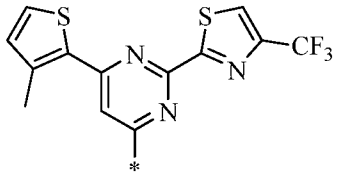
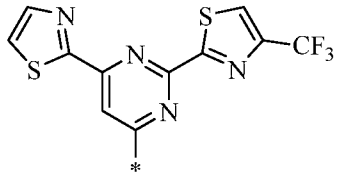
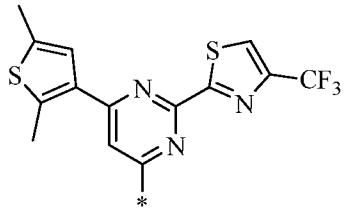
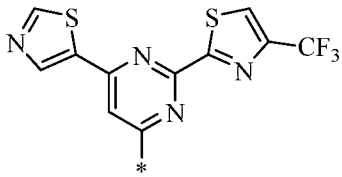
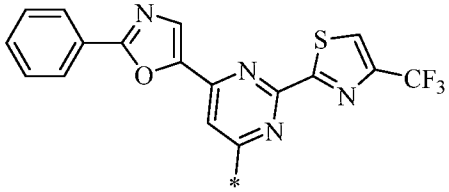
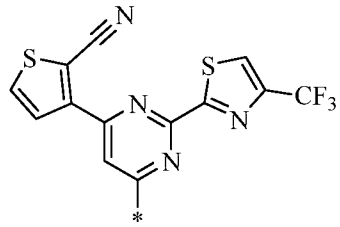
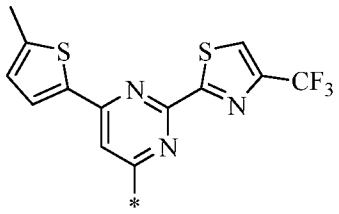
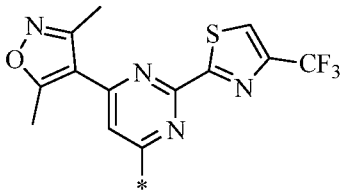
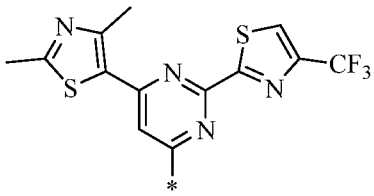
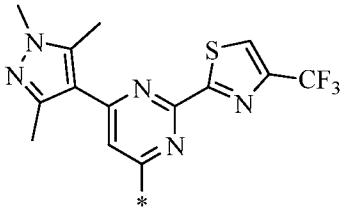
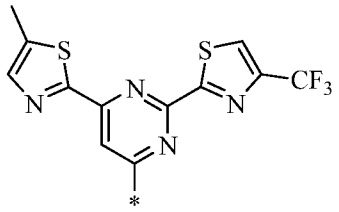
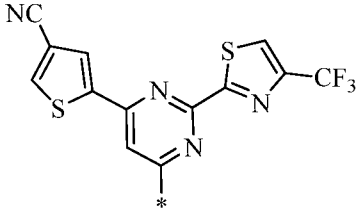
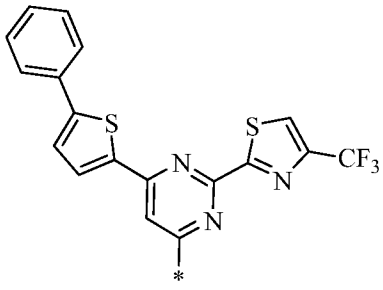
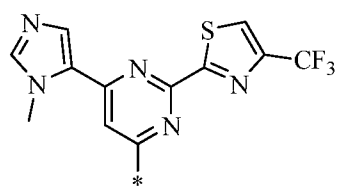
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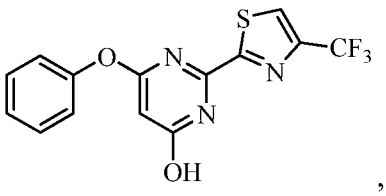
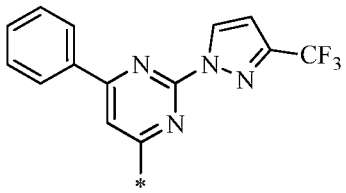
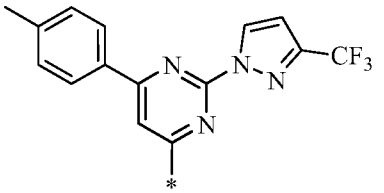
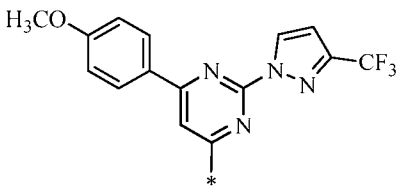
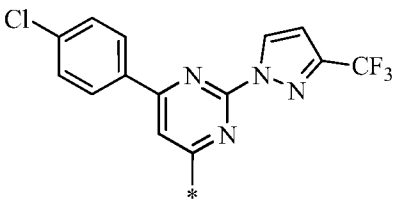
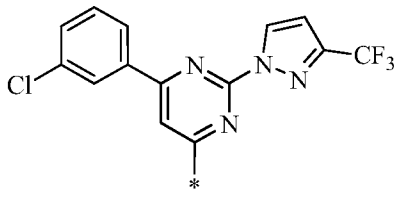
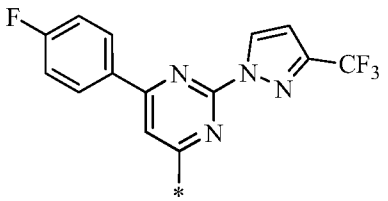
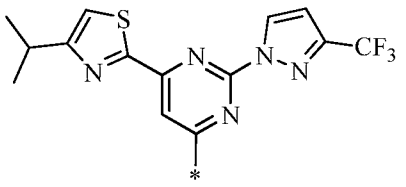
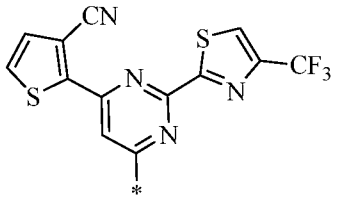
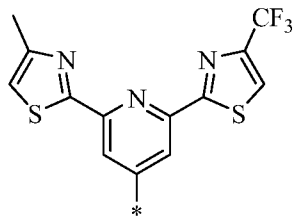
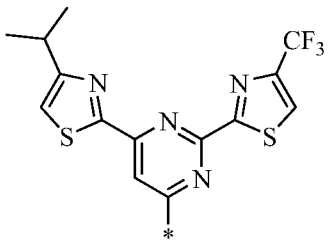
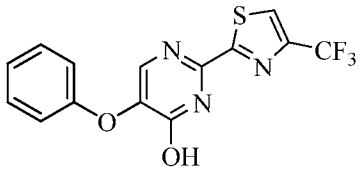
[0088] In certain embodiments, R^B is selected from the group consisting of:


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wherein the symbol * indicates the point of attachment.

[0089] In certain embodiments, R^B is 5-membered heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^B is thiazolyl, optionally substituted with one or more substituents Q. In certain embodiments, R^B is thiazolyl, substituted with two substituents Q. In certain embodiments, R^B is diphenyl-thiazolyl,

wherein the phenyls are each independently optionally substituted with one or more substituents Q. In certain embodiments, R^B is 2,5-diphenyl-thiazol-4-yl, wherein the phenyls are each independently optionally substituted with one or more substituents Q. In certain embodiments, R^B is 2,5-diphenyl-thiazol-4-yl, wherein each phenyl is independently optionally substituted with one or two substituents Q, where each Q is independently halogen or C_{1-6} alkyl, where the alkyl is further optionally substituted with one or two substituents Q. In certain embodiments, R^B is 2,5-diphenyl-thiazol-4-yl, wherein each phenyl is independently optionally substituted with one or two substituents Q, each of which is independently halogen or trifluoromethyl. In certain embodiments, R^B is 2,5-diphenyl-thiazol-4-yl, 2-(chlorophenyl)-5-phenyl-thiazol-4-yl, 5-(chlorophenyl)-2-phenyl-thiazol-4-yl, or 2-(trifluoromethylphenyl)-5-phenyl-thiazol-4-yl. In certain embodiments, R^B is 2,5-diphenyl-thiazol-4-yl, 2-(4-chlorophenyl)-5-phenyl-thiazol-4-yl, 5-(4-chlorophenyl)-2-phenyl-thiazol-4-yl, or 2-(3-trifluoromethylphenyl)-5-phenyl-thiazol-4-yl.

[0090] In certain embodiments, R^1 is hydrogen. In certain embodiments, R^1 is halo. In certain embodiments, R^1 is cyano. In certain embodiments, R^1 is nitro. In certain embodiments, R^1 is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^1 is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^1 is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^1 is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^1 is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^1 is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^1 is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^1 is heterocyclyl, optionally substituted with one or more substituents Q.

[0091] In certain embodiments, R^1 is $-C(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^1 is $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^1 is $-C(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^1 is $-C(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^1 is $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^1 is $-OC(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^1 is $-OC(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^1 is $-OC(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^1

is $-OC(=NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^1 is $-OS(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^1 is $-OS(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^1 is $-OS(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^1 is $-OS(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^1 is $-NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^1 is $-NR^{1a}C(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^1 is $-NR^{1a}C(O)OR^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^1 is $-NR^{1a}C(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^1 is $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each as defined herein. In certain embodiments, R^1 is $-NR^{1a}S(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^1 is $-NR^{1a}S(O)_2R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^1 is $-NR^{1a}S(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^1 is $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^1 is $-P(O)R^{1a}R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^1 is $-P(O)(OR^{1a})R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^1 is $-P(O)(OR^{1a})(OR^{1d})$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^1 is $-SR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^1 is $-S(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^1 is $-S(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^1 is $-S(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^1 is $-S(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein.

[0092] In certain embodiments, R^2 is hydrogen. In certain embodiments, R^2 is halo. In certain embodiments, R^2 is cyano. In certain embodiments, R^2 is nitro. In certain embodiments, R^2 is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^2 is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^2 is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^2 is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^2 is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^2 is phenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^2 is phenyl, optionally substituted with one, two, or three substituents Q, each independently selected from fluoro, chloro,

methyl, and methoxy. In certain embodiments, R^2 is phenyl, fluorophenyl, chlorophenyl, methylphenyl, or methoxyphenyl. In certain embodiments, R^2 is phenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-methylphenyl, or 4-methoxyphenyl. In certain embodiments, R^2 is bicyclic aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^2 is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^2 is benzyl, optionally substituted with one or more substituents Q. In certain embodiments, R^2 is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^2 is monocyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^2 is 5-membered heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^2 is thiazolyl, optionally substituted with one or more substituents Q. In certain embodiments, R^2 is furanyl, thienyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, or thiazolyl, optionally substituted with one, two, or three substituents Q, each of which is independently selected from cyano, methyl, ethyl, propyl, isopropyl, trifluoromethyl, ethynyl, phenyl, benzyl, pyrrolidinyl, and methoxy. In certain embodiments, R^2 is furanyl, thienyl, cyano-thienyl, methyl-thienyl, dimethyl-thienyl,trifluoromethyl-thienyl, phenyl-thienyl, methoxy-thienyl, methyl-pyrazolyl, ethyl-pyrazolyl, trifluoromethyl-pyrazolyl, methyl-trifluoromethyl-pyrazolyl, trimethyl-pyrazolyl, benzyl-pyrazolyl, methyl-imidazolyl, dimethyl-isoxazolyl, phenyl-oxazolyl, thiazolyl, methyl-thiazolyl, isopropyl-thiazolyl, trifluoromethyl-thiazolyl, dimethyl-thiazolyl, ethynyl-thiazolyl, methoxy-thiazolyl, or pyrrolidinyl-thiazolyl. In certain embodiments, R^2 is furan-2-yl, thien-2-yl, thien-3-yl, 2-cyano-thien-3-yl, 3-cyano-thien-2-yl, 4-cyano-thien-2-yl, 2-methyl-thien-3-yl, 3-methyl-thien-2-yl, 4-methyl-thien-3-yl, 5-methyl-thien-2-yl, 5-trifluoromethyl-thien-2-yl, 2,5-dimethyl-thien-3-yl, 5-phenyl-thien-2-yl, 3-methoxy-thien-2-yl, 5-methoxy-thien-2-yl, 1-methyl-pyrazol-4-yl, 1-ethyl-pyrazol-4-yl, 3-trifluoromethyl-pyrazol-1-yl, 1-methyl-3-trifluoromethyl-pyrazol-4-yl, 1,3,5-trimethylpyrazol-4-yl, 1-benzyl-pyrazol-4-yl, 1-methyl-imidazol-2-yl, 1-methyl-imidazol-5-yl, 2,5-dimethyl-isoxazol-4-yl, 2-phenyl-oxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, 4-methyl-thiazol-2-yl, 5-methyl-thiazol-2-yl, 4-isopropyl-thiazol-2-yl, 4-trifluoromethyl-thiazol-2-yl, 2,4-dimethylthiazol-5-yl, 4,5-dimethylthiazol-2-yl, 4-ethynyl-thiazol-2-yl, 2-methoxy-thiazol-4-yl, or 2-pyrrolidin-1-yl-thiazol-4-yl. In certain embodiments, R^2 is 4-isopropyl-thiazol-2-yl, 4-trifluoromethyl-thiazol-2-yl, 4-ethynyl-thiazol-2-yl, or 3-trifluoromethyl-pyrazol-1-yl. In certain embodiments, R^2 is 6-membered heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^2 is bicyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^2 is heterocyclyl, optionally

substituted with one or more substituents Q.

[0093] In certain embodiments, R^2 is $-C(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^2 is $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^2 is $-C(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^2 is $-C(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^2 is $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^2 is $-OC(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^2 is $-OC(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^2 is $-OC(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^2 is $-OC(=NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^2 is $-OS(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^2 is $-OS(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^2 is $-OS(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^2 is $-OS(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^2 is $-NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^2 is $-NR^{1a}C(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^2 is $-NR^{1a}C(O)OR^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^2 is $-NR^{1a}C(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^2 is $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each as defined herein. In certain embodiments, R^2 is $-NR^{1a}S(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^2 is $-NR^{1a}S(O)_2R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^2 is $-NR^{1a}S(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^2 is $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^2 is $-P(O)R^{1a}R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^2 is $-P(O)(OR^{1a})R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^2 is $-P(O)(OR^{1a})(OR^{1d})$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^2 is $-SR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^2 is $-S(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^2 is $-S(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^2 is $-S(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^2 is $-S(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein.

[0094] In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is halo. In certain embodiments, R^3 is cyano. In certain embodiments, R^3 is nitro. In certain embodiments, R^3 is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^3 is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^3 is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^3 is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^3 is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^3 is phenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^3 is phenyl, optionally substituted with one, two, or three substituents Q, each independently selected from fluoro, chloro, methyl, and methoxy. In certain embodiments, R^3 is phenyl, fluorophenyl, chlorophenyl, methylphenyl, or methoxyphenyl. In certain embodiments, R^3 is phenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-methylphenyl, or 4-methoxyphenyl. In certain embodiments, R^3 is bicyclic aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^3 is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^3 is benzyl, optionally substituted with one or more substituents Q. In certain embodiments, R^3 is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^3 is monocyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^3 is 5-membered heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^3 is thiazolyl, optionally substituted with one or more substituents Q. In certain embodiments, R^3 is furanyl, thienyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, thiazolyl, optionally substituted with one, two, or three substituents Q, each of which is independently selected from cyano, methyl, ethyl, propyl, isopropyl, trifluoromethyl, ethynyl, phenyl, benzyl, pyrrolidinyl, and methoxy. In certain embodiments, R^3 is furanyl, thienyl, cyano-thienyl, methyl-thienyl, dimethyl-thienyl,trifluoromethyl-thienyl, phenyl-thienyl, methoxy-thienyl, methyl-pyrazolyl, ethyl-pyrazolyl, trifluoromethyl-pyrazolyl, methyl-trifluoromethyl-pyrazolyl, trimethyl-pyrazolyl, benzyl-pyrazolyl, methyl-imidazolyl, dimethyl-isoxazolyl, phenyl-oxazolyl, thiazolyl, methyl-thiazolyl, isopropyl-thiazolyl, trifluoromethyl-thiazolyl, dimethyl-thiazolyl, ethynyl-thiazolyl, methoxy-thiazolyl, or pyrrolidinyl-thiazolyl. In certain embodiments, R^3 is furan-2-yl, thien-2-yl, thien-3-yl, 2-cyano-thien-3-yl, 3-cyano-thien-2-yl, 4-cyano-thien-2-yl, 2-methyl-thien-3-yl, 3-methyl-thien-2-yl, 4-methyl-thien-3-yl, 5-methyl-thien-2-yl, 5-trifluoromethyl-thien-2-yl, 2,5-dimethyl-thien-3-yl, 5-phenyl-thien-2-yl, 3-methoxy-thien-2-yl, 5-methoxy-thien-2-yl, 1-methyl-pyrazol-4-yl, 1-ethyl-pyrazol-4-yl, 3-trifluoromethyl-

pyrazol-1-yl, 1-methyl-3-trifluoromethyl-pyrazol-4-yl, 1,3,5-trimethylpyrazol-4-yl, 1-benzyl-pyrazol-4-yl, 1-methyl-imidazol-2-yl, 1-methyl-imidazol-5-yl, 2,5-dimethyl-isoxazol-4-yl, 2-phenyl-oxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, 4-methyl-thiazol-2-yl, 5-methyl-thiazol-2-yl, 4-isopropyl-thiazol-2-yl, 4-trifluoromethyl-thiazol-2-yl, 2,4-dimethylthiazol-5-yl, 4,5-dimethylthiazol-2-yl, 4-ethynyl-thiazol-2-yl, 2-methoxy-thiazol-4-yl, or 2-pyrrolidin-1-yl-thiazol-4-yl. In certain embodiments, R^3 is 6-membered heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^3 is bicyclic heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^3 is heterocyclyl, optionally substituted with one or more substituents Q.

[0095] In certain embodiments, R^3 is $-C(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^3 is $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^3 is $-C(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^3 is $-C(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^3 is $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^3 is $-OC(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^3 is $-OC(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^3 is $-OC(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^3 is $-OC(=NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^3 is $-OS(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^3 is $-OS(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^3 is $-OS(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^3 is $-OS(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^3 is $-NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^3 is $-NR^{1a}C(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^3 is $-NR^{1a}C(O)OR^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^3 is $-NR^{1a}C(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^3 is $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each as defined herein. In certain embodiments, R^3 is $-NR^{1a}S(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^3 is $-NR^{1a}S(O)_2R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^3 is $-NR^{1a}S(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^3 is $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^3 is $-P(O)R^{1a}R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^3 is

$-P(O)(OR^{1a})R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^3 is $-P(O)(OR^{1a})(OR^{1d})$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^3 is $-SR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^3 is $-S(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^3 is $-S(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^3 is $-S(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^3 is $-S(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein.

[0096] In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is halo. In certain embodiments, R^4 is cyano. In certain embodiments, R^4 is nitro. In certain embodiments, R^4 is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^4 is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^4 is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^4 is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^4 is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^4 is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^4 is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^4 is heterocyclyl, optionally substituted with one or more substituents Q.

[0097] In certain embodiments, R^4 is $-C(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^4 is $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^4 is $-C(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^4 is $-C(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^4 is $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^4 is $-OC(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^4 is $-OC(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^4 is $-OC(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^4 is $-OC(=NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^4 is $-OS(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^4 is $-OS(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^4 is $-OS(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^4 is $-OS(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^4 is $-NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^4

is $-NR^{1a}C(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^4 is $-NR^{1a}C(O)OR^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^4 is $-NR^{1a}C(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^4 is $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each as defined herein. In certain embodiments, R^4 is $-NR^{1a}S(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^4 is $-NR^{1a}S(O)_2R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^4 is $-NR^{1a}S(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^4 is $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^4 is $-P(O)R^{1a}R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^4 is $-P(O)(OR^{1a})R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^4 is $-P(O)(OR^{1a})(OR^{1d})$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^4 is $-SR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^4 is $-S(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^4 is $-S(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^4 is $-S(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^4 is $-S(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein.

[0098] In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 is halo. In certain embodiments, R^5 is cyano. In certain embodiments, R^5 is nitro. In certain embodiments, R^5 is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^5 is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^5 is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^5 is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^5 is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^5 is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^5 is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^5 is heterocyclyl, optionally substituted with one or more substituents Q.

[0099] In certain embodiments, R^5 is $-C(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^5 is $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^5 is $-C(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^5 is $-C(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined

herein. In certain embodiments, R^5 is $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^5 is $-OC(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^5 is $-OC(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^5 is $-OC(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^5 is $-OC(=NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^5 is $-OS(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^5 is $-OS(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^5 is $-OS(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^5 is $-OS(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^5 is $-NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^5 is $-NR^{1a}C(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^5 is $-NR^{1a}C(O)OR^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^5 is $-NR^{1a}C(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^5 is $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each as defined herein. In certain embodiments, R^5 is $-NR^{1a}S(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^5 is $-NR^{1a}S(O)_2R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^5 is $-NR^{1a}S(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^5 is $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^5 is $-P(O)R^{1a}R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^5 is $-P(O)(OR^{1a})R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^5 is $-P(O)(OR^{1a})(OR^{1d})$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^5 is $-SR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^5 is $-S(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^5 is $-S(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^5 is $-S(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^5 is $-S(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein.

[00100] In certain embodiments, R^6 is hydrogen. In certain embodiments, R^6 is halo. In certain embodiments, R^6 is cyano. In certain embodiments, R^6 is nitro. In certain embodiments, R^6 is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is C_{3-10} cycloalkyl, optionally substituted with

one or more substituents Q. In certain embodiments, R^6 is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^6 is heterocyclyl, optionally substituted with one or more substituents Q.

[00101] In certain embodiments, R^6 is $-C(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^6 is $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^6 is $-C(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^6 is $-C(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^6 is $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^6 is $-OC(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^6 is $-OC(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^6 is $-OC(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^6 is $-OC(=NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^6 is $-OS(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^6 is $-OS(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^6 is $-OS(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^6 is $-OS(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^6 is $-NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^6 is $-NR^{1a}C(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^6 is $-NR^{1a}C(O)OR^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^6 is $-NR^{1a}C(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^6 is $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each as defined herein. In certain embodiments, R^6 is $-NR^{1a}S(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^6 is $-NR^{1a}S(O)_2R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^6 is $-NR^{1a}S(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^6 is $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^6 is $-P(O)R^{1a}R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^6 is $-P(O)(OR^{1a})R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^6 is $-P(O)(OR^{1a})(OR^{1d})$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^6 is $-SR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^6 is $-S(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^6 is $-S(O)_2R^{1a}$,

wherein R^{1a} is as defined herein. In certain embodiments, R^6 is $-S(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^6 is $-S(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein.

[00102] In certain embodiments, R^7 is hydrogen. In certain embodiments, R^7 is halo. In certain embodiments, R^7 is cyano. In certain embodiments, R^7 is nitro. In certain embodiments, R^7 is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^7 is heterocyclyl, optionally substituted with one or more substituents Q.

[00103] In certain embodiments, R^7 is $-C(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^7 is $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^7 is $-C(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^7 is $-C(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^7 is $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^7 is C_{1-6} alkoxy ($-O-C_{1-6}$ alkyl), optionally substituted with one or more substituents Q. In certain embodiments, R^7 is methoxy. In certain embodiments, R^7 is $-OC(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^7 is $-OC(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^7 is $-OC(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^7 is $-OC(=NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^7 is $-OS(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^7 is $-OS(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^7 is $-OS(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^7 is $-OS(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^7 is $-NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^7 is $-NR^{1a}C(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^7 is $-NR^{1a}C(O)OR^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^7 is

$-NR^{1a}C(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^7 is $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each as defined herein. In certain embodiments, R^7 is $-NR^{1a}S(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^7 is $-NR^{1a}S(O)_2R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^7 is $-NR^{1a}S(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^7 is $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^7 is $-P(O)R^{1a}R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^7 is $-P(O)(OR^{1a})R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^7 is $-P(O)(OR^{1a})(OR^{1d})$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^7 is $-SR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^7 is $-S(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^7 is $-S(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^7 is $-S(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^7 is $-S(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein.

[00104] In certain embodiments, R^8 is hydrogen. In certain embodiments, R^8 is halo. In certain embodiments, R^8 is cyano. In certain embodiments, R^8 is nitro. In certain embodiments, R^8 is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^8 is methyl. In certain embodiments, R^8 is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^8 is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^8 is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^8 is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^8 is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^8 is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^8 is heterocyclyl, optionally substituted with one or more substituents Q.

[00105] In certain embodiments, R^8 is $-C(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^8 is $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^8 is $-C(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^8 is $-C(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^8 is $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain

embodiments, R^8 is $-OC(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^8 is $-OC(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^8 is $-OC(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^8 is $-OC(=NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^8 is $-OS(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^8 is $-OS(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^8 is $-OS(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^8 is $-OS(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^8 is $-NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^8 is $-NR^{1a}C(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^8 is $-NR^{1a}C(O)OR^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^8 is $-NR^{1a}C(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^8 is $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each as defined herein. In certain embodiments, R^8 is $-NR^{1a}S(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^8 is $-NR^{1a}S(O)_2R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^8 is $-NR^{1a}S(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^8 is $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^8 is $-P(O)R^{1a}R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^8 is $-P(O)(OR^{1a})R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^8 is $-P(O)(OR^{1a})(OR^{1d})$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^8 is $-SR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^8 is $-S(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^8 is $-S(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^8 is $-S(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^8 is $-S(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein.

[00106] In certain embodiments, R^9 is hydrogen. In certain embodiments, R^9 is halo. In certain embodiments, R^9 is cyano. In certain embodiments, R^9 is nitro. In certain embodiments, R^9 is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^9 is methyl, ethyl, isopropyl, or trifluoromethyl. In certain embodiments, R^9 is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^9 is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^9 is ethynyl. In certain embodiments, R^9 is C_{3-10} cycloalkyl,

optionally substituted with one or more substituents Q. In certain embodiments, R^9 is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^9 is phenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^9 is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^9 is benzyl, optionally substituted with one or more substituents Q. In certain embodiments, R^9 is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^9 is heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, R^9 is pyrrolidinyl, optionally substituted with one or more substituents Q.

[00107] In certain embodiments, R^9 is $-C(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^9 is $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^9 is $-C(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^9 is $-C(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^9 is $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^9 is C_{1-6} alkoxy ($-OC_{1-6}$ alkyl), optionally substituted with one or more substituents Q. In certain embodiments, R^9 is methoxy. In certain embodiments, R^9 is $-OC(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^9 is $-OC(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^9 is $-OC(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^9 is $-OC(=NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^9 is $-OS(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^9 is $-OS(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^9 is $-OS(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^9 is $-OS(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^9 is $-NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^9 is $-NR^{1a}C(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^9 is $-NR^{1a}C(O)OR^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^9 is $-NR^{1a}C(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^9 is $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each as defined herein. In certain embodiments, R^9 is $-NR^{1a}S(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^9 is $-NR^{1a}S(O)_2R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^9 is $-NR^{1a}S(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^9 is $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, wherein

R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^9 is $-P(O)R^{1a}R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^9 is $-P(O)(OR^{1a})R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^9 is $-P(O)(OR^{1a})(OR^{1d})$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^9 is $-SR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^9 is $-S(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^9 is $-S(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^9 is $-S(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^9 is $-S(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein.

[00108] In certain embodiments, R^{1a} is hydrogen. In certain embodiments, R^{1a} is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1a} is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1a} is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1a} is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1a} is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1a} is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1a} is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1a} is heterocyclyl, optionally substituted with one or more substituents Q.

[00109] In certain embodiments, R^{1b} is hydrogen. In certain embodiments, R^{1b} is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1b} is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1b} is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1b} is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1b} is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1b} is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1b} is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1b} is heterocyclyl, optionally substituted with one or more substituents Q.

[00110] In certain embodiments, R^{1c} is hydrogen. In certain embodiments, R^{1c} is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1c} is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments,

R^{1c} is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1c} is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1c} is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1c} is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1c} is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1c} is heterocyclyl, optionally substituted with one or more substituents Q.

[00111] In certain embodiments, R^{1a} and R^{1c} together with the C and N atoms to which they are attached form heterocyclyl, optionally substituted with one or more substituents Q.

[00112] In certain embodiments, R^{1b} and R^{1c} together with the N atom to which they are attached form heterocyclyl, optionally substituted with one or more substituents Q.

[00113] In certain embodiments, R^{1d} is hydrogen. In certain embodiments, R^{1d} is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1d} is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1d} is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1d} is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1d} is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1d} is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1d} is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{1d} is heterocyclyl, optionally substituted with one or more substituents Q.

[00114] In certain embodiments, R^{2a} is hydrogen. In certain embodiments, R^{2a} is halo. In certain embodiments, R^{2a} is cyano. In certain embodiments, R^{2a} is nitro. In certain embodiments, R^{2a} is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2a} is methyl, ethyl, isopropyl, or trifluoromethyl. In certain embodiments, R^{2a} is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2a} is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2a} is ethynyl. In certain embodiments, R^{2a} is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2a} is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2a} is phenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2a}

is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2a} is benzyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2a} is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2a} is heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2a} is pyrrolidinyl, optionally substituted with one or more substituents Q.

[00115] In certain embodiments, R^{2a} is $-C(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2a} is $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2a} is $-C(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{2a} is $-C(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{2a} is $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2a} is C_{1-6} alkoxy ($-OC_{1-6}$ alkyl), optionally substituted with one or more substituents Q. In certain embodiments, R^{2a} is methoxy. In certain embodiments, R^{2a} is $-OC(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2a} is $-OC(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2a} is $-OC(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{2a} is $-OC(=NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{2a} is $-OS(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2a} is $-OS(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2a} is $-OS(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{2a} is $-OS(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{2a} is $-NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{2a} is $-NR^{1a}C(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{2a} is $-NR^{1a}C(O)OR^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{2a} is $-NR^{1a}C(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{2a} is $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each as defined herein. In certain embodiments, R^{2a} is $-NR^{1a}S(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{2a} is $-NR^{1a}S(O)_2R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{2a} is $-NR^{1a}S(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{2a} is $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{2a} is $-P(O)R^{1a}R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{2a} is $-P(O)(OR^{1a})R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments,

R^{2a} is $-P(O)(OR^{1a})(OR^{1d})$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{2a} is $-SR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2a} is $-S(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2a} is $-S(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2a} is $-S(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{2a} is $-S(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein.

[00116] In certain embodiments, R^{2b} is hydrogen. In certain embodiments, R^{2b} is halo. In certain embodiments, R^{2b} is cyano. In certain embodiments, R^{2b} is nitro. In certain embodiments, R^{2b} is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2b} is methyl, ethyl, isopropyl, or trifluoromethyl. In certain embodiments, R^{2b} is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2b} is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2b} is ethynyl. In certain embodiments, R^{2b} is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2b} is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2b} is phenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2b} is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2b} is benzyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2b} is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2b} is heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{2b} is pyrrolidinyl, optionally substituted with one or more substituents Q.

[00117] In certain embodiments, R^{2b} is $-C(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2b} is $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2b} is $-C(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{2b} is $-C(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{2b} is $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2b} is C_{1-6} alkoxy ($-OC_{1-6}$ alkyl), optionally substituted with one or more substituents Q. In certain embodiments, R^{2b} is methoxy. In certain embodiments, R^{2b} is $-OC(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2b} is $-OC(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2b} is $-OC(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{2b} is $-OC(=NR^{1a})NR^{1b}R^{1c}$,

wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{2b} is $-OS(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2b} is $-OS(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2b} is $-OS(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{2b} is $-OS(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{2b} is $-NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{2b} is $-NR^{1a}C(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{2b} is $-NR^{1a}C(O)OR^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{2b} is $-NR^{1a}C(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{2b} is $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each as defined herein. In certain embodiments, R^{2b} is $-NR^{1a}S(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{2b} is $-NR^{1a}S(O)_2R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{2b} is $-NR^{1a}S(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{2b} is $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{2b} is $-P(O)R^{1a}R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{2b} is $-P(O)(OR^{1a})R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{2b} is $-P(O)(OR^{1a})(OR^{1d})$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{2b} is $-SR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2b} is $-S(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2b} is $-S(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{2b} is $-S(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{2b} is $-S(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein.

[00118] In certain embodiments, R^{3a} is hydrogen. In certain embodiments, R^{3a} is halo. In certain embodiments, R^{3a} is cyano. In certain embodiments, R^{3a} is nitro. In certain embodiments, R^{3a} is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3a} is methyl, ethyl, isopropyl, or trifluoromethyl. In certain embodiments, R^{3a} is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3a} is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3a} is ethynyl. In certain embodiments, R^{3a} is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3a} is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3a} is phenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3a}

is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3a} is benzyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3a} is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3a} is heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3a} is pyrrolidinyl, optionally substituted with one or more substituents Q.

[00119] In certain embodiments, R^{3a} is $-C(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3a} is $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3a} is $-C(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{3a} is $-C(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{3a} is $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3a} is C_{1-6} alkoxy ($-OC_{1-6}$ alkyl), optionally substituted with one or more substituents Q. In certain embodiments, R^{3a} is methoxy. In certain embodiments, R^{3a} is $-OC(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3a} is $-OC(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3a} is $-OC(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{3a} is $-OC(=NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{3a} is $-OS(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3a} is $-OS(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3a} is $-OS(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{3a} is $-OS(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{3a} is $-NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{3a} is $-NR^{1a}C(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{3a} is $-NR^{1a}C(O)OR^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{3a} is $-NR^{1a}C(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{3a} is $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each as defined herein. In certain embodiments, R^{3a} is $-NR^{1a}S(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{3a} is $-NR^{1a}S(O)_2R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{3a} is $-NR^{1a}S(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{3a} is $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{3a} is $-P(O)R^{1a}R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{3a} is $-P(O)(OR^{1a})R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments,

R^{3a} is $-P(O)(OR^{1a})(OR^{1d})$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{3a} is $-SR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3a} is $-S(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3a} is $-S(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3a} is $-S(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{3a} is $-S(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein.

[00120] In certain embodiments, R^{3b} is hydrogen. In certain embodiments, R^{3b} is halo. In certain embodiments, R^{3b} is cyano. In certain embodiments, R^{3b} is nitro. In certain embodiments, R^{3b} is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3b} is methyl, ethyl, isopropyl, or trifluoromethyl. In certain embodiments, R^{3b} is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3b} is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3b} is ethynyl. In certain embodiments, R^{3b} is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3b} is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3b} is phenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3b} is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3b} is benzyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3b} is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3b} is heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{3b} is pyrrolidinyl, optionally substituted with one or more substituents Q.

[00121] In certain embodiments, R^{3b} is $-C(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3b} is $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3b} is $-C(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{3b} is $-C(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{3b} is $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3b} is C_{1-6} alkoxy ($-OC_{1-6}$ alkyl), optionally substituted with one or more substituents Q. In certain embodiments, R^{3b} is methoxy. In certain embodiments, R^{3b} is $-OC(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3b} is $-OC(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3b} is $-OC(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{3b} is $-OC(=NR^{1a})NR^{1b}R^{1c}$,

wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{3b} is $-OS(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3b} is $-OS(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3b} is $-OS(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{3b} is $-OS(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{3b} is $-NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{3b} is $-NR^{1a}C(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{3b} is $-NR^{1a}C(O)OR^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{3b} is $-NR^{1a}C(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{3b} is $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each as defined herein. In certain embodiments, R^{3b} is $-NR^{1a}S(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{3b} is $-NR^{1a}S(O)_2R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{3b} is $-NR^{1a}S(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{3b} is $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{3b} is $-P(O)R^{1a}R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{3b} is $-P(O)(OR^{1a})R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{3b} is $-P(O)(OR^{1a})(OR^{1d})$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{3b} is $-SR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3b} is $-S(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3b} is $-S(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{3b} is $-S(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{3b} is $-S(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein.

[00122] In certain embodiments, R^{4a} is hydrogen. In certain embodiments, R^{4a} is halo. In certain embodiments, R^{4a} is cyano. In certain embodiments, R^{4a} is nitro. In certain embodiments, R^{4a} is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4a} is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4a} is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4a} is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4a} is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4a} is phenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4a} is phenyl, optionally substituted with one, two, or three substituents Q. In certain embodiments, R^{4a} is

phenyl, optionally substituted with one, two, or three substituents Q, wherein each Q is independently chloro or trifluoromethyl. In certain embodiments, R^{4a} is phenyl, chlorophenyl, or trifluoromethyl-phenyl. In certain embodiments, R^{4a} is phenyl, 4-chlorophenyl, or 3-trifluoromethyl-phenyl. In certain embodiments, R^{4a} is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4a} is benzyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4a} is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4a} is heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4a} is pyrrolidinyl, optionally substituted with one or more substituents Q.

[00123] In certain embodiments, R^{4a} is $-C(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4a} is $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4a} is $-C(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{4a} is $-C(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{4a} is $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4a} is C_{1-6} alkoxy ($-OC_{1-6}$ alkyl), optionally substituted with one or more substituents Q. In certain embodiments, R^{4a} is methoxy. In certain embodiments, R^{4a} is $-OC(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4a} is $-OC(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4a} is $-OC(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{4a} is $-OC(=NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{4a} is $-OS(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4a} is $-OS(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4a} is $-OS(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{4a} is $-OS(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{4a} is $-NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{4a} is $-NR^{1a}C(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{4a} is $-NR^{1a}C(O)OR^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{4a} is $-NR^{1a}C(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{4a} is $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each as defined herein. In certain embodiments, R^{4a} is $-NR^{1a}S(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{4a} is $-NR^{1a}S(O)_2R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{4a} is $-NR^{1a}S(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{4a} is $-NR^{1a}S(O)_2NR^{1b}R^{1c}$,

wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{4a} is $-P(O)R^{1a}R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{4a} is $-P(O)(OR^{1a})R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{4a} is $-P(O)(OR^{1a})(OR^{1d})$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{4a} is $-SR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4a} is $-S(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4a} is $-S(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4a} is $-S(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{4a} is $-S(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein.

[00124] In certain embodiments, R^{4b} is hydrogen. In certain embodiments, R^{4b} is halo. In certain embodiments, R^{4b} is cyano. In certain embodiments, R^{4b} is nitro. In certain embodiments, R^{4b} is C_{1-6} alkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4b} is C_{2-6} alkenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4b} is C_{2-6} alkynyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4b} is C_{3-10} cycloalkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4b} is C_{6-14} aryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4b} is phenyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4b} is phenyl, optionally substituted with one, two, or three substituents Q. In certain embodiments, R^{4b} is phenyl, optionally substituted with one, two, or three substituents Q, wherein each Q is independently chloro or trifluoromethyl. In certain embodiments, R^{4b} is phenyl, chlorophenyl, or trifluoromethyl-phenyl. In certain embodiments, R^{4b} is phenyl, 4-chlorophenyl, or 3-trifluoromethyl-phenyl. In certain embodiments, R^{4b} is C_{7-15} aralkyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4b} is benzyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4b} is heteroaryl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4b} is heterocyclyl, optionally substituted with one or more substituents Q. In certain embodiments, R^{4b} is pyrrolidinyl, optionally substituted with one or more substituents Q.

[00125] In certain embodiments, R^{4b} is $-C(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4b} is $-C(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4b} is $-C(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{4b} is $-C(NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined

herein. In certain embodiments, R^{4b} is $-OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4b} is C_{1-6} alkoxy ($-OC_{1-6}$ alkyl), optionally substituted with one or more substituents Q. In certain embodiments, R^{4b} is methoxy. In certain embodiments, R^{4b} is $-OC(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4b} is $-OC(O)OR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4b} is $-OC(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{4b} is $-OC(=NR^{1a})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{4b} is $-OS(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4b} is $-OS(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4b} is $-OS(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{4b} is $-OS(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{4b} is $-NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{4b} is $-NR^{1a}C(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{4b} is $-NR^{1a}C(O)OR^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{4b} is $-NR^{1a}C(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{4b} is $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} are each as defined herein. In certain embodiments, R^{4b} is $-NR^{1a}S(O)R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{4b} is $-NR^{1a}S(O)_2R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{4b} is $-NR^{1a}S(O)NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{4b} is $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, wherein R^{1a}, R^{1b}, and R^{1c} are each as defined herein. In certain embodiments, R^{4b} is $-P(O)R^{1a}R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{4b} is $-P(O)(OR^{1a})R^{1d}$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{4b} is $-P(O)(OR^{1a})(OR^{1d})$, wherein R^{1a} and R^{1d} are each as defined herein. In certain embodiments, R^{4b} is $-SR^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4b} is $-S(O)R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4b} is $-S(O)_2R^{1a}$, wherein R^{1a} is as defined herein. In certain embodiments, R^{4b} is $-S(O)NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein. In certain embodiments, R^{4b} is $-S(O)_2NR^{1b}R^{1c}$, wherein R^{1b} and R^{1c} are each as defined herein.

[00126] In certain embodiments, U^1 is O. In certain embodiments, U^1 is S. In certain embodiments, U^1 is N. In certain embodiments, U^1 is CR^9, where R^9 is as defined herein. In certain embodiments, U^1 is CH. In certain embodiments, U^1 is NR^9, where R^9 is as defined herein. In certain embodiments, U^1 is NH.

[00127] In certain embodiments, V^1 is O. In certain embodiments, V^1 is S. In certain embodiments, V^1 is N. In certain embodiments, V^1 is CR^9, where R^9 is as defined herein. In certain embodiments, V^1 is CH. In certain embodiments, V^1 is NR^9, where R^9 is as defined herein. In certain embodiments, V^1 is NH.

[00128] In certain embodiments, W^1 is O. In certain embodiments, W^1 is S. In certain embodiments, W^1 is N. In certain embodiments, W^1 is CR^9, where R^9 is as defined herein. In certain embodiments, W^1 is CH. In certain embodiments, W^1 is NR^9, where R^9 is as defined herein. In certain embodiments, W^1 is NH.

[00129] In certain embodiments, X^1 is O. In certain embodiments, X^1 is S. In certain embodiments, X^1 is N. In certain embodiments, X^1 is CR^9, where R^9 is as defined herein. In certain embodiments, X^1 is CH. In certain embodiments, X^1 is NR^9, where R^9 is as defined herein. In certain embodiments, X^1 is NH.

[00130] In certain embodiments, Y^1 is C. In certain embodiments, Y^1 is N.

[00131] In certain embodiments, U^2 is O. In certain embodiments, U^2 is S. In certain embodiments, U^2 is N. In certain embodiments, U^2 is CR^9, where R^9 is as defined herein. In certain embodiments, U^2 is CH. In certain embodiments, U^2 is NR^9, where R^9 is as defined herein. In certain embodiments, U^2 is NH.

[00132] In certain embodiments, V^2 is O. In certain embodiments, V^2 is S. In certain embodiments, V^2 is N. In certain embodiments, V^2 is CR^9, where R^9 is as defined herein. In certain embodiments, V^2 is CH. In certain embodiments, V^2 is NR^9, where R^9 is as defined herein. In certain embodiments, V^2 is NH.

[00133] In certain embodiments, W^2 is O. In certain embodiments, W^2 is S. In certain embodiments, W^2 is N. In certain embodiments, W^2 is CR^9, where R^9 is as defined herein. In certain embodiments, W^2 is CH. In certain embodiments, W^2 is NR^9, where R^9 is as defined herein. In certain embodiments, W^2 is NH.

[00134] In certain embodiments, X^2 is O. In certain embodiments, X^2 is S. In certain embodiments, X^2 is N. In certain embodiments, X^2 is CR^9, where R^9 is as defined herein. In certain embodiments, X^2 is CH. In certain embodiments, X^2 is NR^9, where R^9 is as defined herein. In certain embodiments, X^2 is NH.

[00135] In certain embodiments, Y^2 is C. In certain embodiments, Y^2 is N.

[00136] In certain embodiments, U^3 is O. In certain embodiments, U^3 is S. In certain embodiments, U^3 is N. In certain embodiments, U^3 is CR^9, where R^9 is as defined herein. In certain embodiments, U^3 is CH. In certain embodiments, U^3 is NR^9, where R^9 is as defined herein. In certain embodiments, U^3 is NH.

[00137] In certain embodiments, V^3 is O. In certain embodiments, V^3 is S. In certain embodiments, V^3 is N. In certain embodiments, V^3 is CR^9, where R^9 is as defined herein. In certain embodiments, V^3 is CH. In certain embodiments, V^3 is NR^9, where R^9 is as defined herein. In certain embodiments, V^3 is NH.

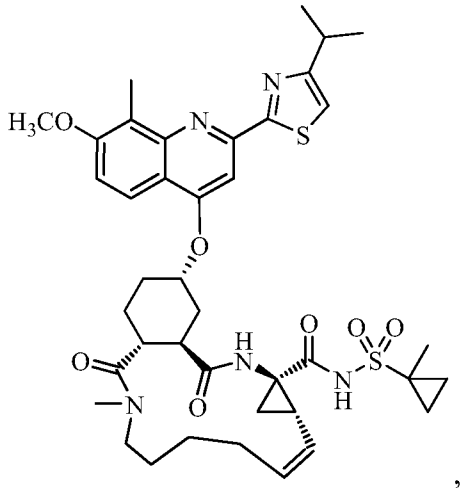
[00138] In certain embodiments, W^3 is O. In certain embodiments, W^3 is S. In certain embodiments, W^3 is N. In certain embodiments, W^3 is CR^9, where R^9 is as defined herein. In certain embodiments, W^3 is CH. In certain embodiments, W^3 is NR^9, where R^9 is as defined herein. In certain embodiments, W^3 is NH.

[00139] In certain embodiments, X^3 is O. In certain embodiments, X^3 is S. In certain embodiments, X^3 is N. In certain embodiments, X^3 is CR^9, where R^9 is as defined herein. In certain embodiments, X^3 is CH. In certain embodiments, X^3 is NR^9, where R^9 is as defined herein. In certain embodiments, X^3 is NH.

[00140] In certain embodiments, Y^3 is C. In certain embodiments, Y^3 is N.

[00141] In certain embodiments, Z is CR^1, where R^1 is as defined herein. In certain embodiments, Z is CH. In certain embodiments, Z is N.

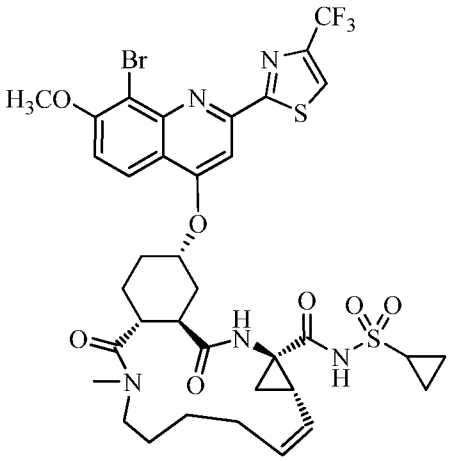
[00142] In one embodiment, the compound provided herein is



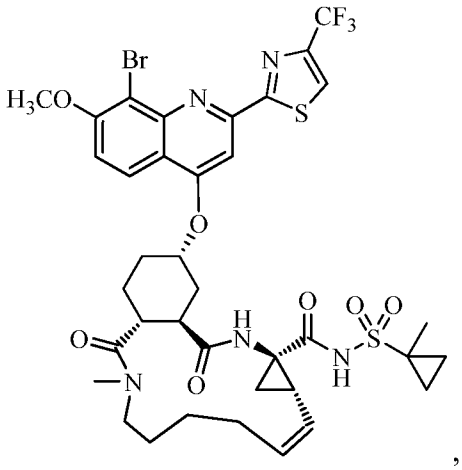
A101

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, and prodrug thereof.

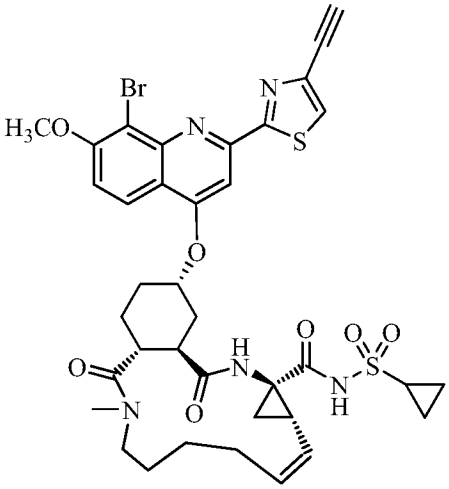
[00143] In another embodiment, the compound provided herein is selected from:



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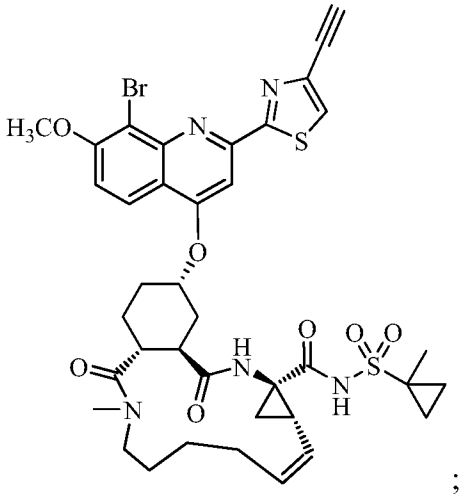


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, and

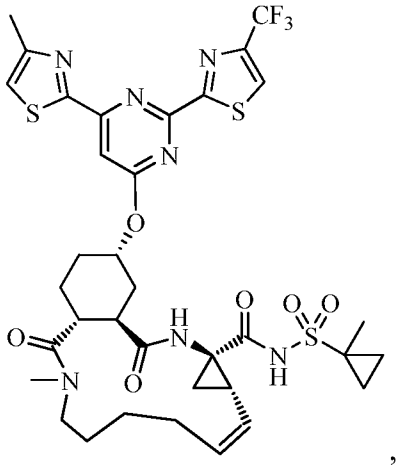


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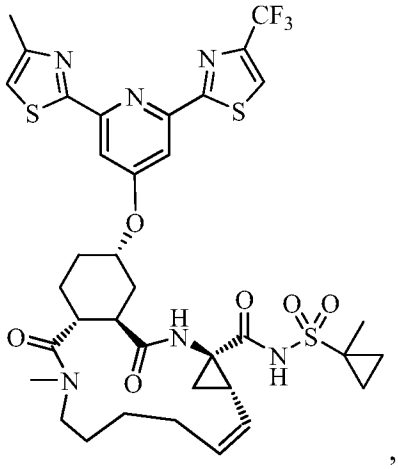
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and isotopic variants thereof; and pharmaceutically acceptable salts, solvates, and prodrugs thereof.

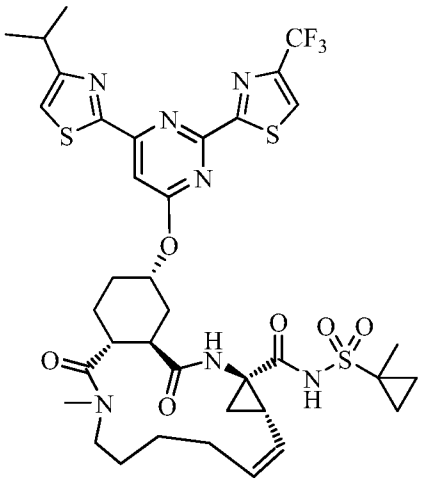
[00144] In yet another embodiment, the compound provided herein is selected from:



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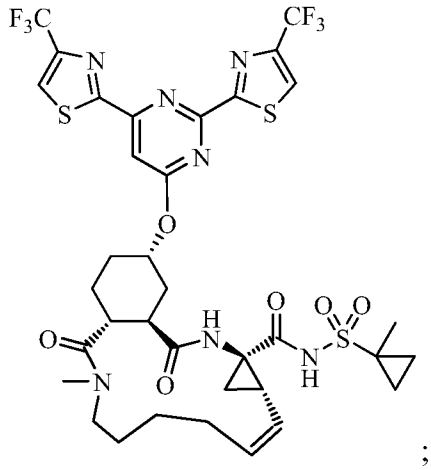


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, and

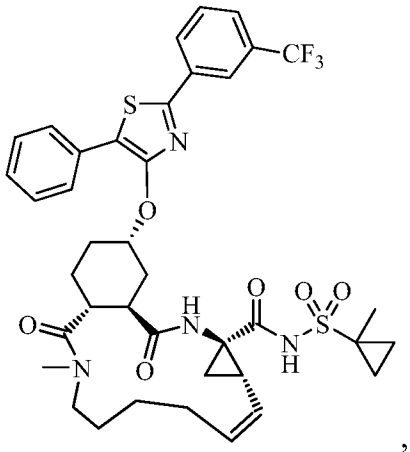


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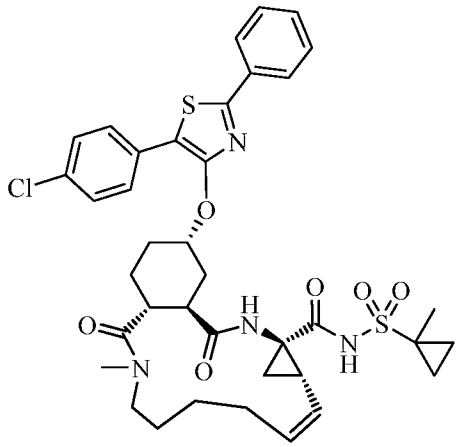
and isotopic variants thereof; and pharmaceutically acceptable salts, solvates, and prodrugs thereof.

[00145] In still another embodiment, the compound provided herein is selected from:



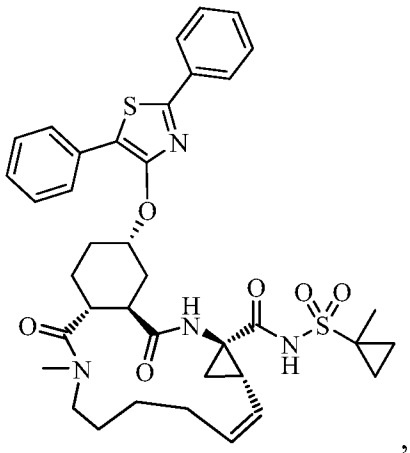
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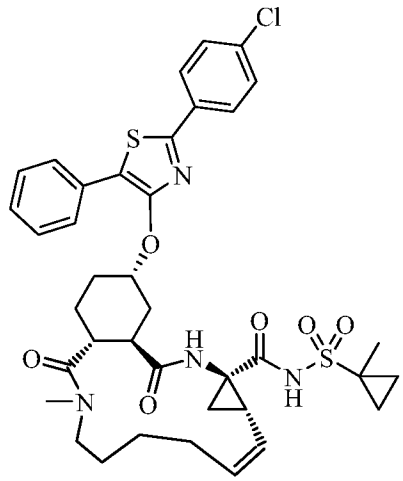
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and



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;

and isotopic variants thereof; and pharmaceutically acceptable salts, solvates, and prodrugs thereof.

[00146] The compounds provided herein are intended to encompass all possible stereoisomers, unless a particular stereochemistry is specified. Where the compound provided herein contains an alkenyl or alkenylene group, the compound may exist as one or a mixture of geometric *cis*/*trans* (or Z/E) isomers. Where structural isomers are interconvertible, the compound may exist as a single tautomer or a mixture of tautomers. This can take the form of proton tautomerism in the compound that contains, for example, an imino, keto, or oxime group; or so-called valence tautomerism in the compound that contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

[00147] The compounds provided herein may be enantiomerically pure, such as a

single enantiomer or a single diastereomer, or be stereoisomeric mixtures, such as a mixture of enantiomers, *e.g.*, a racemic mixture of two enantiomers; or a mixture of two or more diastereomers. As such, one of skill in the art will recognize that administration of a compound in its (*R*) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (*S*) form. Conventional techniques for the preparation/isolation of individual enantiomers include synthesis from a suitable optically pure precursor, asymmetric synthesis from achiral starting materials, or resolution of an enantiomeric mixture, for example, chiral chromatography, recrystallization, resolution, diastereomeric salt formation, or derivatization into diastereomeric adducts followed by separation.

[00148] When the compound provided herein contains an acidic or basic moiety, it may also be provided as a pharmaceutically acceptable salt. *See*, Berge *et al.*, *J. Pharm. Sci.* **1977**, *66*, 1-19; and *Handbook of Pharmaceutical Salts, Properties, and Use*; Stahl and Wermuth, Ed.; Wiley-VCH and VHCA: Zurich, Switzerland, 2002.

[00149] Suitable acids for use in the preparation of pharmaceutically acceptable salts include, but are not limited to, acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, boric acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1*S*)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, cyclohexanesulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid, α-oxoglutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, lauric acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, perchloric acid, phosphoric acid, L-pyroglutamic acid, saccharic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, undecylenic acid, and valeric acid.

[00150] Suitable bases for use in the preparation of pharmaceutically acceptable salts, including, but not limited to, inorganic bases, such as magnesium hydroxide, calcium

hydroxide, potassium hydroxide, zinc hydroxide, or sodium hydroxide; and organic bases, such as primary, secondary, tertiary, and quaternary, aliphatic and aromatic amines, including L-arginine, benethamine, benzathine, choline, deanol, diethanolamine, diethylamine, dimethylamine, dipropylamine, diisopropylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylamine, ethylenediamine, isopropylamine, *N*-methyl-glucamine, hydrabamine, 1*H*-imidazole, L-lysine, morpholine, 4-(2-hydroxyethyl)-morpholine, methylamine, piperidine, piperazine, propylamine, pyrrolidine, 1-(2-hydroxyethyl)-pyrrolidine, pyridine, quinuclidine, quinoline, isoquinoline, secondary amines, triethanolamine, trimethylamine, triethylamine, N-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, and tromethamine.

[00151] The compound provided herein may also be provided as a prodrug, which is a functional derivative of the compound, for example, of Formula I, and is readily convertible into the parent compound *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent compound. They may, for instance, be bioavailable by oral administration whereas the parent compound is not. The prodrug may also have enhanced solubility in pharmaceutical compositions over the parent compound. A prodrug may be converted into the parent drug by various mechanisms, including enzymatic processes and metabolic hydrolysis. *See,* Harper, *Progress in Drug Research* **1962**, *4*, 221-294; Morozowich *et al.* in *Design of Biopharmaceutical Properties through Prodrugs and Analogs*; Roche Ed., APHA Acad. Pharm. Sci.: 1977; Gangwar *et al.*, *Des. Biopharm. Prop. Prodrugs Analogs*, **1977**, 409-421; Bundgaard, *Arch. Pharm. Chem.* **1979**, *86*, 1-39; Farquhar *et al.*, *J. Pharm. Sci.* **1983**, *72*, 324-325; Wernuth in *Drug Design: Fact or Fantasy*; Jolles *et al.* Eds.; Academic Press: London, 1984; pp 47-72; *Design of Prodrugs*; Bundgaard *et al.* Eds.; Elsevier: 1985; Fleisher *et al.*, *Methods Enzymol.* **1985**, *112*, 360-381; Stella *et al.*, *Drugs* **1985**, *29*, 455-473; *Bioreversible Carriers in Drug in Drug Design, Theory and Application*; Roche Ed.; APHA Acad. Pharm. Sci.: 1987; Bundgaard, *Controlled Drug Delivery* **1987**, *17*, 179-96; Waller *et al.*, *Br. J. Clin. Pharmac.* **1989**, *28*, 497-507; Balant *et al.*, *Eur. J. Drug Metab. Pharmacokinet.* **1990**, *15*, 143-53; Freeman *et al.*, *J. Chem. Soc., Chem. Commun.* **1991**, 875-877; Bundgaard, *Adv. Drug Delivery Rev.* **1992**, *8*, 1-38; Nathwani and Wood, *Drugs* **1993**, *45*, 866-94; Friis and Bundgaard, *Eur. J. Pharm. Sci.* **1996**, *4*, 49-59; Fleisher *et al.*, *Adv. Drug Delivery Rev.* **1996**, *19*, 115-130; Sinhababu and Thakker, *Adv. Drug Delivery Rev.* **1996**, *19*, 241-273; Taylor, *Adv. Drug Delivery Rev.* **1996**, *19*, 131-148; Gaignault *et al.*, *Pract. Med. Chem.* **1996**, 671-696; Browne, *Clin. Neuropharmacol.* **1997**, *20*, 1-12; Valentino and Borchardt, *Drug Discovery Today* **1997**, *2*, 148-155; Pauletti *et*

al., *Adv. Drug. Delivery Rev.* **1997**, *27*, 235-256; Mizen *et al.*, *Pharm. Biotech.* **1998**, *11*, 345-365; Wiebe and Knaus, *Adv. Drug Delivery Rev.* **1999**, *39*, 63-80; Tan *et al.*, *Adv. Drug Delivery Rev.* **1999**, *39*, 117-151; Balimane and Sinko, *Adv. Drug Delivery Rev.* **1999**, *39*, 183-209; Wang *et al.*, *Curr. Pharm. Design* **1999**, *5*, 265-287; Han *et al.*, *AAPS Pharmsci.* **2000**, *2*, 1-11; Asgharnejad in *Transport Processes in Pharmaceutical Systems*; Amidon *et al.*, Eds.; Marcell Dekker: 2000; pp 185-218; Sinha *et al.*, *Pharm. Res.* **2001**, *18*, 557-564; Anand *et al.*, *Expert Opin. Biol. Ther.* **2002**, *2*, 607-620; Rao, *Resonace* **2003**, 19-27; Sloan *et al.*, *Med. Res. Rev.* **2003**, *23*, 763-793; Patterson *et al.*, *Curr. Pharm. Des.* **2003**, *9*, 2131-2154; Hu, *IDrugs* **2004**, *7*, 736-742; Robinson *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 14527-14532; Erion *et al.*, *J. Pharmacol. Exp. Ther.* **2005**, *312*, 554-560; Fang *et al.*, *Curr. Drug Discov. Technol.* **2006**, *3*, 211-224; Stanczak *et al.*, *Pharmacol. Rep.* **2006**, *58*, 599-613; Sloan *et al.*, *Pharm. Res.* **2006**, *23*, 2729-2747; Stella *et al.*, *Adv. Drug Deliv. Rev.* **2007**, *59*, 677-694; Gomes *et al.*, *Molecules* **2007**, *12*, 2484-2506; Krafz *et al.*, *ChemMedChem* **2008**, *3*, 20-53; Rautio *et al.*, *AAPS J.* **2008**, *10*, 92-102; Rautio *et al.*, *Nat. Rev. Drug. Discov.* **2008**, *7*, 255-270; Pavan *et al.*, *Molecules*, **2008**, *13*, 1035-1065; Sandros *et al.*, *Molecules* **2008**, *13*, 1156-1178; Singh *et al.*, *Curr. Med. Chem.* **2008**, *15*, 1802-1826; Onishi *et al.*, *Molecules*, **2008**, *13*, 2136-2155; Huttunen *et al.*, *Curr. Med. Chem.* **2008**, *15*, 2346-2365; and Serafin *et al.*, *Mini Rev. Med. Chem.* **2009**, *9*, 481-497.

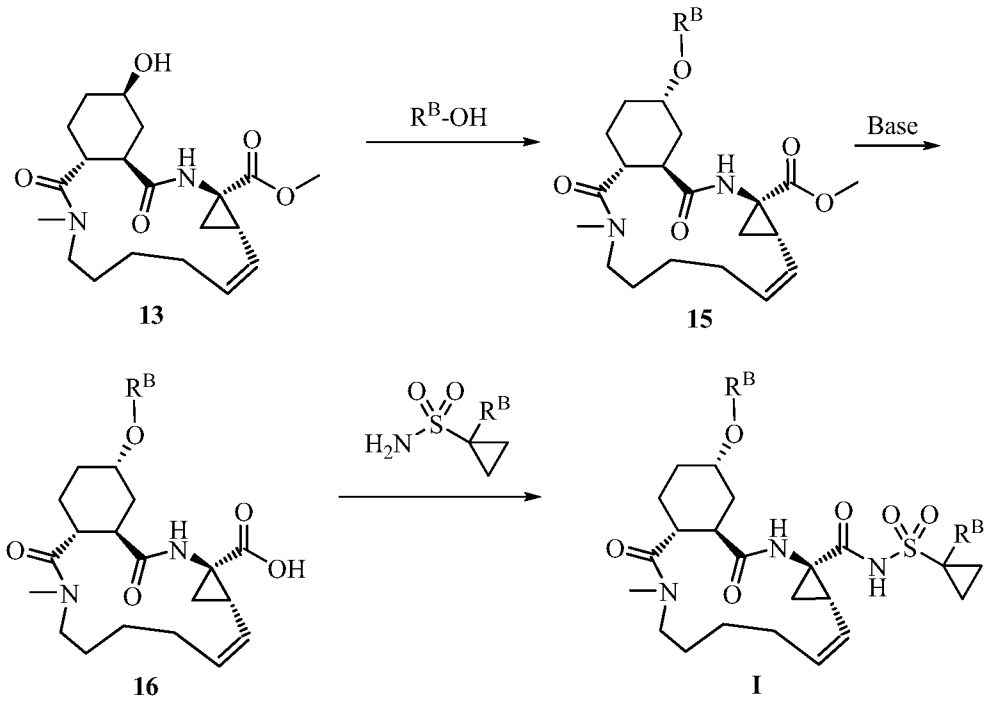
Methods of Synthesis

[00152] The compound provided herein can be prepared, isolated, or obtained by any method known to one of skill in the art. For example, a compound of Formula I can be prepared as shown in Scheme I. A variety of R^B-OH groups can be introduced at the hydroxyl position of compound **13** using various chemistries to form an ether linkage with conversion of the stereochemistry at that position, including, one-step reactions, *e.g.*, Mitsunobu; and two-step reactions, *e.g.*, nucleophilic substitution, where the hydroxyl of compound **13** is first converted into a reactive leaving group, such as a sulfonate ester. Nonlimiting sulfonate esters include methansulfonate (mesylate), ethansulfonate (esylate), *p*-toluensulfonate (tosylate), 4-bromobenzenesulfonate, and trifluoromethanesulfonate (triflate) esters.

[00153] The starting materials used in the synthesis of the compounds provided herein are either commercially available or can be readily prepared. Suitable examples of R^6 groups can be found, *e.g.*, in U.S. Appl. Publ. Nos. 2009/0202480; and 2010/0260710; and U.S.

Appl. Serial No. 12/850,534; the disclosure of each of which is incorporated herein by reference in its entirety.

Scheme I



Pharmaceutical Compositions

[00154] Provided herein are pharmaceutical compositions comprising a compound provided herein, *e.g.*, a compound of Formula I, as an active ingredient, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug; and a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

[00155] Suitable excipients are well known to those skilled in the art, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art, including, but not limited to, the method of administration. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary

amines are particularly susceptible to such accelerated decomposition. Consequently, provided herein are pharmaceutical compositions and dosage forms that contain little, if any, lactose, or other mono- or di-saccharides. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient. In one embodiment, lactose-free compositions comprise an active ingredient provided herein, a binder/filler, and a lubricant. In another embodiment, lactose-free dosage forms comprise an active ingredient, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

[00156] The compound provided herein may be administered alone, or in combination with one or more other compounds provided herein. The pharmaceutical compositions that comprise a compound provided herein, *e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, can be formulated in various dosage forms for oral, parenteral, and topical administration. The pharmaceutical compositions can also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated-, fast-, targeted-, programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Delivery Technology*, 2nd ed.; Rathbone *et al.*, Eds.; Marcel Dekker, Inc.: New York, NY, 2008).

[00157] In one embodiment, the pharmaceutical compositions are provided in a dosage form for oral administration, which comprise a compound provided herein, *e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more pharmaceutically acceptable excipients or carriers.

[00158] In another embodiment, the pharmaceutical compositions are provided in a dosage form for parenteral administration, which comprise a compound provided herein, *e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more pharmaceutically acceptable excipients or carriers.

[00159] In yet another embodiment, the pharmaceutical compositions are provided in a

dosage form for topical administration, which comprise a compound provided herein, *e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more pharmaceutically acceptable excipients or carriers.

[00160] The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete a unit suitable for administration to a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. For example, a 100 mg unit dose contains about 100 mg of an active ingredient in a packaged tablet or capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

[00161] The pharmaceutical compositions provided herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

A. Oral Administration

[00162] The pharmaceutical compositions provided herein for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions,

emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

[00163] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (*e.g.*, STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The amount of a binder or filler in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

[00164] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The amount of a diluent in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

[00165] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[00166] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

[00167] Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine

oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

[00168] It should be understood that many carriers and excipients may serve a plurality of functions, even within the same formulation.

[00169] The pharmaceutical compositions provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[00170] The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful

in the formation of chewable tablets and lozenges.

[00171] The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[00172] The pharmaceutical compositions provided herein for oral administration can be provided in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquid or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl) acetal of a lower alkyl aldehyde, *e.g.*, acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be measured conveniently for administration.

[00173] Other useful liquid and semisolid dosage forms include, but are not limited to, those containing the active ingredient(s) provided herein, and a dialkylated mono- or poly-

alkylene glycol, including, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These formulations can further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.

[00174] The pharmaceutical compositions provided herein for oral administration can be also provided in the forms of liposomes, micelles, microspheres, or nanosystems. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[00175] The pharmaceutical compositions provided herein for oral administration can be provided as non-effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[00176] Coloring and flavoring agents can be used in all of the above dosage forms.

[00177] The pharmaceutical compositions provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

B. Parenteral Administration

[00178] The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

[00179] The pharmaceutical compositions provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral

administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy*, supra).

[00180] The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

[00181] Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (*e.g.*, polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methyl-2-pyrrolidone, *N,N*-dimethylacetamide, and dimethyl sulfoxide.

[00182] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (*e.g.*, benzethonium chloride), methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose,

and polyvinylpyrrolidone. Suitable emulsifying agents are those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

[00183] When the pharmaceutical compositions provided herein are formulated for multiple dosage administration, the multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungistatic concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[00184] In one embodiment, the pharmaceutical compositions for parenteral administration are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

[00185] The pharmaceutical compositions provided herein for parenteral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00186] The pharmaceutical compositions provided herein for parenteral administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

[00187] Suitable inner matrixes include, but are not limited to,

polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

[00188] Suitable outer polymeric membranes include but are not limited to, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

C. Topical Administration

[00189] The pharmaceutical compositions provided herein can be administered topically to the skin, orifices, or mucosa. The topical administration, as used herein, includes (intra)dermal, conjunctival, intracorneal, intraocular, ophthalmic, auricular, transdermal, nasal, vaginal, urethral, respiratory, and rectal administration.

[00190] The pharmaceutical compositions provided herein can be formulated in any dosage forms that are suitable for topical administration for local or systemic effect, including emulsions, solutions, suspensions, creams, gels, hydrogels, ointments, dusting powders, dressings, elixirs, lotions, suspensions, tinctures, pastes, foams, films, aerosols, irrigations, sprays, suppositories, bandages, and dermal patches. The topical formulation of the pharmaceutical compositions provided herein can also comprise liposomes, micelles, microspheres, nanosystems, and mixtures thereof.

[00191] Pharmaceutically acceptable carriers and excipients suitable for use in the topical formulations provided herein include, but are not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, penetration enhancers,

cryoprotectants, lyoprotectants, thickening agents, and inert gases.

[00192] The pharmaceutical compositions can also be administered topically by electroporation, iontophoresis, phonophoresis, sonophoresis, or microneedle or needle-free injection, such as POWDERJECT™ (Chiron Corp., Emeryville, CA), and BIOJECT™ (Bioject Medical Technologies Inc., Tualatin, OR).

[00193] The pharmaceutical compositions provided herein can be provided in the forms of ointments, creams, and gels. Suitable ointment vehicles include oleaginous or hydrocarbon vehicles, including lard, benzoinated lard, olive oil, cottonseed oil, and other oils, white petrolatum; emulsifiable or absorption vehicles, such as hydrophilic petrolatum, hydroxystearin sulfate, and anhydrous lanolin; water-removable vehicles, such as hydrophilic ointment; water-soluble ointment vehicles, including polyethylene glycols of varying molecular weight; emulsion vehicles, either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, including cetyl alcohol, glyceryl monostearate, lanolin, and stearic acid (*see*, *Remington: The Science and Practice of Pharmacy*, supra). These vehicles are emollient but generally require addition of antioxidants and preservatives.

[00194] Suitable cream base can be oil-in-water or water-in-oil. Suitable cream vehicles may be water-washable, and contain an oil phase, an emulsifier, and an aqueous phase. The oil phase is also called the "internal" phase, which is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation may be a nonionic, anionic, cationic, or amphoteric surfactant.

[00195] Gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the liquid carrier. Suitable gelling agents include, but are not limited to, crosslinked acrylic acid polymers, such as carbomers, carboxypolyalkylenes, and CARBOPOL®; hydrophilic polymers, such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers, and polyvinylalcohol; cellulosic polymers, such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose; gums, such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be

dispersed by trituration, mechanical mixing, and/or stirring.

[00196] The pharmaceutical compositions provided herein can be administered rectally, urethrally, vaginally, or perivaginally in the forms of suppositories, pessaries, bougies, poultices or cataplasm, pastes, powders, dressings, creams, plasters, contraceptives, ointments, solutions, emulsions, suspensions, tampons, gels, foams, sprays, or enemas. These dosage forms can be manufactured using conventional processes as described in *Remington: The Science and Practice of Pharmacy*, supra.

[00197] Rectal, urethral, and vaginal suppositories are solid bodies for insertion into body orifices, which are solid at ordinary temperatures but melt or soften at body temperature to release the active ingredient(s) inside the orifices. Pharmaceutically acceptable carriers utilized in rectal and vaginal suppositories include bases or vehicles, such as stiffening agents, which produce a melting point in the proximity of body temperature, when formulated with the pharmaceutical compositions provided herein; and antioxidants as described herein, including bisulfite and sodium metabisulfite. Suitable vehicles include, but are not limited to, cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol), spermaceti, paraffin, white and yellow wax, and appropriate mixtures of mono-, di- and triglycerides of fatty acids, and hydrogels, such as polyvinyl alcohol, hydroxyethyl methacrylate, and polyacrylic acid;. Combinations of the various vehicles can also be used. Rectal and vaginal suppositories may be prepared by compressing or molding. The typical weight of a rectal and vaginal suppository is about 2 to about 3 g.

[00198] The pharmaceutical compositions provided herein can be administered ophthalmically in the forms of solutions, suspensions, ointments, emulsions, gel-forming solutions, powders for solutions, gels, ocular inserts, and implants.

[00199] The pharmaceutical compositions provided herein can be administered intranasally or by inhalation to the respiratory tract. The pharmaceutical compositions can be provided in the form of an aerosol or solution for delivery using a pressurized container, pump, spray, atomizer, such as an atomizer using electrohydrodynamics to produce a fine mist, or nebulizer, alone or in combination with a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. The pharmaceutical compositions can also be provided as a dry powder for insufflation, alone or in combination with an inert carrier such as lactose or phospholipids; and nasal drops. For intranasal use, the powder can

comprise a bioadhesive agent, including chitosan or cyclodextrin.

[00200] Solutions or suspensions for use in a pressurized container, pump, spray, atomizer, or nebulizer can be formulated to contain ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active ingredient provided herein; a propellant as solvent; and/or a surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

[00201] The pharmaceutical compositions provided herein can be micronized to a size suitable for delivery by inhalation, such as about 50 micrometers or less, or about 10 micrometers or less. Particles of such sizes can be prepared using a comminuting method known to those skilled in the art, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

[00202] Capsules, blisters, and cartridges for use in an inhaler or insufflator can be formulated to contain a powder mix of the pharmaceutical compositions provided herein; a suitable powder base, such as lactose or starch; and a performance modifier, such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate. Other suitable excipients or carriers include, but are not limited to, dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose, and trehalose. The pharmaceutical compositions provided herein for inhaled/intranasal administration can further comprise a suitable flavor, such as menthol and levomenthol; and/or sweeteners, such as saccharin and saccharin sodium.

[00203] The pharmaceutical compositions provided herein for topical administration can be formulated to be immediate release or modified release, including delayed-, sustained-, pulsed-, controlled-, targeted, and programmed release.

D. Modified Release

[00204] The pharmaceutical compositions provided herein can be formulated as a modified release dosage form. As used herein, the term "modified release" refers to a dosage form in which the rate or place of release of the active ingredient(s) is different from that of an immediate dosage form when administered by the same route. Modified release dosage forms include, but are not limited to, delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention

dosage forms. The pharmaceutical compositions in modified release dosage forms can be prepared using a variety of modified release devices and methods known to those skilled in the art, including, but not limited to, matrix controlled release devices, osmotic controlled release devices, multiparticulate controlled release devices, ion-exchange resins, enteric coatings, multilayered coatings, microspheres, liposomes, and combinations thereof. The release rate of the active ingredient(s) can also be modified by varying the particle sizes and polymorphorism of the active ingredient(s).

[00205] Examples of modified release include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,958,458; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,270,798; 6,375,987; 6,376,461; 6,419,961; 6,589,548; 6,613,358; 6,623,756; 6,699,500; 6,793,936; 6,827,947; 6,902,742; 6,958,161; 7,255,876; 7,416,738; 7,427,414; 7,485,322; Bussemer *et al.*, *Crit. Rev. Ther. Drug Carrier Syst.* **2001**, *18*, 433-458; *Modified-Release Drug Delivery Technology*, 2nd ed.; Rathbone *et al.,* Eds.; Marcel Dekker AG: 2005; Maroni *et al.*, *Expert. Opin. Drug Deliv.* **2005**, *2*, 855-871; Shi *et al.*, *Expert Opin. Drug Deliv.* **2005**, *2*, 1039-1058; *Polymers in Drug Delivery*; Ijeoma *et al.*, Eds.; CRC Press LLC: Boca Raton, FL, 2006; Badawy *et al.*, *J. Pharm. Sci.* **2007**, *9*, 948-959; *Modified-Release Drug Delivery Technology*, supra; Conway, *Recent Pat. Drug Deliv. Formul.* **2008**, *2*, 1-8; Gazzaniga *et al.*, *Eur. J. Pharm. Biopharm.* **2008**, *68*, 11-18; Nagarwal *et al.*, *Curr. Drug Deliv.* **2008**, *5*, 282-289; Gallardo *et al.*, *Pharm. Dev. Technol.* **2008**, *13*, 413-423; Chrzanowski, *AAPS PharmSciTech.* **2008**, *9*, 635-638; Chrzanowski, *AAPS PharmSciTech.* **2008**, *9*, 639-645; Kalantzi *et al.*, *Recent Pat. Drug Deliv. Formul.* **2009**, *3*, 49-63; Saigal *et al.*, *Recent Pat. Drug Deliv. Formul.* **2009**, *3*, 64-70; and Roy *et al.*, *J. Control Release* **2009**, *134*, 74-80.

1. Matrix Controlled Release Devices

[00206] The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated using a matrix controlled release device known to those skilled in the art. *See*, Takada *et al.* in *Encyclopedia of Controlled Drug Delivery;* Mathiowitz Ed.; Wiley: 1999; Vol 2.

[00207] In certain embodiments, the pharmaceutical compositions provided herein in a

modified release dosage form is formulated using an erodible matrix device, which is water-swellable, erodible, or soluble polymers, including, but not limited to, synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

[00208] Materials useful in forming an erodible matrix include, but are not limited to, chitin, chitosan, dextran, and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum, and scleroglucan; starches, such as dextrin and maltodextrin; hydrophilic colloids, such as pectin; phosphatides, such as lecithin; alginates; propylene glycol alginate; gelatin; collagen; cellulosics, such as ethyl cellulose (EC), methylethyl cellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), and ethyl hydroxyethyl cellulose (EHEC); polyvinyl pyrrolidone; polyvinyl alcohol; polyvinyl acetate; glycerol fatty acid esters; polyacrylamide; polyacrylic acid; copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT®, Rohm America, Inc., Piscataway, NJ); poly(2-hydroxyethyl-methacrylate); polylactides; copolymers of L-glutamic acid and ethyl-L-glutamate; degradable lactic acid-glycolic acid copolymers; poly-D-(-)-3-hydroxybutyric acid; and other acrylic acid derivatives, such as homopolymers and copolymers of butylmethacrylate, methyl methacrylate, ethyl methacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, and (trimethylaminoethyl)methacrylate chloride.

[00209] In certain embodiments, the pharmaceutical compositions provided herein are formulated with a non-erodible matrix device. The active ingredient(s) is dissolved or dispersed in an inert matrix and is released primarily by diffusion through the inert matrix once administered. Materials suitable for use as a non-erodible matrix device include, but are not limited to, insoluble plastics, such as polyethylene, polypropylene, polyisoprene, polyisobutylene, polybutadiene, polymethylmethacrylate, polybutylmethacrylate, chlorinated polyethylene, polyvinylchloride, methyl acrylate-methyl methacrylate copolymers, ethylene-vinyl acetate copolymers, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubbers, epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer,

ethylene/vinyloxyethanol copolymer, polyvinyl chloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, silicone rubbers, polydimethylsiloxanes, and silicone carbonate copolymers; hydrophilic polymers, such as ethyl cellulose, cellulose acetate, crospovidone, and cross-linked partially hydrolyzed polyvinyl acetate; and fatty compounds, such as carnauba wax, microcrystalline wax, and triglycerides.

[00210] In a matrix controlled release system, the desired release kinetics can be controlled, for example, *via* the polymer type employed, the polymer viscosity, the particle sizes of the polymer and/or the active ingredient(s), the ratio of the active ingredient(s) versus the polymer, and other excipients or carriers in the compositions.

[00211] The pharmaceutical compositions provided herein in a modified release dosage form can be prepared by methods known to those skilled in the art, including direct compression, dry or wet granulation followed by compression, and melt-granulation followed by compression.

2. Osmotic Controlled Release Devices

[00212] The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated using an osmotic controlled release device, including, but not limited to, one-chamber system, two-chamber system, asymmetric membrane technology (AMT), and extruding core system (ECS). In general, such devices have at least two components: (a) a core which contains an active ingredient; and (b) a semipermeable membrane with at least one delivery port, which encapsulates the core. The semipermeable membrane controls the influx of water to the core from an aqueous environment of use so as to cause drug release by extrusion through the delivery port(s).

[00213] In addition to the active ingredient(s), the core of the osmotic device optionally includes an osmotic agent, which creates a driving force for transport of water from the environment of use into the core of the device. One class of osmotic agents is water-swellable hydrophilic polymers, which are also referred to as "osmopolymers" and "hydrogels." Suitable water-swellable hydrophilic polymers as osmotic agents include, but are not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP

copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl, cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

[00214] The other class of osmotic agents is osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-toluenesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

[00215] Osmotic agents of different dissolution rates can be employed to influence how rapidly the active ingredient(s) is initially delivered from the dosage form. For example, amorphous sugars, such as MANNOGEM™ EZ (SPI Pharma, Lewes, DE) can be used to provide faster delivery during the first couple of hours to promptly produce the desired therapeutic effect, and gradually and continually release of the remaining amount to maintain the desired level of therapeutic or prophylactic effect over an extended period of time. In this case, the active ingredient(s) is released at such a rate to replace the amount of the active ingredient metabolized and excreted.

[00216] The core can also include a wide variety of other excipients and carriers as described herein to enhance the performance of the dosage form or to promote stability or processing.

[00217] Materials useful in forming the semipermeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking. Examples of

suitable polymers useful in forming the coating, include plasticized, unplasticized, and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxylated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly(acrylic) acids and esters and poly-(methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00218] Semipermeable membrane can also be a hydrophobic microporous membrane, wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed in U.S. Pat. No. 5,798,119. Such hydrophobic but water-vapor permeable membrane are typically composed of hydrophobic polymers such as polyalkenes, polyethylene, polypropylene, polytetrafluoroethylene, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinylidene fluoride, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00219] The delivery port(s) on the semipermeable membrane can be formed post-coating by mechanical or laser drilling. Delivery port(s) can also be formed in situ by erosion of a plug of water-soluble material or by rupture of a thinner portion of the membrane over an indentation in the core. In addition, delivery ports can be formed during coating process, as in the case of asymmetric membrane coatings of the type disclosed in U.S. Pat. Nos. 5,612,059 and 5,698,220.

[00220] The total amount of the active ingredient(s) released and the release rate can substantially by modulated *via* the thickness and porosity of the semipermeable membrane, the composition of the core, and the number, size, and position of the delivery ports.

[00221] The pharmaceutical compositions in an osmotic controlled-release dosage form can further comprise additional conventional excipients or carriers as described herein

to promote performance or processing of the formulation.

[00222] The osmotic controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art. *See, Remington: The Science and Practice of Pharmacy*, supra; Santus and Baker, *J. Controlled Release* **1995**, *35*, 1-21; Verma *et al.*, *Drug Development and Industrial Pharmacy* **2000**, *26*, 695-708; and Verma *et al.*, *J. Controlled Release* **2002**, *79*, 7-27.

[00223] In certain embodiments, the pharmaceutical compositions provided herein are formulated as AMT controlled-release dosage form, which comprises an asymmetric osmotic membrane that coats a core comprising the active ingredient(s) and other pharmaceutically acceptable excipients or carriers. *See*, U.S. Pat. No. 5,612,059 and International Publ. No. WO 2002/17918. The AMT controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art, including direct compression, dry granulation, wet granulation, and a dip-coating method.

[00224] In certain embodiments, the pharmaceutical compositions provided herein are formulated as ESC controlled-release dosage form, which comprises an osmotic membrane that coats a core comprising the active ingredient(s), a hydroxylethyl cellulose, and other pharmaceutically acceptable excipients or carriers.

3. Multiparticulate Controlled Release Devices

[00225] The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated as a multiparticulate controlled release device, which comprises a multiplicity of particles, granules, or pellets, ranging from about 10 μm to about 3 mm, about 50 μm to about 2.5 mm, or from about 100 μm to about 1 mm in diameter. Such multiparticulates can be made by the processes known to those skilled in the art, including wet-and dry-granulation, extrusion/spheronization, roller-compaction, melt-congealing, and by spray-coating seed cores. *See,* for example, *Multiparticulate Oral Drug Delivery*; Ghebre-Sellassie Ed.; Marcel Dekker: 1994; and *Pharmaceutical Pelletization Technology*; Ghebre-Sellassie Ed.; Marcel Dekker: 1989.

[00226] Other excipients or carriers as described herein can be blended with the pharmaceutical compositions to aid in processing and forming the multiparticulates. The resulting particles can themselves constitute the multiparticulate device or can be coated by

various film-forming materials, such as enteric polymers, water-swellable, and water-soluble polymers. The multiparticulates can be further processed as a capsule or a tablet.

4. Targeted Delivery

[00227] The pharmaceutical compositions provided herein can also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated, including liposome-, resealed erythrocyte-, and antibody-based delivery systems. Examples include, but are not limited to, those disclosed in U.S. Pat. Nos. 5,709,874; 5,759,542; 5,840,674; 5,900,252; 5,972,366; 5,985,307; 6,004,534; 6,039,975; 6,048,736; 6,060,082; 6,071,495; 6,120,751; 6,131,570; 6,139,865; 6,253,872; 6,271,359; 6,274,552; 6,316,652; and 7,169,410.

Methods of Use

[00228] In one embodiment, provided herein are methods for treating or preventing a hepatitis C viral infection in a subject, which comprises administering to a subject a therapeutically effective amount of a compound provided herein, *e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In one embodiment, the subject is a mammal. In another embodiment, the subject is a human.

[00229] As used herein, the term "hepatitis C virus" or "HCV" refers to a viral species or a genetic variation thereof, a pathogenic strain of which causes hepatitis C. Examples of HCV include, but are not limited to, HCV genotypes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11, and subtype 1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4a, 4b, 4c, 4d, 4e, 5a, 6a, 7a, 7b, 8a, 8b, 9a, 10a, and 11a.

[00230] In one embodiment, the hepatitis C viral infection is caused by HCV genotype 1. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 1a. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 1b. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 1c.

[00231] In another embodiment, the hepatitis C viral infection is caused by HCV genotype 2. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 2a. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype

2b. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 2c.

[00232] In yet another embodiment, the hepatitis C viral infection is caused by HCV genotype 3. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 3a. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 3b.

[00233] In yet another embodiment, the hepatitis C viral infection is caused by HCV genotype 4. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 4a. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 4b. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 4c. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 4d. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 4e.

[00234] In yet another embodiment, the hepatitis C viral infection is caused by HCV genotype 5. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 5a.

[00235] In yet another embodiment, the hepatitis C viral infection is caused by HCV genotype 6. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 6a.

[00236] In yet another embodiment, the hepatitis C viral infection is caused by HCV genotype 7. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 7a. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 7b.

[00237] In yet another embodiment, the hepatitis C viral infection is caused by HCV genotype 8. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 8a. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 8b.

[00238] In yet another embodiment, the hepatitis C viral infection is caused by HCV genotype 9. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 9a.

[00239] In yet another embodiment, the hepatitis C viral infection is caused by HCV

genotype 10. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 10a.

[00240] In still another embodiment, the hepatitis C viral infection is caused by HCV genotype 11. In certain embodiments, the hepatitis C viral infection is caused by HCV subtype 11a.

[00241] In another embodiment, provided herein is a method for inhibiting replication of a virus in a host, which comprises contacting the host with a therapeutically effective amount of a compound provided herein, *e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In one embodiment, the host is a cell. In another embodiment, the host is a human cell. In yet another embodiment, the host is a mammal. In still another embodiment, the host is human.

[00242] In certain embodiments, administration of a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof) results in a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99% or more reduction in the replication of the virus relative to a subject without administration of the compound, as determined at 1 day, 2 days, 3 days, 4 days, 5 days, 10 days, 15 days, or 30 days after the administration by a method known in the art, *e.g.*, determination of viral titer.

[00243] In certain embodiments, administration of a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof) results in a 1, 2, 3, 4, 5, 10, 15, 20, 25, 50, 75, 100-fold or more reduction in the replication of the virus relative to a subject without administration of the compound, as determined at 1 day, 2 days, 3 days, 4 days, 5 days, 10 days, 15 days, or 30 days after the administration by a method known in the art.

[00244] In certain embodiments, administration of a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof) results in a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99% or more reduction in the viral titer relative to a subject without administration of the compound, as determined at 1 day, 2 days, 3 days, 4 days, 5 days, 10 days, 15 days, or 30 days after the administration by a method

known in the art.

[00245] In certain embodiments, administration of a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof) results in a 1, 2, 3, 4, 5, 10, 15, 20, 25, 50, 75, 100 or more fold reduction in the viral titer relative to a subject without administration of the compound, as determined at 1 day, 2 days, 3 days, 4 days, 5 days, 10 days, 15 days, or 30 days after the administration by a method known in the art.

[00246] In yet another embodiment, provided herein is a method for inhibiting the replication of an HCV virus, which comprises contacting the virus with a therapeutically effective amount of a compound provided herein, *e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00247] In certain embodiments, the contacting of the virus with a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof) results in a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99% or more reduction in the virus titer relative to the virus without such contact, as determined at 1 day, 2 days, 3 days, 4 days, 5 days, 10 days, 15 days, or 30 days after the initial contact, by a method known in the art.

[00248] In certain embodiments, the contacting of the virus with a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof) results in a 1, 2, 3, 4, 5, 10, 15, 20, 25, 50, 75, 100 or more fold reduction in the viral titer relative to the virus without such contact, as determined at 1 day, 2 days, 3 days, 4 days, 5 days, 10 days, 15 days, or 30 days after the initial contact, by a method known in the art.

[00249] In one embodiment, the virus is a hepatitis C virus. In another embodiment, the virus is HCV genotype 1. In one embodiment, the virus is HCV subtype 1a. In yet certain embodiments, the virus is HCV subtype 1b. In certain embodiments, the virus is HCV subtype 1c.

[00250] In another embodiment, the virus is HCV genotype 2. In certain embodiments, the virus is HCV subtype 2a. In certain embodiments, the virus is HCV subtype 2b. In

certain embodiments, the virus is HCV subtype 2c.

[00251] In yet another embodiment, the virus is HCV genotype 3. In certain embodiments, the virus is HCV subtype 3a. In certain embodiments, the virus is HCV subtype 3b.

[00252] In yet another embodiment, the virus is HCV genotype 4. In certain embodiments, the virus is HCV subtype 4a. In certain embodiments, the virus is HCV subtype 4b. In certain embodiments, the virus is HCV subtype 4c. In certain embodiments, the virus is HCV subtype 4e.

[00253] In yet another embodiment, the virus is HCV genotype 5. In certain embodiments, the virus is HCV subtype 5a.

[00254] In yet another embodiment, the virus is HCV genotype 6. In certain embodiments, the virus is HCV subtype 6a.

[00255] In yet another embodiment, the virus is HCV genotype 7. In certain embodiments, the virus is HCV subtype 7a. In certain embodiments, the virus is HCV subtype 7b.

[00256] In yet another embodiment, the virus is HCV genotype 8. In certain embodiments, the virus is HCV subtype 8a. In certain embodiments, the virus is HCV subtype 8b.

[00257] In yet another embodiment, the virus is HCV genotype 9. In certain embodiments, the virus is HCV subtype 9a.

[00258] In yet another embodiment, the virus is HCV genotype 10. In certain embodiments, the virus is HCV subtype 10a.

[00259] In still another embodiment, the virus is HCV genotype 11. In certain embodiments, the virus is HCV subtype 11a.

[00260] In yet another embodiment, provided herein is a method for treating, preventing, or ameliorating one or more symptoms of a liver disease or disorder associated with an HCV infection, comprising administering to a subject a therapeutically effective amount of the compound provided herein, *e.g.*, a compound of Formula I, including an

isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof. Non-limiting examples of diseases associated with HCV infection include chronic hepatitis, cirrhosis, hepatocarcinoma, or extra hepatic manifestation.

[00261] In still another embodiment, provided herein is a method for inhibiting the activity of a serine protease, which comprises contacting the serine protease with an effective amount of a compound provided herein, *e.g.*, a compound of Formula I, including an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In one embodiment, the serine protease is hepatitis C NS3 protease. In another embodiment, the serine protease is HCV protease. In yet another embodiment, the serine protease is HCV NS3/4A protease.

[00262] In one embodiment, the HCV protease is genotype 1 NS3/4A protease. In certain embodiments, the HCV protease is subtype 1a NS3/4A protease. In certain embodiments, the HCV protease is subtype 1b NS3/4A protease. In certain embodiments, the HCV protease is subtype 1c NS3/4A protease.

[00263] In another embodiment, the HCV protease is genotype 2 NS3/4A protease. In certain embodiments, the HCV protease is subtype 2a NS3/4A protease. In certain embodiments, the HCV protease is subtype 2b NS3/4A protease. In certain embodiments, the HCV protease is subtype 2c NS3/4A protease.

[00264] In yet another embodiment, the HCV protease is genotype 3 NS3/4A protease. In certain embodiments, the HCV protease is subtype 3a NS3/4A protease. In certain embodiments, the HCV protease is genotype 3b NS3/4A protease.

[00265] In yet another embodiment, the HCV protease is genotype 4 NS3/4A protease. In certain embodiments, the HCV protease is subtype 4a NS3/4A protease. In certain embodiments, the HCV protease is genotype 4b NS3/4A protease. In certain embodiments, the HCV protease is subtype 4c NS3/4A protease. In certain embodiments, the HCV protease is genotype 4d NS3/4A protease.

[00266] In yet another embodiment, the HCV protease is genotype 5 NS3/4A protease. In certain embodiments, the HCV protease is subtype 5a NS3/4A protease.

[00267] In yet another embodiment, the HCV protease is genotype 6 NS3/4A protease.

In certain embodiments, the HCV protease is subtype 6a NS3/4A protease.

[00268] In yet another embodiment, the HCV protease is genotype 7 NS3/4A protease. In certain embodiments, the HCV protease is subtype 7a NS3/4A protease. In certain embodiments, the HCV protease is genotype b NS3/4A protease.

[00269] In yet another embodiment, the HCV protease is genotype 8 NS3/4A protease. In certain embodiments, the HCV protease is subtype 8a NS3/4A protease. In certain embodiments, the HCV protease is genotype 8b NS3/4A protease.

[00270] In yet another embodiment, the HCV protease is genotype 9 NS3/4A protease. In certain embodiments, the HCV protease is subtype 9a NS3/4A protease.

[00271] In yet another embodiment, the HCV protease is genotype 10 NS3/4A protease. In certain embodiments, the HCV protease is subtype 10a NS3/4A protease.

[00272] In yet another embodiment, the HCV protease is genotype 11 NS3/4A protease. In certain embodiments, the HCV protease is subtype 11a NS3/4A protease.

[00273] Depending on the condition, disorder, or disease, to be treated and the subject's condition, a compound provided herein may be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, intracerebroventricular (ICV), intracistemal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (*e.g.*, transdermal or local) routes of administration, and may be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

[00274] The dose may be in the form of one, two, three, four, five, six, or more sub-doses that are administered at appropriate intervals per day. The dose or sub-doses can be administered in the form of dosage units containing from about 0.1 to about 1,000 milligram, from about 0.1 to about 500 milligrams, or from 0.5 about to about 100 milligram active ingredient(s) per dosage unit, and if the condition of the patient requires, the dose can, by way of alternative, be administered as a continuous infusion.

[00275] In certain embodiments, an appropriate dosage level is about 0.01 to about 100 mg per kg patient body weight per day (mg/kg per day), about 0.01 to about 50 mg/kg per day, about 0.01 to about 25 mg/kg per day, or about 0.05 to about 10 mg/kg per day, which

may be administered in single or multiple doses. A suitable dosage level may be about 0.01 to about 100 mg/kg per day, about 0.05 to about 50 mg/kg per day, or about 0.1 to about 10 mg/kg per day. Within this range the dosage may be about 0.01 to about 0.1, about 0.1 to about 1.0, about 1.0 to about 10, or about 10 to about 50 mg/kg per day.

Combination Therapy

[00276] The compounds provided herein may also be combined or used in combination with other therapeutic agents useful in the treatment and/or prevention of an HCV infection.

[00277] As used herein, the term "in combination" includes the use of more than one therapy (*e.g.*, one or more prophylactic and/or therapeutic agents). However, the use of the term "in combination" does not restrict the order in which therapies (*e.g.*, prophylactic and/or therapeutic agents) are administered to a subject with a disease or disorder. A first therapy (*e.g.*, a prophylactic or therapeutic agent such as a compound provided herein) can be administered prior to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy (*e.g.*, a prophylactic or therapeutic agent) to the subject. Triple therapy is also contemplated herein.

[00278] As used herein, the term "synergistic" includes a combination of a compound provided herein and another therapy (*e.g.*, a prophylactic or therapeutic agent) which has been or is currently being used to prevent, treat, or manage a condition, disorder, or disease, which is more effective than the additive effects of the therapies. A synergistic effect of a combination of therapies (*e.g.*, a combination of prophylactic or therapeutic agents) permits the use of lower dosages of one or more of the therapies and/or less frequent administration of said therapies to a subject with a condition, disorder, or disease. The ability to utilize lower dosages of a therapy (*e.g.*, a prophylactic or therapeutic agent) and/or to administer said therapy less frequently reduces the toxicity associated with the administration of said therapy to a subject without reducing the efficacy of said therapy in the prevention, treatment, or management of a condition, disorder, or disease). In addition, a synergistic effect can

result in improved efficacy of agents in the prevention, treatment, or management of a condition, disorder, or disease. Finally, a synergistic effect of a combination of therapies (*e.g.*, a combination of prophylactic or therapeutic agents) may avoid or reduce adverse or unwanted side effects associated with the use of either therapy alone.

[00279] The compound provided herein can be administered in combination or alternation with another therapeutic agent, such as an anti-HCV agent. In combination therapy, effective dosages of two or more agents are administered together, whereas in alternation or sequential-step therapy, an effective dosage of each agent is administered serially or sequentially. The dosages given will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

[00280] It has been recognized that drug-resistant variants of HCV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs due to the mutation of a gene that encodes for an enzyme used in viral replication. The efficacy of a drug against the viral infection can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation from that caused by the principle drug. Alternatively, the pharmacokinetics, biodistribution, or other parameters of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus.

[00281] In certain embodiments, the pharmaceutical compositions provided herein further comprise a second antiviral agent as described herein. In certain embodiments, the compound provided herein is combined with one or more agents selected from the group consisting of an interferon, ribavirin, amantadine, an interleukin, a NS3 protease inhibitor, a cysteine protease inhibitor, a phenanthrenequinone, a thiazolidine, a benzanilide, a helicase inhibitor, a polymerase inhibitor, a nucleotide analogue, a gliotoxin, a cerulenin, an antisense phosphorothioate oligodeoxynucleotide, an inhibitor of IRES-dependent translation, and a ribozyme. In one embodiment, the second antiviral agent is an interferon. In another embodiment, the interferon is selected from the group consisting of pegylated interferon

alpha 2a, interferon alfacon-1, natural interferon, ALBUFERON®, interferon beta-1a, omega interferon, interferon alpha, interferon gamma, interferon tau, interferon delta, and interferon gamma-1b.

[00282] In certain embodiments, the compound provided herein is combined with a HCV protease inhibitor, including, but not limited to, Medivir HCV protease inhibitor (Medivir/Tibotec); ITMN-191 (InterMune); SCH 503034 (Schering); VX950 (Vertex); substrate-based NS3 protease inhibitors as disclosed in DE 19914474, WO 98/17679, WO 98/22496, WO 99/07734, and Attwood *et al.*, *Antiviral Chemistry and Chemotherapy* **1999**, *10*, 259-273; non-substrate-based NS3 protease inhibitors, including 2,4,6-trihydroxy-3-nitro-benzamide derivatives (Sudo *et al.*, *Biochem. Biophys. Res. Commun.* **1997**, *238*, 643-647), a phenanthrenequinone (Chu *et al.*, *Tetrahedron Letters* **1996**, *37*, 7229-7232), RD3-4082, RD3-4078, SCH 68631, and SCH 351633 (Chu *et al.*, *Bioorganic and Medicinal Chemistry Letters* **1999**, *9*, 1949-1952); and Eglin C, a potent serine protease inhibitor (Qasim *et al.*, *Biochemistry* **1997**, *36*, 1598-1607).

[00283] Other suitable protease inhibitors for the treatment of HCV include those disclosed in, for example, U.S. Pat. No. 6,004,933, which discloses a class of cysteine protease inhibitors of HCV endopeptidase 2.

[00284] Additional hepatitis C virus NS3 protease inhibitors include those disclosed in, for example, Llinàs-Brunet *et al.*, *Bioorg. Med. Chem. Lett.* **1998**, *8,* 1713-1718; Steinkühler *et al.*, *Biochemistry* **1998**, *37*, 8899-8905; U.S. Pat. Nos.: 5,538,865; 5,990,276; 6,143,715; 6,265,380; 6,323,180; 6,329,379; 6,410,531; 6,420,380; 6,534,523; 6,608,027; 6,642,204; 6,653,295; 6,727,366; 6,838,475; 6,846,802; 6,867,185; 6,869,964; 6,872,805; 6,878,722; 6,908,901; 6,911,428; 6,995,174; 7,012,066; 7,041,698; 7,091,184; 7,169,760; 7,176,208; 7,208,600; and 7,491,794; U.S. Pat. Appl. Publ. Nos.: 2002/0016294, 2002/0016442; 2002/0032175; 2002/0037998; 2004/0229777; 2005/0090450; 2005/0153877; 2005/176648; 2006/0046956; 2007/0021330; 2007/0021351; 2007/0049536; 2007/0054842; 2007/0060510; 2007/0060565; 2007/0072809; 2007/0078081; 2007/0078122; 2007/0093414; 2007/0093430; 2007/0099825; 2007/0099929; 2007/0105781, 2008/0152622, 2009/0035271, 2009/0035272, 2009/0111969, 2009/0111982, 2009/0123425, 2009/0130059, 2009/148407, 2009/0156800, 2009/0169510, 2009/0175822, and 2009/0180981; and International Pat. Appl. Publ. Nos.: WO 98/17679; WO 98/22496; WO 99/07734; WO 00/09543; WO 00/59929; WO 02/08187; WO 02/08251; WO 02/08256; WO 02/08198; WO 02/48116; WO 02/48157; WO 02/48172;

WO 02/60926; WO 03/53349; WO 03/64416; WO 03/64455; WO 03/64456; WO 03/66103; WO 03/99274; WO 03/99316; WO 2004/032827; WO 2004/043339; WO 2005/037214; WO 2005/037860; WO 2006/000085; WO 2006/119061; WO 2006/122188; WO 2007/001406; WO 2007/014925; WO 2007/014926; WO 2007/015824, WO 2007/056120, WO 2008/019289, WO 2008/021960, WO 2008/022006, WO 2009/053828, WO 2009/058856, WO 2009/073713, WO 2009/073780, WO 2009/080542, WO 2009/082701, WO 2009/082697, WO 2009/085978, and WO 2008/086161; the disclosure of each of which is incorporated herein by reference in its entirety.

[00285] Other protease inhibitors include thiazolidine derivatives, such as RD-1-6250, RD4 6205, and RD4 6193, which show relevant inhibition in a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate (Sudo *et al.*, *Antiviral Research* **1996**, *32*, 9-18); and thiazolidines and benzanilides identified in Kakiuchi *et al.*, *FEBS Lett.* **1998**, *421*, 217-220; and Takeshita *et al.*, *Analytical Biochemistry* **1997**, *247*, 242-246.

[00286] Suitable helicase inhibitors include, but are not limited to, those disclosed in U.S. Pat. No. 5,633,358; and International Pat. Appl. Publ. No. WO 97/36554.

[00287] Suitable nucleotide polymerase inhibitors include, but are not limited to, gliotoxin (Ferrari *et al.*, *Journal of Virology* **1999**, *73*, 1649-1654) and cerulenin (Lohmann *et al.*, *Virology* **1998**, *249*, 108-118).

[00288] Suitable interfering RNA (iRNA) based antivirals include, but are not limited to, short interfering RNA (siRNA) based antivirals, such as Sirna-034 and those described in International Pat. Appl. Publ. Nos.WO/03/070750 and WO 2005/012525, and U.S. Pat. Appl. Publ. No. 2004/0209831.

[00289] Suitable antisense phosphorothioate oligodeoxynucleotides (S-ODN) complementary to sequence stretches in the 5' non-coding region (NCR) of HCV virus include, but are not limited to those described in Alt *et al.*, *Hepatology* **1995**, *22*, 707-717, and nucleotides 326-348 comprising the 3' end of the NCR and nucleotides 371-388 located in the core coding region of HCV RNA (Alt *et al.*, *Archives of Virology* **1997**, *142*, 589-599; and Galderisi *et al.*, *Journal of Cellular Physiology* **1999**, *181*, 251-257);

[00290] Suitable inhibitors of IRES-dependent translation include, but are not limited to, those described in Japanese Pat. Appl. Publ. Nos.: JP 08268890 and JP 10101591.

[00291] Suitable ribozymes include those disclosed in, for example, U.S. Pat. Nos. 6,043,077; 5,869,253; and 5,610,054.

[00292] Suitable nucleoside analogs include, but are not limited to, the compounds described in U.S. Pat. Nos.: 6,660,721; 6,777,395; 6,784,166; 6,846,810; 6,927,291; 7,094,770; 7,105,499; 7,125,855; and 7,202,224; U.S. Pat. Appl. Publ. Nos. 2004/0121980; 2005/0009737; 2005/0038240; and 2006/0040890; and International Pat. Appl. Publ. Nos: WO 99/43691; WO 01/32153; WO 01/60315; WO 01/79246; WO 01/90121, WO 01/92282, WO 02/18404; WO 02/32920, WO 02/48165, WO 02/057425; WO 02/057287; WO 2004/002422, WO 2004/002999, and WO 2004/003000.

[00293] Other miscellaneous compounds that can be used as second agents include, for example, 1-amino-alkylcyclohexanes (U.S. Pat. No. 6,034,134), alkyl lipids (U.S. Pat. No. 5,922,757), vitamin E and other antioxidants (U.S. Pat. No. 5,922,757), squalene, amantadine, bile acids (U.S. Pat. No. 5,846,964), N-(phosphonacetyl)-L-aspartic acid (U.S. Pat. No. 5,830,905), benzenedicarboxamides (U.S. Pat. No. 5,633,388), polyadenylic acid derivatives (U.S. Pat. No. 5,496,546), 2',3'-dideoxyinosine (U.S. Pat. No. 5,026,687), benzimidazoles (U.S. Pat. No. 5,891,874), plant extracts (U.S. Pat. Nos. 5,725,859; 5,837,257; and 6,056,961), and piperidines (U.S. Pat. No. 5,830,905).

[00294] In certain embodiments, one or more compounds provided herein are administered in combination or alternation with an anti-hepatitis C virus interferon, including, but not limited to, INTRON® A (interferon alfa-2b), PEGASYS® (Peginterferon alfa-2a) ROFERON® A (recombinant interferon alfa-2a), INFERGEN® (interferon alfacon-1), and PEG-INTRON® (pegylated interferon alfa-2b). In one embodiment, the anti-hepatitis C virus interferon is INFERGEN®, IL-29 (PEG-Interferon lambda), R7025 (Maxy-alpha), BELEROFON®, oral interferon alpha, BLX-883 (LOCTERON®), omega interferon, MULTIFERON®, medusa interferon, ALBUFERON®, or REBIF®.

[00295] In certain embodiments, one or more compounds provided herein are administered in combination or alternation with an anti-hepatitis C virus polymerase inhibitor, such as ribavirin, viramidine, NM 283 (valopicitabine), PSI-6130, R1626, HCV-796, and R7128.

[00296] In certain embodiments, the one or more compounds provided herein are administered in combination with ribavirin and an anti-hepatitis C virus interferon, such as

INTRON® A (interferon alfa-2b), PEGASYS® (Peginterferon alfa-2a), ROFERON® A (recombinant interferon alfa-2a), INFERGEN® (interferon alfacon-1), and PEG-INTRON® (pegylated interferon alfa-2b),

[00297] In certain embodiments, one or more compounds provided herein are administered in combination or alternation with an anti-hepatitis C virus protease inhibitor, such as ITMN-191, SCH 503034, VX950 (telaprevir), and Medivir HCV protease inhibitor.

[00298] In certain embodiments, one or more compounds provided herein are administered in combination or alternation with an anti-hepatitis C virus vaccine, including, but not limited to, TG4040, PEVIPRO™, CGI-5005, HCV/MF59, GV1001, IC41, and INNO0101 (E1).

[00299] In certain embodiments, one or more compounds provided herein are administered in combination or alternation with an anti-hepatitis C virus monoclonal antibody, such as AB68 and XTL-6865 (formerly HepX-C); or an anti-hepatitis C virus polyclonal antibody, such as cicavir.

[00300] In certain embodiments, one or more compounds provided herein are administered in combination or alternation with an anti-hepatitis C virus immunomodulator, such as ZADAXIN® (thymalfasin), NOV-205, and oglufanide.

[00301] In certain embodiments, one or more compounds provided herein are administered in combination or alternation with NEXAVAR®, doxorubicin, PI-88, amantadine, JBK-122, VGX-410C, MX-3253 (celgosivir), SUVUS® (BIVN-401 or virostat), PF-03491390 (formerly IDN-6556), G126270, UT-231B, DEBIO-025, EMZ702, ACH-0137171, MitoQ, ANA975, AVI-4065, bavituximab (tarvacin), ALINIA® (nitrazoxanide), and PYN17.

[00302] The compounds provided herein can also be administered in combination with other classes of compounds, including, but not limited to, (1) alpha-adrenergic agents; (2) antiarrhythmic agents; (3) anti-atherosclerotic agents, such as ACAT inhibitors; (4) antibiotics, such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; (5) anticancer agents and cytotoxic agents, *e.g.*, alkylating agents, such as nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazenes; (6) anticoagulants, such as acenocoumarol, argatroban, bivalirudin, lepirudin, fondaparinux, heparin, phenindione,

warfarin, and ximelagatran; (7) anti-diabetic agents, such as biguanides (*e.g.*, metformin), glucosidase inhibitors (*e.g.*, acarbose), insulins, meglitinides (*e.g.*, repaglinide), sulfonylureas (*e.g.*, glimepiride, glyburide, and glipizide), thiozolidinediones (*e.g.*, troglitazone, rosiglitazone, and pioglitazone), and PPAR-gamma agonists; (8) antifungal agents, such as amorolfine, amphotericin B, anidulafungin, bifonazole, butenafine, butoconazole, caspofungin, ciclopirox, clotrimazole, econazole, fenticonazole, filipin, fluconazole, isoconazole, itraconazole, ketoconazole, micafungin, miconazole, naftifine, natamycin, nystatin, oxyconazole, ravuconazole, posaconazole, rimocidin, sertaconazole, sulconazole, terbinafine, terconazole, tioconazole, and voriconazole; (9) antiinflammatories, *e.g.*, non-steroidal anti-inflammatory agents, such as aceclofenac, acemetacin, amoxiprin, aspirin, azapropazone, benorilate, bromfenac, carprofen, celecoxib, choline magnesium salicylate, diclofenac, diflunisal, etodolac, etoricoxib, faislamine, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, ketorolac, lornoxicam, loxoprofen, lumiracoxib, meclofenamic acid, mefenamic acid, meloxicam, metamizole, methyl salicylate, magnesium salicylate, nabumetone, naproxen, nimesulide, oxyphenbutazone, parecoxib, phenylbutazone, piroxicam, salicyl salicylate, sulindac, sulfinpyrazone, suprofen, tenoxicam, tiaprofenic acid, and tolmetin; (10) antimetabolites, such as folate antagonists, purine analogues, and pyrimidine analogues; (11) anti-platelet agents, such as GPIIb/IIIa blockers (*e.g.*, abciximab, eptifibatide, and tirofiban), P2Y(AC) antagonists (*e.g.*, clopidogrel, ticlopidine and CS-747), cilostazol, dipyridamole, and aspirin; (12) antiproliferatives, such as methotrexate, FK506 (tacrolimus), and mycophenolate mofetil; (13) anti-TNF antibodies or soluble TNF receptor, such as etanercept, rapamycin, and leflunimide; (14) aP2 inhibitors; (15) beta-adrenergic agents, such as carvedilol and metoprolol; (16) bile acid sequestrants, such as questran; (17) calcium channel blockers, such as amlodipine besylate; (18) chemotherapeutic agents; (19) cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib and rofecoxib; (20) cyclosporins; (21) cytotoxic drugs, such as azathioprine and cyclophosphamide; (22) diuretics, such as chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzothiazide, ethacrynic acid, ticrynafen, chlorthalidone, furosenide, muzolimine, bumetanide, triamterene, amiloride, and spironolactone; (23) endothelin converting enzyme (ECE) inhibitors, such as phosphoramidon; (24) enzymes, such as L-asparaginase; (25) Factor VIIa Inhibitors and Factor Xa Inhibitors; (26) farnesyl-protein transferase inhibitors; (27) fibrates; (28) growth factor inhibitors, such as modulators of PDGF activity; (29) growth hormone secretagogues; (30) HMG CoA reductase inhibitors, such as pravastatin, lovastatin, atorvastatin, simvastatin,

NK-104 (a.k.a. itavastatin, nisvastatin, or nisbastatin), and ZD-4522 (also known as rosuvastatin, atavastatin, or visastatin); neutral endopeptidase (NEP) inhibitors; (31) hormonal agents, such as glucocorticoids (*e.g.*, cortisone), estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing hormone-releasing hormone antagonists, and octreotide acetate; (32) immunosuppressants; (33) mineralocorticoid receptor antagonists, such as spironolactone and eplerenone; (34) microtubule-disruptor agents, such as ecteinascidins; (35) microtubule-stabilizing agents, such as pacitaxel, docetaxel, and epothilones A-F; (36) MTP Inhibitors; (37) niacin; (38) phosphodiesterase inhibitors, such as PDE III inhibitors (*e.g.*, cilostazol) and PDE V inhibitors (*e.g.*, sildenafil, tadalafil, and vardenafil); (39) plant-derived products, such as vinca alkaloids, epipodophyllotoxins, and taxanes; (40) platelet activating factor (PAF) antagonists; (41) platinum coordination complexes, such as cisplatin, satraplatin, and carboplatin; (42) potassium channel openers; (43) prenyl-protein transferase inhibitors; (44) protein tyrosine kinase inhibitors; (45) renin inhibitors; (46) squalene synthetase inhibitors; (47) steroids, such as aldosterone, beclometasone, betamethasone, deoxycorticosterone acetate, fludrocortisone, hydrocortisone (cortisol), prednisolone, prednisone, methylprednisolone, dexamethasone, and triamcinolone; (48) TNF-alpha inhibitors, such as tenidap; (49) thrombin inhibitors, such as hirudin; (50) thrombolytic agents, such as anistreplase, reteplase, tenecteplase, tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prourokinase, and anisoylated plasminogen streptokinase activator complex (APSAC); (51) thromboxane receptor antagonists, such as ifetroban; (52) topoisomerase inhibitors; (53) vasopeptidase inhibitors (dual NEP-ACE inhibitors), such as omapatrilat and gemopatrilat; and (54) other miscellaneous agents, such as, hydroxyurea, procarbazine, mitotane, hexamethylmelamine, and gold compounds.

[00303] The compounds provided herein can also be provided as an article of manufacture using packaging materials well known to those of skill in the art. *See*, *e.g.*, U.S. Pat. Nos. 5,323,907; 5,052,558; and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

[00304] Provided herein also are kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a subject. In

certain embodiments, the kit provided herein includes a container and a dosage form of a compound provided herein, including a single enantiomer, a racemic mixture, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00305] In certain embodiments, the kit includes a container comprising a dosage form of the compound provided herein, including a single enantiomer, a racemic mixture, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in a container comprising one or more other therapeutic agent(s) described herein.

[00306] Kits provided herein can further include devices that are used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, needle-less injectors drip bags, patches, and inhalers. The kits provided herein can also include condoms for administration of the active ingredients.

[00307] Kits provided herein can further include pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: aqueous vehicles, including, but not limited to, Water for Injection USP, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles, including, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles, including, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[00308] The disclosure will be further understood by the following non-limiting examples.

EXAMPLES

[00309] As used herein, the symbols and conventions used in these processes, schemes and examples, regardless of whether a particular abbreviation is specifically defined, are

consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Specifically, but without limitation, the following abbreviations may be used in the examples and throughout the specification: g (grams); mg (milligrams); mL (milliliters); μL (microliters); L (liter); mM (millimolar); μM (micromolar); Hz (Hertz); MHz (megahertz); mmol (millimoles); eq. (equivalent); hr or hrs (hours); min (minutes); MS (mass spectrometry); NMR (nuclear magnetic resonance); ESI (electrospray ionization); ACN (acetonitrile); $CDCl_3$ (deuterated chloroform); DCM (dichloromethane); DMF (*N*,*N*-dimethylformamide); DMSO (dimethylsulfoxide); DMSO-d_6 (deuterated dimethylsulfoxide); EtOAc (ethyl acetate); EtOH (ethanol); Et_2O (diethylether); MeOH (methanol); PE (petrolium ether); TBDME (tert-butyldimethylether); THF (tetrahydrofuran); DIPEA (*N*,*N*-diisopropylethylamine); TEA (triethylamine); DBU (1,8-diazabicyclo[5.4.0]undec-7-ene); DMAP (4-dimethylaminopyridine); AIBN (1,1'-azobis(cyclohexanecarbonitrile); CDI (carbonyldiimidazole); EDCI or EDC (*N'*-ethyl-*N*-(3-dimethylaminopropyl)-carbodiimide); TBTU (O-(benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate); Me (methyl); Et (ethyl); *i*Pr (isopropyl); *t*Bu (*tert*-butyl); Boc (*tert*-butoxylcarbony); Cbz (benzylcarbomate); Fmoc (9-fluorenylmethyl carbomate); Bn (benzyl); PMB (*para*-methoxy benzyl); Bs (4-bromo-benzenesulfonyl); TMS (trimethylsilyl); TsOH (tosylic acid); TsO (tosylate); DEAD (diethylazodicarboxylate), DIAD (diisopropylazodicarboxylate); PPh_3 (triphenylphosphine); AcCl (acetyl chloride); TFA (trifluoroacetic acid); TBAF (tetra-*n*-butylammonium fluoride); tBuOK (potassium *tert*-butoxide); TBDPSCl (*tert*-butyl diphenylchlorosilane); and Zhan IB catalyst ((1,3-dimesitylimidazolidin-2-yl)(5-(*N*,*N*-dimethylsulfamoyl)-2-isopropoxybenzylidene)-ruthenium(V) chloride).

[00310] For all of the following examples, standard work-up and purification methods known to those skilled in the art can be utilized. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions conducted at room temperature unless otherwise noted. Synthetic methodologies herein are intended to exemplify the applicable chemistry through the use of specific examples and are not indicative of the scope of the disclosure.

[00311] The starting materials used in the examples described herein are either commercially available or can be prepared by a method known to one of skill in the art. For example, the starting materials, *N*-methylhex-5-en-1-amine tosylate salt, (1*R*,2*S*)-methyl 1-

amino-2-vinylcyclopropanecarboxylate, and methyl-cyclopropylsulfonamide, were made according the procedures as described in U.S. Appl. Publ. Nos. 2009/0202480; and 2010/0260710; and U.S. Appl. Serial No. 12/850,534; the disclosure of each of which is incorporated herein by reference in its entirety.

Example A

HCV Protease Assay

[00312] *General procedure:* Measurement of the inhibitory effect of compounds on HCV protease activity was performed using the HiLyte Fluor™ TR/QXL™ 610 FRET peptide from AnaSpec, Inc. (San Jose, CA) under conditions developed in-house using 2-3 nM HCV NS3-NS4A protease, which was produced according to the method of Taremi *et al.* (*Protein Science,* **1998**, *7*, 2143-2149). The compounds were tested at a variety of concentrations in assay buffer containing a final DMSO concentration of 5%. Reactions were allowed to proceed for 60 min at 30° C and fluorescence measurements were recorded with a PerkinElmer Victor^3 V 1420 Multilabel Counter. The IC_{50} values were determined from the percent inhibition versus concentration data using a sigmoidal non-linear regression analysis based on four parameters with XLfit 4.1 software.

Example B

HCV Replicon Assay

[00313] *General procedure:* The HCV luciferase replicon assay measures the ability of a test compound to inhibit HCV replication in cell culture after 3 days of treatment in a human hepatoma cell line (Huh-7) bearing a HCV replicon containing a luciferase-neomycin phosphotransferase fusion gene. The inhibition of HCV replication was measured by quantification of luciferase protein expression. Briefly, Huh-7 cells containing either the HCV genotype 1a H77 strain or genotype 1b Con1 strain subgenomic luciferase replicon (H1a-luc or Zluc, respectively) were grown in DMEM containing glucose, L-glutamine and sodium pyruvate, 10% fetal bovine serum (FBS), 100 IU/mL penicillin, 100 µg/mL streptomycin, 2 mM GlutaMAX, non-essential amino acids and 0.25 (H1a-luc) or 0.5 (Zluc) mg/mL G418. GlutaMAX was obtained from Invitrogen, Corp.; all other media reagents were obtained from Mediatech, Inc. For dose-response testing, the cells were seeded in 96-well plates at 1 x 10^4 (H1a-luc) or 7.5 x 10^3 (Zluc) cells/well in a volume of 50 µL, and incubated at 37 °C/5% CO_2. Three hours after plating, 50 µL of ten 5-fold serial dilutions of

compound were added, and cell cultures were incubated at 37 °C/5% CO_2 for 72 hours. In all cases, Huh-7 cells lacking the HCV replicon served as negative control. To assess luciferase expression, the media/compound was removed from the plates and ONE-glo Luciferase assay reagent (Promega) was added to each well. The assay plates were shaken for 3 minutes at room temperature and luciferase activity for each well was measured with a 1 sec read time on the Victor^{3}V multilabel counter using a 700 nm cut-off filter (Perkin Elmer). EC_{50} values were calculated from dose response curves from the resulting best-fit equations determined by Microsoft Excel and XLfit 4.1 software.

[00314] For cytotoxicity evaluation, Zluc cells were treated with compounds as described above and cellular viability was monitored using the Cell Titer 96 AQueous One Solution Cell Proliferation Assay (Promega). Plates were then read at 490 nm in a Victor^{3}V 1420 multilabel counter (Perkin Elmer) and CC_{50} concentrations were determined using Microsoft Excel and XLfit 4.1 software.

[00315] The biological results are summarized in Tables 1 and 2, wherein A represents a value smaller than 10 nM, B represents a value between 10 nM to 100 nM, C represents a value between 100 nM to 1 μM, D represents a value between 1 μM to 10 μM, and E represents a value greater than 10 μM.

[00316] In Table 1, the values of FS with 45% HS were determined using the genotype 1b HCV replicon luciferase screening assay using Zluc cells, except that activity in the presence of 10% fetal calf serum (FCS) or 45% human serum (HS) was determined in parallel. The fold shift (FS) with 45% HS is the EC_{50} value in the presence of 45% HS divided by the EC_{50} value in the presence of 10% FCS. FS (1a/1b) is the EC_{50} value against genotype 1a HCV divided by the EC_{50} value against the genotype 1b in the replicon luciferase screening assay.

[00317] In Table 2, fold shift was obtained using the transient transfection assay, where the activity of a compound against a mutated replicon was compared to a wild-type replicon. The FS against a mutant is the EC_{50} value against the mutant replicon divided by the EC_{50} value against the wild-type replicon.

TABLE 1

Cmpd	IC_{50} Against HS3/4A							EC_{50} Against Relpicon			CC_{50}	FS with 45% HS
	1a	1b	2a	3a	4a	5a	6a	1a	1b	FS (1a/1b)		
17a	A	A	A	B	A	A	A	A	A	8	E	29
17b	A	A	A	C	A	A	A	A	A	6	E	80
A101	A	A	B	>C	A	B	A	B	A	6	E	>40
C101	A	A	A	A	A	A	A	A	A	7	E	16
C102		A		A				A	A	5	E	
C103		A		A				A	A	6	E	
C104		A		B				A	A	5	E	
D101		B		>B				D	B	147	E	
D103		B		>B				D	B	113	E	
D104		B		>B				E	B	188	E	

TABLE 2. Activity Against Genotype 1b NS3 Mutant Replicons

Cmpd	Fold shift from wild-type						
	V36M	T54A	Q80R	R155K	A156T	D168E	D168V
17a	2.4	1.5	2.4	5.9	22.7	22.3	1762
17b	2.3	0.9	2.3	9.8	42.2	40	3398
A101	2.4	1.1	0.8	15.7	52.8	38.4	2,756
C101	2.3	0.8	3.3	162.4	3.3	14.5	68.6

Example C

HCV in vitro Infection Core ELISA Assay

[00318] *Generation of Recombinant JFH-1 Virus Stocks*: The recombinant JFH-1 HCV virus used in the HCV *in vitro* infection assay was generated by transfection of HPC cells with JFH-1 RNA produced by *in vitro* transcription. The JFH-1 DNA template was derived synthetically using sequence information derived from NCBI Accession # AB047639 (Wakita, *et al.*, *Nat. Med.* **2005**, 11:791-796). Source: DNA2.0, Menlo Park, CA. The

cDNA for the JFH-1 HCV clone was synthesized by DNA2.0 and contains a T7 promoter to drive the transcription of the JFH-1 genomic RNA. This plasmid was amplified using the Hi-Speed Plasmid Midi kit (Qiagen) according to the manufacturer's instructions. Thirty micrograms of purified DNA was digested overnight at 37 °C with 300 U XbaI. The digested DNA served as a template for the *in vitro* transcription of the JFH-1 genomic RNA using the MEGAScript T7 kit (Ambion) as instructed by the manufacturer. The JFH-1 RNA product was resuspended to 1 μg/μL in RNA storage solution (Ambion). The quality of the JFH-1 RNA was verified by agarose gel electrophoresis (1.2% E-gel) prior to electroporation.

[00319] Complete growth media for Huh-7 and HPC cells (Huh-7 media) was prepared as follows: DMEM (containing glucose, L-glutamine and sodium pyruvate), 10% FBS, 100 IU/mL penicillin, 100 μg/mL streptomycin, 2 mM GlutaMAX, 1% MEM non-essential amino acids. Subconfluent HPC cells were treated with trypsin-EDTA, collected with Huh-7 media, and centrifuged at 1,500 rpm for 5 min at 4 °C in an Allegra 6R centrifuge (Beckman Coulter) in a 50 mL conical tube. The cells were then rinsed twice by resuspending the cells in 50 mL of PBS and centrifuging at 1,500 rpm for 5 min at 4 °C.

[00320] JFH-1 RNA was electroporated into HPC cells using a Thermo Scientific Hybaid OptiBuffer kit (containing buffer A, solution B and compounds C and D). After washing, the HPC cells were resuspended in OptiBuffer buffer A at $1x10^7$ cells/mL, and 400 μL ($4x10^6$ cells) was transferred to a 1.5 mL RNase-free microfuge tube and gently centrifuged at 2,000 rpm in a Microfuge 18 (Beckman Coulter) centrifuge at room temperature for 5 minutes. During this centrifugation step, the electroporation medium was prepared by mixing 2.5 mL of OptiBuffer solution B with 1 vial of OptiBuffer compound C (5.5 mg of ATP), 1 vial of OptiBuffer compound D (7.7 mg of glutathione) and 2.5 mL of autoclaved water. After aspirating the supernatant, the cell pellet was resuspended in 400 μL of electroporation medium. JFH-1 RNA (8 μg) was added to the resuspended cells, whereupon they were transferred to a 0.4 cm cuvette and electroporated in a Bio-Rad GenePulser XCell electroporation module with a single pulse at 960 μf, 270 V and maximum resistance. A mock transfection, without RNA, was electroporated as a negative control. Growth media (600 μL) was immediately added to the cuvette. Cells were then transferred into a 15 mL conical tube containing 3.4 mL of Huh-7 media. Approximately $1.2x10^5$ cells were seeded into each well of a Corning Costar 6-well plate and incubated at 37 °C with 5% CO_2.

[00321] When confluent, the transfected HPC cells were trypsinized and split into new 75 cm^2 flasks. Once confluent, cultures were split into 225 cm^2 flasks and continuously split 1:5 when confluent. At each split, conditioned media was collected from the 225 cm^2 flasks and centrifuged at 2,000 rpm for 10 min in a table-top centrifuge. Aliquots of this virus stock were stored at -80 °C for future use.

[00322] *Core ELISA*: The HCV in vitro infection core ELISA assay measures the ability of a test compound to inhibit replication of an infectious HCV (strain JFH-1; genotype 2a) in cell culture. Recently, an *in vitro* infection model identified by Wakita *et al.* (*Nat. Med.* **2005**, 11:791-796) was found to replicate in retinoic acid-indu^{c}ible gene I (RIG-I)-deficient or cluster of differentiation (CD)-81-positive Huh-7 hepatoma cell lines. We have developed this model for determining the efficacy of antiviral compounds against an infectious virus *in vitro* using HCV producing cells (HPC), a proprietary Huh-7-derived cell sublineage capable of propagating the JFH-1 HCV virus. The readout of the assay is quantification of HCV core protein by ELISA 5 days post infection with JFH-1 virus and treatment with a test compound.

[00323] Ninety-six-well collagen-coated plates were seeded with HPC cells at a density of $2.5x10^3$ cells per well in 50 µL of Huh-7 media. Compound stock solutions were made up freshly in Huh-7 media (DMEM (containing glucose, L-glutamine and sodium pyruvate), 10% FBS, 100 IU/mL penicillin, 100 µg/mL streptomycin, 2 mM GlutaMAX, 1% MEM non-essential amino acids) as 4X stock. Nine additional 5-fold drug dilutions were prepared from the 4X stocks in Huh-7 media. At least 4 hours after HPC cells were seeded, the media in the 96-well culture plates was aspirated and 50 µL of each drug dilution and 100 µL of JFH-1 HCV was added to each well.

[00324] At 16 hrs post treatment and infection, the virus inoculum was removed by aspiration. The cultures were treated at the same final concentrations of drug diluted to 1X in Huh-7 media to a final volume of 200 µL. Cells were incubated in the presence of drug for 4 additional days at 37°C/5% CO_2.

[00325] Media was removed from the plates by aspiration. Cells were fixed with 250 µL 1:1 acetone:methanol for 90 seconds, washed once in PBS and then three times with 1X KPL wash solution. The assay plates were then blocked with 150 µL/well 10% FBS-TNE (50 mM Tris-HCl (pH 7.5; Sigma), 100 mM NaCl, 1 mM EDTA with 10% FBS) for 1 hr at room temperature. Cells were washed three times with 1X KPL wash solution and incubated

with 100 µL/well anti-hepatitis C core mAb (1 mg/mL stock diluted 1:500 in 10% FBS-TNE) for 2 hours at 37 °C. Cells were washed three times with 1X KPL wash solution and incubated with 100 µL/well HRP-goat anti-mouse antibody (diluted 1:2,500 in 10% FBS-TNE) for 1 hr at 37 °C.

[00326] OPD solution was prepared using 1 OPD tablet + 12 mL citrate/phosphate buffer (16 mM citric acid, 27 mM Na_2HPO_4) plus 5 µL 30% H_2O_2 per plate. Cells were washed three times with 1X KPL wash solution and developed with 100 µL/well OPD solution for 30 minutes in the dark at room temperature. The reaction was stopped with 100 µL/well of 2N H_2SO_4, and absorbance measured at A_{490} nm in a Victor^3 V 1420 multilabel counter (Perkin Elmer). The EC_{50} values for each compound were calculated from dose response curves from the resulting best-fit equations determined by Microsoft Excel and XLfit 4.1 software. The negative control for inhibition of virus replication was untreated HPC cells infected with the JFH-1 HCV virus strain. The negative ELISA control was untreated, uninfected HPC cells. The positive ELISA control was untreated HPC cells infected the JFH-1 HCV virus strain.

Example D

Luciferase replicon transient transfection assay

[00327] *General procedure:* The luciferase replicon transient transfection assay measures the ability of a test compound to inhibit the replication of a transiently-transfected HCV luciferase-bearing wild-type or mutant replicon in human hepatoma cells that had been cured of the HCV replicon with IFN (cured GS4.1). The mutant replicons bear a specific single-site mutation in NS3 that is known to confer resistance to protease inhibitors currently in development. The inhibition of HCV replication was measured by quantification of luciferase protein expression. This assay has been validated using a panel of replicons bearing known protease inhibitor resistance mutations and their respective reference compounds. Briefly, subconfluent cured GS4.1 cells in OptiBuffer (ThermoElectron Corp.) were electroporated with 40 µg of wild-type or mutant luciferase-bearing HCV replicon RNA. The cells were then seeded in 96-well opaque white plates at $2.4x10^4$ cells/well in 150 µL/well in Huh-7 media (DMEM containing glucose, L-glutamine and sodium pyruvate, 10% fetal bovine serum, 100 IU/mL penicillin, 100 µg/mL streptomycin, 2 mM GlutaMAX, and 1X MEM non-essential amino acids [Mediatech, Inc. and Invitrogen Corp.]) and incubated for 4 hours at 37°C/5% CO_2. Ten 1:5 dilutions of each compound were made in Huh-7 media

at concentrations that were 4X higher than the final concentrations to be tested and 50 µL/well was added to the transfected cells. Untreated, mock-transfected cells served as a negative control of luciferase expression. The plates were incubated at 37°C/5% CO_2 for 4 days whereupon the media was removed and 50 µL of ONE-glo luciferase substrate (Promega) was added to each well. The plates were agitated on a rotating platform at room temperature for 3 minutes and read in a Victor^{3}V microplate reader (Perkin-Elmer) using a 700 nm cut-off filter with a 1 second read time. EC_{50} values were calculated from dose response curves from the resulting best-fit equations determined by Microsoft Excel and XLfit 4.1 software.

Example E

MTS Cytotoxicity Assay

[00328] The *cytotoxicity assay* measures the viability of cells after treatment with a test compound for 5 days. The assay readout is the bioreduction of the yellow MTS tetrazolium compound to a purple formazan product. This conversion is mediated by NADPH or NADH and is directly proportional to the number of live cells in a culture.

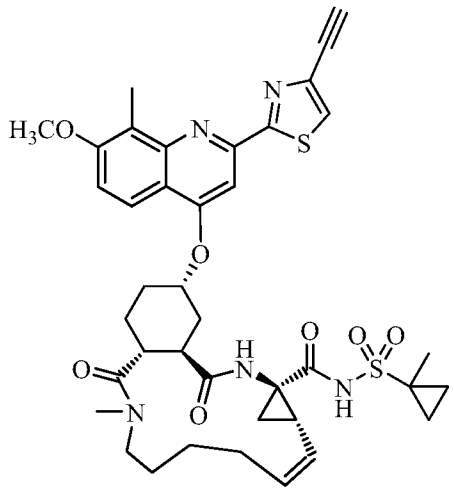
[00329] Ninety-six-well Corning Costar plates were seeded with HPC cells at a density of $3.0x10^3$ cells per well in 50 µL of Huh-7 media. Compound stock solutions were made up freshly in Huh-7 media as 2X stocks. Seven additional 3-fold drug dilutions were prepared from the 2X stocks in Huh-7 media for a total of 8 dilutions.

[00330] At least 4 hours after HPC cells were seeded, 50 µL of each drug dilution was added to the cultures. At 16 hrs post treatment, the existing media was removed by aspiration. Cultures were treated at the same final concentrations of drug diluted to 1X in Huh-7 medium to a final volume of 100 µL. Cells were incubated for 4 additional days at 37°C/5% CO_2 in the presence of drug.

[00331] After 5 days of treatment, the CellTiter 96® Aqueous One Solution cell proliferation assay was performed by adding 20 µL of MTS solution to each well. The plates were then incubated at 37°C/5% CO_2 for 3 hours. Plates were read at A_{490} nm in a Victor^3 V 1420 multilabel counter (Perkin Elmer) and CC_{50} concentrations were determined using Microsoft Excel and XLfit 4.1 software. The positive control for cell death: culture wells containing only Huh-7 medium. The negative control for cell death: culture wells containing untreated, uninfected HPC cells.

Reference Example 1

Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid{18-[2-(4-ethynyl-thiazol-2-yl)-7-methoxy-8-methyl-quinolin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **17a**



17a

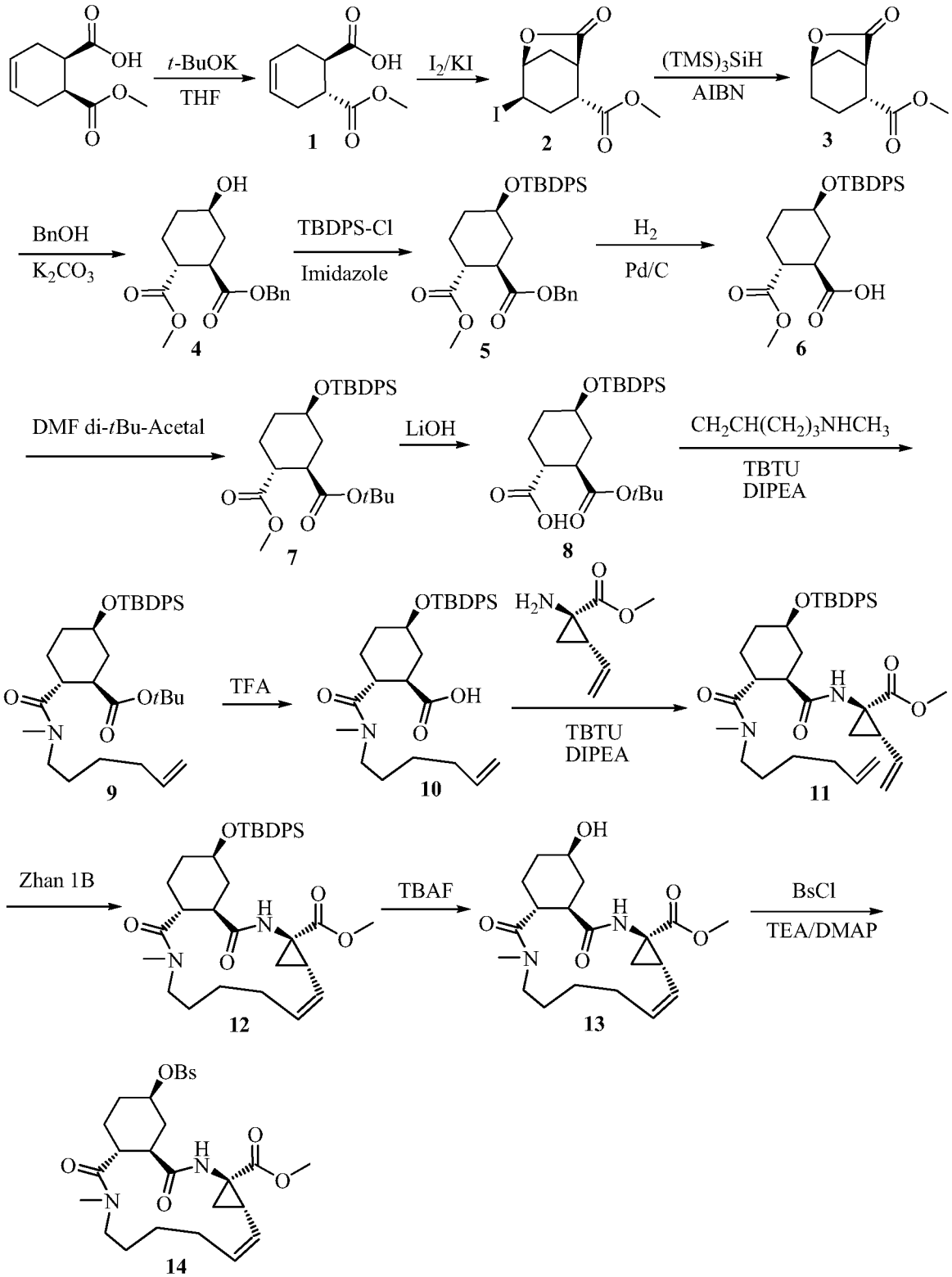
[00332] The synthesis of compound **17a** is shown in Schemes 1 and 2, where R^B is 2-(4-ethynyl-thiazol-2-yl)-7-methoxy-8-methyl-quinolin-4-yl.

[00333] Preparation of (1*R*,2*R*) 1-methyl-*cis*-1,2,3,6-tetrahydrophtalate **1**. To a suspension of *t*BuOK (9.66 g, 1.5 eq.) in anhydrous THF (50 mL) was added slowly a solution of (1*S*,2*R*)-1-methyl-*cis*-1,2,3,6-tetrahydrophtalate (10.57 g, 1 eq.) in anhydrous THF (125 mL) under nitrogen at 0°C. The solution was stirred at room temperature for 2 hrs. The reaction mixture was concentrated under reduced pressure. The mixture was acidified to pH 1 with 2 N HCl and extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude compound was used directly in the next step without further purification. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.22 (m, 2H), 2.46 (m, 2H), 2.86-2.88 (m, 2H), 3.71 (s, 3H), 5.68-5.72 (m, 2H), 8.88 (brs, 1H).

[00334] Preparation of (1*R*,2*R*,4*R*,5*S*)-4-iodo-7-oxo-6-oxa-bicyclo[3.2.1]-octane-2-carboxylic acid methyl ester **2**. To a stirred solution of compound **1** (8.34 g, 1 eq.) in DCM (110 mL) were added I_2 (34.2 g, 3 eq.), KI (44.9 g, 6 eq.), $NaHCO_3$ (11.3 g, 3 eq.), and distilled H_2O (170 mL). The reaction mixture was stirred in darkness for 2 days. Saturated $Na_2S_2O_3$ aqueous solution (500 mL) was added and the mixture was extracted with DCM (2 x 500 mL). Organics were washed sequentially with H_2O (500 mL) and brine (500 mL), dried

over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by chromatography on silica gel (petroleum ether/EtOAc) to yield compound **2** as a yellow-brown oil in 52% yield. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.68-1.73 (m, 4H), 2.82-2.85 (m, 2H), 3.60 (s, 3H).

Scheme 1



[00335] Preparation of (1*R*,2*R*,5*R*)-7-oxo-6-oxa-bicyclo [3,2,1] octane-2-carboxylic acid methyl ester **3**. To a solution of compound **2** (1.24 g, 1.0 eq.) in toluene (12 mL) was added tris(trimethylsilyl)silane (1.48 mL, 1.2 eq.) with stirring, followed addition of 1,1'-azobis(cyclohexanecarbonitrile) (AIBN) (98 mg, 0.1 eq.). The reaction mixture was stirred at 90 °C for 1.5 hrs. The solution was cooled down to room temperature, quenched with 5% citric acid solution, and extracted with EtOAc (50 mL). Organics were washed sequentially with H_2O (30 mL), saturated $NaHCO_3$ aqueous solution (30 mL), and brine (30 mL), and concentrated under reduced pressure to yield a colourless oil. Crude material was purified by chromatography on silica gel (petroleum ether/EtOAc) to yield compound **3** as white crystals in 71% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.68-1.73 (m, 4H), 2.05-2.18 (m, 2H), 2.82-2.85 (m, 2H), 3.60 (s, 3H), 4.71 (m, 1H).

[00336] Preparation of (1*R*,2*R*,4*R*)-4-hydroxy-cyclohexane-1,2-dicarboxylic acid 2-benzyl ester 1-methyl ester **4**. To a stirred solution of compound **3** (1.85 g, 1 eq.), in dry DMF (10 mL) were added benzyl alcohol (1.25 mL, 1.2 eq.) and K_2CO_3 (2.8 g, 2 eq.). The reaction mixture was stirred for 16 hrs under nitrogen. Water was then added and the reaction was extracted with TBDME. The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated under reduced pressure, and purified by chromatography on silica gel (DCM/MeOH) to yield compound **4** as beige solid in 70% yield.

[00337] Preparation of (1*R*,2*R*,*4R*)-4-(*tert*-butyl-diphenyl-silanyloxy)-cyclohexane-1,2-dicarboxylic acid 2-benzyl ester 1-methyl ester **5**. To a solution of compound **4** (10.9 mmol) in DMF (35 mL) were added TBDPSCl (24.0 mmol) and imidazole (32.7 mmol). The reaction mixture was stirred at room temperature for 16 hrs. The reaction mixture was then diluted with DCM (140 mL) and washed sequentially with 1N HCl (140 mL) and H_2O (140 mL). Organics were dried, concentrated, and purified by silica gel chromatography (PE/EtOAc) to yield compound **5** as a colourless oil in 65% yield.

[00338] Preparation of (1*R*,2*R*,4*R*)-4-(*tert*-butyl-diphenyl-silanyloxy)-cyclohexane-1,2-dicarboxylic acid 1-methyl ester **6**. To a solution of compound **5** (12.2 mmol) in anhydrous EtOH (50 mL) was added Pd/C 10% (20 % w/w). The vessel was flushed with nitrogen and H_2 was added. The reaction mixture was stirred under hydrogen atmosphere for 16 hrs. The catalyst was filtered off and washed several times with EtOH. The filtrate was concentrated *in vacuo* to yield compound **6** as a colourless oil in a quantitative yield.

[00339] Preparation of (1*R*,2*R*,4*R)*-4-(*tert*-butyl-diphenyl-silanyloxy)-cyclohexane-1,2-dicarboxylic acid 2-*tert*-butyl ester 1-methyl ester **7**. To a solution of compound **6** (5.67 mmol) in anhydrous toluene (13 mL) at 110 °C was added *N*,*N*-dimethylformamide di-*tert*-butylacetal (22.7 mmol) dropwise. The reaction mixture was refluxed for 1.5 hrs. The mixture was cooled down to room temperature, and washed sequentially with H_2O (30 mL), sat $NaHCO_3$ (30 mL), and brine (30 mL). Organics were dried and concentrated under reduced pressure to yield compound **7** as a yellow oil in 82% yield.

[00340] Preparation of (1*R*,2*R*,4*R*)-4-(*tert*-butyl-diphenyl-silanyloxy)-cyclohexane-1,2-dicarboxylic acid 2-*tert*-butyl ester **8**. A solution of compound **7** (4.2 mmol) and LiOH (16.8 mmol) in THF/H_2O 1/1 (40 mL) was stirred at room temperature for 16 hrs. The reaction mixture was neutralized with 1N HCl to pH 2, and then extracted with DCM (100 mL). Organics were concentrated under reduced pressure and purified by chromatography on silica gel (Cyclohexane/EtOAc) to yield compound **8** as pale yellow oil in 63% yield.

[00341] Preparation of (1*R*,2*R*,4*R*)-5-(*tert*-butyl-diphenyl-silanyloxy)-2-(hex-5-enyl-methyl-carbamoyl)-cyclohexanecarboxylic acid *tert*-butyl ester **9**. To a cold solution of compound **8** (1.80 mmol), *O*-(benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (2.17 mmol), and *N*-methylhex-5-en-1-amine tosylate salt (2.17 mmol) in DMF (100 mL) was added diisopropyl ethyl amine (5.4 mmol) dropwise at 0 °C under nitrogen atmosphere. The reaction mixture was stirred overnight at room temperature, and then quenched with water and extracted with diethyl ether. The organic layer was washed with brine, and then dried over magnesium sulphate. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to yield compound **9** as a beige solid in 85% yield. MS (ESI, EI^+): *m/z* = 578 (MH^+).

[00342] Preparation of (1*R*,2*R*,4*R*)-5-(*tert*-butyl-diphenyl-silanyloxy)-2-(hex-5-enyl-methyl-carbamoyl)-cyclohexanecarboxylic acid **10**. To a solution of compound **9** (1.07 mmol) in anhydrous DCM (70 mL) was added TFA (42.6 mmol) slowly. The reaction mixture was stirred at room temperature for 16 hrs. The reaction mixture was concentrated and purified by silica gel chromatography (DCM/MeOH) to yield compound **10** as a yellow oil in 48% yield. MS (ESI, EI^+): *m/z* = 522 (MH^+).

[00343] Preparation of (1*R*,2*S*)-methyl 1-((1*R*,2*R*,5*R*)-5-(*tert*-butyldiphenylsilyloxy)-2-(hex-5-enyl(methyl)carbamoyl)cyclohexanecarboxamido)-2-vinylcyclopropanecarboxylate

11. Compound **11** was synthesized from compound **10** and (1*R*,2*S*)-methyl 1-amino-2-vinylcyclopropanecarboxylate as described for compound **9** to yield compound **11** as a yellow oil in 76% yield. MS (ESI, EI^+): *m/z* = 645 (MH^+).

[00344] Preparation of *(*1*R*,4*R*,6*R*,15*R*,18*R*)-18-(*tert*-butyl-diphenyl-silanyloxy)-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid methyl ester **12**. To a solution of compound **11** (0.74 mmol) in dichloroethane (700 mL), degassed for 45 min by bubbling nitrogen, was Zhan 1B (4%, 22 mg) at 80 °C under continuous degassing with nitrogen. After the reaction was refluxed for 1 hr, a second portion of Zhan 1B (22 mg) was added. After heating for 1.5 hr, the reaction mixture was cooled down to room temperature, poured onto a silica pad, and eluted with DCM. The crude material was purified by chromatography on silica gel (DCM/MeOH) to yield compound **12** as a brown solid in 81% yield. MS (ESI, EI^+): *m/z* = 617 (MH^+).

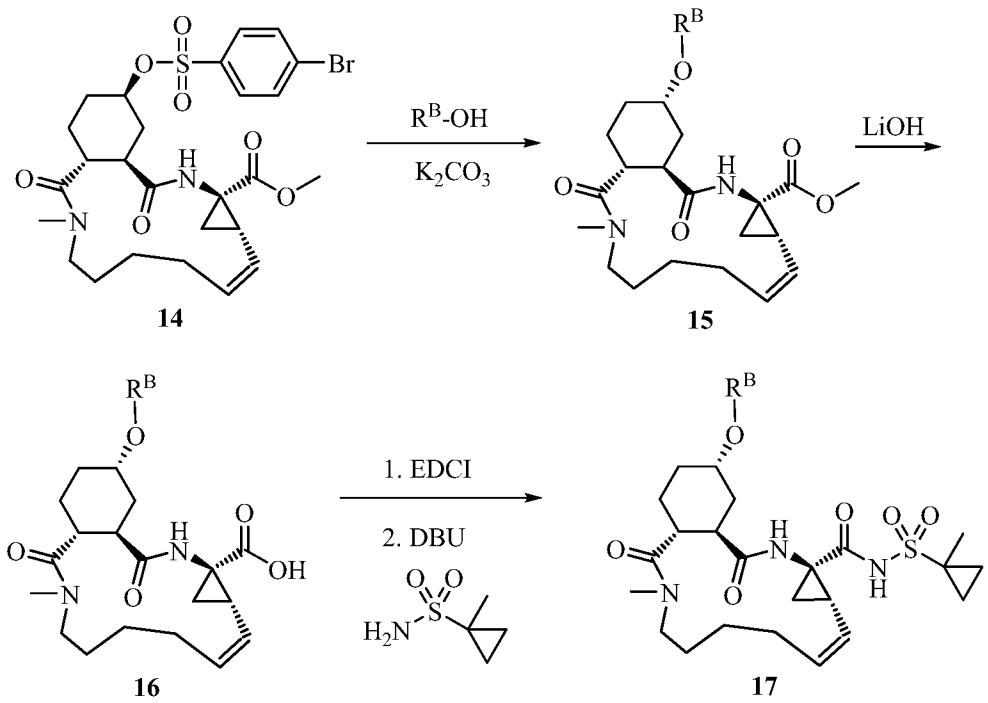
[00345] Preparation of (1*R*,4*R*,6*R*,15*R*,18*R*)-18-hydroxy-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid methyl ester **13**. To a solution of compound **12** (0.6 mmol) in dry THF (12 mL) was added dropwise a solution of tetrabutylammonium fluoride (1M in THF, 12 mL). The reaction was stirred at room temperature overnight, and then concentrated. The residue was dissolved in MeOH and purified by semi preparative HPLC (RP18) to yield compound **13**, which was used without further purification directly in the next step. MS (ESI, EI^+): *m/z* = 379 (MH^+).

[00346] Preparation of (1*R*,4*R*,6*R*,15*R*,18*R*)-18-(4-bromo-benzenesulfonyloxy)-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid methyl ester **14**. To a mixture of compound **13** (0.13 mmol), TEA (0.39 mmol), and DMAP (0.009 mmol) in anhydrous DCM (0.3 mL) was added 4-bromobenzenesulfonyl chloride (0.17 mmol) in DCM (0.15 mL) dropwise. The reaction mixture was stirred at room temperature under nitrogen for 16 hrs. The crude material was washed sequentially with 0.5N HCl and 2.5% $NaHCO_3$. The organics were concentrated to yield compound **14** as a yellow oil in a quantitative yield. MS (ESI, EI^+): *m/z* = 598 (MH^+).

[00347] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-18-[2-(4-ethynyl-thiazol-2-yl)-7-methoxy-8-methyl-quinolin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid methyl ester **15a**. To a solution of compound **14** (0.13 mmol) and 2-(4-ethynyl-thiazol-2-yl)-7-methoxy-8-methyl-quinolin-4-ol (0.14 mmol) in NMP (0.5 mL)

was added K_2CO_3 (0.19 mmol). The reaction mixture was heated at 70 °C for 2 days. The crude material was purified by silica gel chromatography (PE/EtOAc) to yield compound **15a** as a beige solid. MS (ESI, EI^+): *m/z* = 657 (MH^+).

Scheme 2

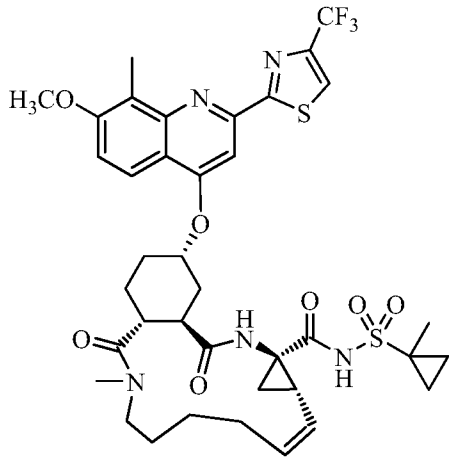


[00348] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-18-[2-(4-ethynyl-thiazol-2-yl)-7-methoxy-8-methyl-quinolin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid **16a**. Compound **16a** was synthesized from compound **15a** as described for compound **8** to yield compound **16a** as a beige solid. MS (ESI, EI^+): *m/z* = 643 (MH^+).

[00349] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid{18-[2-(4-ethynyl-thiazol-2-yl)-7-methoxy-8-methyl-quinolin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **17a**. To a solution of compound **16a** (0.03 mmol) in DCM (2 mL) was added EDCI (0.062 mmol) under nitrogen. The reaction mixture was stirred at room temperature for 2 hrs. Methyl-cyclopropylsulfonamide (0.00012 mmol) and DBU (0.12 mmol) were then added and the reaction was stirred at room temperature for 16 hrs. DCM was then added, and the mixture was washed with water and brine. The solvent was evaporated and the crude material was purified by silica gel chromatography (DCM/MeOH) to yield compound **17a** as a white solid. MS (ESI, EI^+): *m/z* = 760 (MH^+).

Reference Example 2

Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid-{18-[7-methoxy-8-methyl-2-(4-trifluoromethyl-thiazol-2-yl)-quinolin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **17b**



17b

[00350] The synthesis of compound **17b** is shown in Scheme 2, where R^B is 7-methoxy-8-methyl-2-(4-trifluoromethyl-thiazol-2-yl)-quinolin-4-yl.

[00351] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-18-[7-methoxy-8-methyl-2-(4-trifluoromethyl-thiazol-2-yl)-quinolin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid methyl ester **15b**. Compound **15b** was synthesized from compound **14** (1.42 mmol) and 7-methoxy-8-methyl-2-(4-(trifluoromethyl)thiazol-2-yl)quinolin-4-ol (1.52 mmol) as described for compound **15a** (eluent: DCM to DCM/EtOAc) to give compound **15b** as a yellow solid in 19% yield. MS (ESI, EI^+): *m/z* = 701.2 (MH^+).

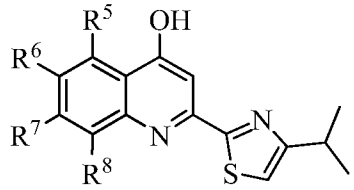
[00352] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-18-[7-methoxy-8-methyl-2-(4-trifluoromethyl-thiazol-2-yl)-quinolin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid **16b**. To a stirred solution of compound **15b** (0.271 mmol) in THF (3.3 mL) was added CH_3OH (1.6 mL). The reaction mixture was cooled down to 10 °C and a solution of LiOH (3.25 mmol) in H_2O (5 mL) was added dropwise. The reaction mixture was allowed to reach to room temperature and stirred for 42 hrs. The solvent were removed partially, H_2O (10 ml) was added, and the mixture was acidified to pH 2 with 1N HCl. The reaction mixture was extracted with DCM and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to

give compound **16b** as yellow solid in quantitative yield. MS (ESI, EI^+): *m/z* = 687.3 (MH^+).

[00353] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid-{18-[7-methoxy-8-methyl-2-(4-trifluoromethyl-thiazol-2-yl)-quinolin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **17b**. Compound **17b** was synthesized from compound **16b** (0.271 mmol) as described for compound **17a**. After the dilution with DCM, the mixture was washed sequentially with a solution of citric acid 5%, water, and brine. The organic layer was dried, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: DCM to DCM/CH_3OH 10%) and preparative HPLC to give compound **17b** in 45% yield. MS (ESI, EI^+): *m/z* = 804.3 (MH^+).

Example 1

Preparation of 2-(4-isopropylthiazol-2-yl)-substituted quinolin-4-ols **218**



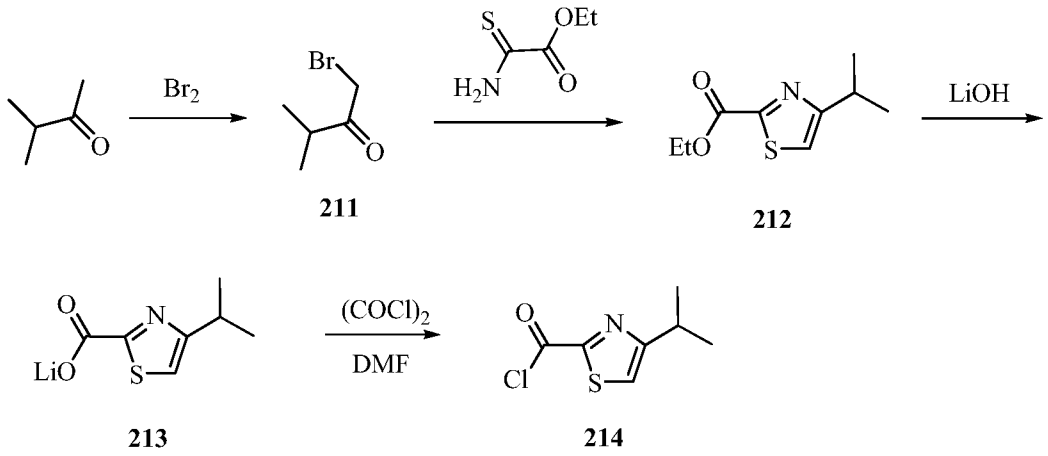
218a: R^5 = H, R^6 = H, R^7 = OCH_3, R^8 = H
218b: R^5 = H, R^6 = H, R^7 = OCH_3, R^8 = CH_3
218c: R^5 = H, R^6 = H, R^7 = OCH_3, R^8 = F
218d: R^5 = H, R^6 = H, R^7 = OCH_3, R^8 = Cl
218e: R^5 = OCH_3, $R^{6'}$ = H, R^7 = OCH_3, R^8 = H
218f: R^5 = H, R^6 = OCH_3, R^7 = H, R^8 = CH_3
218g: R^5 = H, R^6 = OCH_3, R^7 = Cl, R^8 = H
218h: R^5 = H, R^6 = H, R^7 = OCH_3, R^8 = Br

[00354] The syntheses of compounds **218** are shown in Schemes 3 to 5, where R^5, R^6, R^7, and R^8 in compounds **201**, **215** to **217**, and **220** to **222** are each as defined in compounds **218**.

[00355] Preparation of 1-bromo-3-methylbutan-2-one **211**. To a solution of 3-methyl-2-butanone (40.7 g, 1 eq.) in ethanol (391 mL) was added bromide (62.4 g, 0.83 eq.) under nitrogen at 0°C over 30 min. The reaction mixture was stirred at 0°C for 4 hrs, then quenched with 1M aqueous sodium metabisulfite (100 mL) and extracted with petroleum ether (750 mL). The organic layer was washed twice with water (100 mL), twice with a cold saturated aqueous bicarbonate, and then brine. The organic layer was dried over sodium sulfate and then concentrated under reduced pressure. The product was purified by

distillation under vacuum to yield compound **211** as colourless oil in 42% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.17 (d, J = 6.98 Hz, 6H), 2.99 (m, J = 6.98 Hz, 1H), 3.99 (s, 2H).

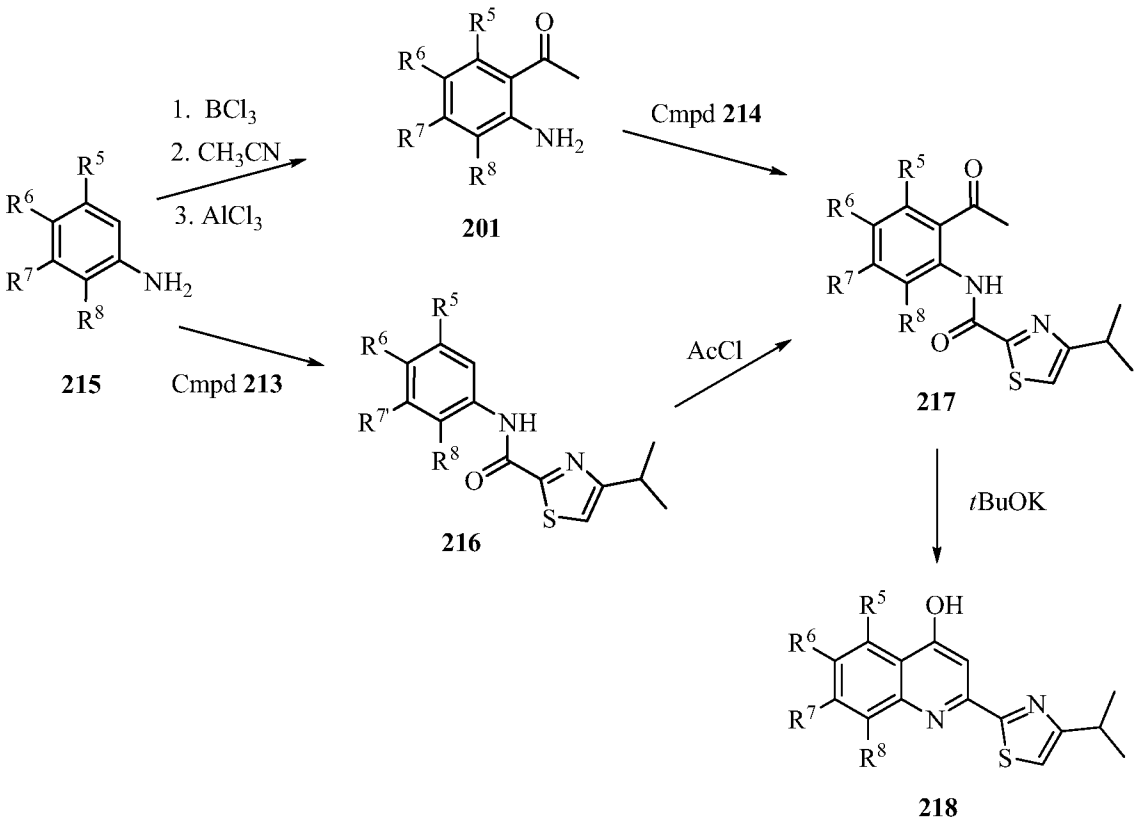
Scheme 3



211 **212** **213** **214**

Method A:

Scheme 4



201 **215** **216** **217** **218**

[00356] Preparation of ethyl 4-isopropylthiazole-2-carboxylate **212**. A solution of compound **211** (3.5 g, 1.25 eq.) and ethylthioxamate (2.3 g, 1 eq.) in ethanol (40 mL) was heated to 80 °C for 6 hrs, and then cooled to 0 °C. The reaction mixture was diluted with water and EtOAc, and then neutralized to pH 7 with NH_3 (28%). The aqueous layer was extracted with EtOAc. The combined organic layers were dried over sodium sulfate and then removed under reduced pressure. The residue was purified by chromatography on silica gel to yield compound **212** as yellow oil in quantitative yield. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.25 (d, J = 6.73 Hz, 6H), 1.31 (t, J = 7.24 Hz, 3H), 3.11 (hep, J = 6.73 Hz, 1H), 4.35 (q, J = 7.24 Hz, 2H), 7.72 (s, 1H).

[00357] Preparation of 4-isopropylthiazole-2-carboxylic acid, lithium salt **213**. To a solution of compound **212** (26 g, 1 eq.) in a mixture of MeOH (78 mL) and THF (260 mL), lithium hydroxide (2.8 g, 0.9 eq.) was added. The reaction mixture was stirred at room temperature overnight. The solvents were then removed under reduced pressure. The residue was triturated with petroleum ether (500 mL), filtrated, washed with petroleum ether, and dried under vacuum to yield compound **213** as a beige solid in 56% yield. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.21 (d, J = 6.73 Hz, 6H), 2.95 (hep, J = 6.73 Hz, 1H), 7.19 (s, 1H).

[00358] Preparation of 4-isopropylthiazole-2-carbonyl chloride **214**. Oxalyl chloride (2.9 g, 1.5 eq.) was added dropwise under nitrogen at 0 °C to a suspension of compound **213** (1.8 g, 1 eq.) in DCM (25 mL) and DMF (50 µL). The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for additional 90 min. Lithium chloride salt was removed from the reaction mixture through filtration. The solvent was then removed under reduced pressure to give compound **214** as yellow oil in quantitative yield, which was stored under nitrogen and used directly in the next step without further purification.

[00359] Preparation of 1-(2-amino-4-methoxyphenyl)ethanone **201a**. Trichloroborane (1M, 82 mL, 1 eq.) in DCM was added dropwise to a solution of meta-anisidine **215a** (10 g, 1 eq.) in toluene (56 mL) under nitrogen at 0-5 °C over 1 hr. After stirred for 10 min at 0 °C, ACN (5.2 mL, 1.20 eq.) was added. After the reaction mixture was stirred for additional 1 hr at 0 °C, aluminium(III) chloride (11.9 g, 1.1 eq.) was added at 0 °C. The reaction mixture was stirred at 50 °C for 16 hrs. The reaction mixture was then cooled down to 0 °C, and propan-2-ol (38 mL) was added over 10 min, followed by addition of water (110 mL) over 30 min. The reaction mixture was heated to 50 °C for 3 hrs. After cooling down to 0 °C, aqueous solution of sodium hydroxide (25%) was added. The aqueous layer was extracted

with toluene (100 mL). The combined organic layers were washed with NaOH (25 %), brine, and dried over sodium sulfate. The solvent was removed to yield compound **201a** as a yellow solid in 63 % yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.52 (s, 3H), 3.80 (s, 3H), 6.07 (d, J = 2.43, 1H), 6.23 (dd, J = 2.43 and 8.98 Hz, 1H), 6.43 (br s, 2H), 7.63 (d, J = 8.98 Hz).

[00360] Preparation of 1-(2-amino-3-methyl-4-methoxyphenyl)ethanone **201b**. Compound **201b** was synthesized from 3-methoxy-2-methylaniline **215b** as a yellow solid in 23% yield, according to the procedure as described for compound **215a**. MS (ESI, EI$^+$): *m/z* = 180 (MH^+).

[00361] Preparation of 1-(2-amino-4-chloro-5-methoxy-phenyl)-ethanone **201g**. Compound **201g** was synthesized from 3-chloro-4-methoxy-aniline **215g** as a brown solid in 50% yield, according to the procedure as described for compound **215a**. MS (ESI, EI$^+$): *m/z* = 200 (MH^+).

[00362] Preparation of *N*-(3,5-dimethoxy-phenyl)-4-isopropylthiazole-2-carboxamide **216e**. To a stirred solution of compound **213** (1.38 g, 7.8 mmol) in DCM (50 mL) under nitrogen was added oxalyl chloride (1.16 g, 9.1 mmol). The reaction mixture was stirred at room temperature for 90 min. The solution was filtered under nitrogen and washed with DCM. The filtrate was concentrated under reduced pressure and the residue was dissolved in dioxane (20 mL). 3,5-Dimethoxyaniline (1 g, 6.5 mmol) in dioxane (9 mL) was added dropwise. The reaction mixture was stirred at room temperature for 90 min. Solvent was removed under reduced pressure and the crude material was purified by chromatography on silica gel (EtOAc/DCM) to yield compound **216e** as a white solid in 90% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.35 (s, 3H), 1.37 (s, 3H), 3.14-3.17 (m, 1H), 3.82 (s, 6H), 6.30 (brs, 1H), 6.97 (d, J = 2.30 Hz, 2H), 7.19 (s, 1H); MS (ESI, EI$^+$): *m/z* = 307 (MH^+).

[00363] Preparation of *N*-(2-acetyl-5-methoxyphenyl)-4-isopropylthiazole-2-carboxamide **217a**. Under nitrogen, a solution of compound **201a** (3 g, 1 eq.) in 1,4-dioxane (30 mL) was added at 0 °C to a solution of compound **214** (4.1 g, 1.2 eq.) in 1,4-dioxane. The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to yield compound as a beige solid **217a** in 75% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) (ppm) 1.43 (d, J = 6.98 Hz, 6H), 2.65 (s, 3H), 3.26 (hep, J = 6.98 Hz, 1H), 3.92 (s, 3H), 6.69 (dd, J

= 2.59 and 8.80 Hz, 1H), 7.2 (d, J = 0.84, 1H), 7.87 (d, J = 8.9 Hz, 1H), 8.58 (d, J = 2.59 Hz, 1H), 13.5 (br s, 1H); MS (ESI, EI^+): m/z = 319 (MH^+).

[00364] Preparation of *N*-(6-acetyl-2-methyl-3-methoxyphenyl)-4-isopropylthiazole-2-carboxamide **217b**. Compound **217b** was synthesized from compound **201b** and compound **214** as a beige solid in 66% yield, according to the procedure as described for compound **217a**. MS (ESI, EI^+): m/z = 333 (MH^+).

[00365] Preparation of *N*-(6-acetyl-2-fluoro-3-methoxyphenyl)-4-isopropylthiazole-2-carboxamide **217c**. Compound **217c** was synthesized from 1-(2-amino-3-fluoro-4-methoxyphenyl)ethanone and compound **214** as a beige solid in 84% yield, according to the procedure as described for compound **217a**. MS (ESI, EI^+): m/z = 337 (MH^+).

[00366] Preparation of *N*-(6-acetyl-2-chloro-3-methoxyphenyl)-4-isopropylthiazole-2-carboxamide **217d**. Compound **217d** was synthesized from 1-(2-amino-3-chloro-4-methoxyphenyl)ethanone and compound **214** as a beige solid in 80% yield, according to the procedure as described for compound **217a**. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.47 (s, 3H), 1.48 (s, 3H), 2.57 (s, 3H), 3.34-3.41 (quint, J = 6.90 Hz, 1H), 3.98 (s, 3H), 6.86 (d, J = 8.48 Hz, 1H), 7.64 (d, J = 8.48 Hz, 1H), 8.07 (s, 1H); MS (ESI, EI^-): m/z = 351 (MH^-); MS (ESI, EI^+): m/z = 353 (MH^+).

[00367] Preparation of *N*-(6-acetyl-3-chloro-4-methoxyphenyl)-4-isopropylthiazole-2-carboxamide **217g**. Compound **217d** was synthesized from compounds **201g** and **214** as a beige solid in 69% yield, according to the procedure as described for compound **217a**. MS (ESI, EI^+): m/z = 354 (MH^+).

[00368] Preparation of *N*-(2-acetyl-3,5-dimethoxy-phenyl)-4-isopropylthiazole-2-carboxamide **217e**. To a suspension of Et_2AlCl (1.61 g, 12.04 mmol) in DCM at 0 °C was added acetyl chloride (630 mg, 8.02 mmol). The mixture was stirred at 0°C for 30 min. Compound **216e** (1.23 g, 4.01 mmol) was then added and the reaction mixture was stirred at 80 °C for 90 min. The reaction was poured in ice and DCM was added. The organic layers were separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (EtOAc/DCM) to yield compound **217e** as a white solid in 82% yield. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.41 (s, 3H), 1.43 (s, 3H), 2.63 (s, 3H), 3.20-3.27 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 6.27 (d, J =2.30, 1H), 7.19 (s, 1H), 8.12 (d, J = 2.30 Hz, 1H).

[00369] Preparation of 2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-ol **218a**. To a solution of compound **217a** (4.312 g, 1 eq.) in *t*BuOH (60 mL) was added potassium *t*-butoxide (3.8 g, 2.5 eq.) under nitrogen. The mixture was stirred at 70 °C for 16 hrs, and then cooled down to 0 °C and quenched with MeOH (10 mL) and acetic acid (2.5 mL). The solvent was removed under reduced pressure and the residue was triturated in a mixture of MeOH/water, isolated by filtration, washed with ACN, and then petroleum ether to yield compound **218a** as a yellow solid in 71% yield. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.32 (d, J = 6.98 Hz, 6H), 3.14 (m, 1H), 3.89 (s, 3H),7.06 (br s, 1H), 7.50-7.66 (m, 3H), 8 (d, J = 9.05 Hz, 1H), 11.62 (br s, 1H); MS (ESI, EI$^+$): m/z = 301 (MH$^+$).

[00370] Preparation of 2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-ol **218b**. Compound **218b** was synthesized from compound **217b** as a yellow solid in 60% yield, according to the procedure as described for compound **218a**. MS (ESI, EI$^+$): m/z = 315 (MH$^+$).

[00371] Preparation of 2-(4-isopropylthiazol-2-yl)-8-fluoro-7-methoxyquinolin-4-ol **218c**. Compound **218c** was synthesized from compound **217c** as a yellow solid in 90% yield, according to the procedure as described for compound **218a**. MS (ESI, EI$^+$): m/z = 319 (MH$^+$).

[00372] Preparation of 2-(4-isopropylthiazol-2-yl)-5,7-dimethoxyquinolin-4-ol **218e**. Compound **218e** was synthesized from compound **217e** as a yellow solid in 60% yield, according to the procedures as described for compound **218a**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.37 (s, 3H), 1.39 (s, 3H), 3.15-3.22 (m, 1H), 3.95 (s, 3H), 4.05 (s, 3H), 6.45 (s, 1H), 7.03 (s, 2H), 7.62 (brs, 1H), 9.55 (s, 1H); MS (ESI, EI$^+$): m/z = 331(MH$^+$).

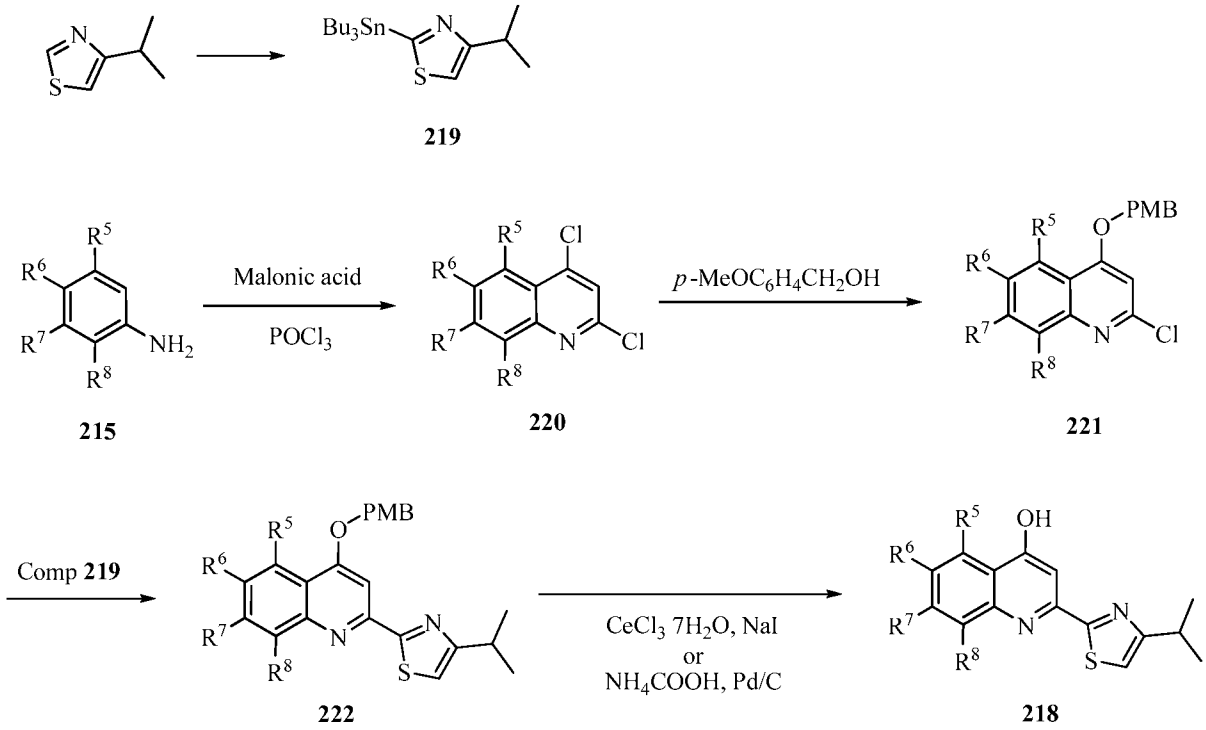
[00373] Preparation of 7-chloro-2-(4-isopropylthiazol-2-yl)-6-methoxyquinolin-4-ol **218g**. Compound **218g** was synthesized from compound **217g** as a yellow solid in 70% yield, according to the procedures as described for compound **218a**. MS (ESI, EI$^+$): m/z = 335 (MH$^+$).

[00374] Preparation of 8-bromo-7-methoxy-2-(4-isopropyl-thiazol-2-yl)-quinolin-4-ol **218h**. Compound **218h** was synthesized according to the procedures as described for compounds **217a** and **218a**, and in WO 2007014919, the disclosure of which is incorporated herein by reference in its entirety. MS (ESI, EI$^+$): m/z = 380 (MH$^+$).

Method B:

[00375] Preparation of 4-isopropyl-2-tributylstannanyl-thiazole **219**. To a stirred solution of 4-isopropylthiazole (9 g, 71 mmol) in anhydrous THF (100 mL) at -78 °C was added nBuLi (40 mL, 99 mmol). The reaction was stirred for 1 hr and the temperature reached -40 °C. The reaction mixture was cooled to -78°C and tri-*n*-butyltinchloride (23 g, 71 mmol) was added. The reaction mixture was stirred at room temperature for 48 hrs. Water was added and solvent was evaporated under reduced pressure. The residue was partioned between water and EtOAc. Organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield compound **219** as colorless oil in 55% yield. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.88-1.62 (m, 27H), 1.40 (s, 3H), 1.42 (s, 3H), 3.17-3.24 (m, 1H).

Scheme 5



[00376] Preparation of 2,4,8-trichloro-7-methoxyquinoline **220d**. A mixture of 2-chloro-3-methoxyaniline hydrochloride **215d** (15 g, 1 eq.), malonic acid (12.06 g, 1.5 eq.), and phosphorus oxochloride (80 mL) was refluxed for 16 hrs. The reaction mixture was slowly poured into water and extracted with DCM. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified on silica pad, eluted with DCM, to yield compound **220d** as a white solid in 74% yield. ^1H

NMR ($CDCl_3$, 376 MHz) δ 4.10 (s, 3H), 7.43 (t, J = 4.88 Hz, 2H), 8.12 (d, J = 9.48 Hz, 1H).

[00377] Preparation of 2,4-dichloro-8-methyl-7-methoxyquinoline **220b**. Compound **220b** was synthesized from 2-methyl-3-methoxyaniline hydrochloride **215b** and malonic acid as a white powder in 43% yield, following the procedure as described for compound **220d**. ^1H NMR ($CDCl_3$, 376 MHz) δ (ppm) 2.62 (s, 3H), 4.03 (s, 3H), 7.34 (s, 1H), 7.37 (d, J = 9.02 Hz, 1H), 8.05 (d, J = 9.02 Hz, 1H).

[00378] Preparation of 2,4-dichloro-6-methoxy-8-methyl-quinoline **220f**. A mixture of 4-methoxy-2-methyl aniline **215f** (5 g, 36.45 mmol), malonic acid (5.68 g, 54.67 mmol) in phosphorus oxide trichloride (36 mL) was refluxed for 16 hrs. The reaction mixture was then poured dropwise into cooled water (400 mL), extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by chromatography on silica gel (DCM) to yield compound **220f** as a beige solid in 43% yield. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.72 (s, 3H), 3.95 (s, 3H), 7.27-7.28 (m, 2H), 7.47 (s, 1H).

[00379] Preparation of 2,8-dichloro-7-methoxy-4-(4-methoxy-benzyloxy)-quinoline **221d**. NaH (60% in oil) (670 mg, 1.2 eq.) was added portionwise to a stirred solution of *p*-methoxybenzylalcohol (2.31 g, 1.2 eq.) and 15-crown-5 (3.32 mL, 1.2 eq.) in anhydrous DMF (10 mL). The mixture was stirred at room temperature for 30 min. Compound **220d** (3.66 g, 1 eq.) in anhydrous DMF (25 mL) was then added and the reaction mixture was stirred at room temperature for 16 hrs. The reaction mixture was then poured into water (300 mL), extracted with EtOAC, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by chromatography on silica gel (petroleum ether/DCM, 50/50) to give compound **221d** as a yellow solid in 38% yield. ^1H NMR ($CDCl_3$, 376 MHz) δ (ppm) 3.86 (s, 3H), 4.05 (s, 3H), 5.20 (s, 2H), 6.77 (s, 1H), 6.98 (d, J = 8.53 Hz, 2H), 7.23 (d, J = 9.41, 1H), 7.42 (d, J = 8.53 Hz, 2H), 8.08 (d, J = 9.41 Hz, 1H).

[00380] Preparation of 2-chloro-8-methyl-7-methoxy-4-(4-methoxy-benzyloxy)-quinoline **221b**. Compound **221b** was synthesized from compound **220b** as a white powder in 50% yield, following the procedure as described for compound **221d**. ^1H NMR ($CDCl_3$, 376 MHz) δ (ppm) 2.60 (s, 3H), 3.85 (s, 3H), 3.97 (s, 3H), 5.18 (s, 2H), 6.69 (s, 1H), 6.97 (d, J = 8.57 Hz, 1H), 7.19 (d, J = 8.57 Hz, 1H), 7.42 (d, J = 8.57 Hz, 1H), 8.02 (d, J = 8.57 Hz, 1H).

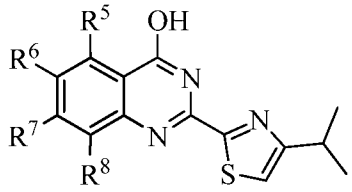
[00381] Preparation of 2-chloro-6-methoxy-4-(4-methoxybenzyloxy)-8-methyl-quinoline **221f**. Compound **221f** was synthesized from compound **220f** as a white solid in 58% yield, following the procedure as described for compound **221d**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.68 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 5.11 (s, 2H), 6.72 (s, 1H), 6.97 (d, J = 9.03 Hz, 2H), 7.15 (dd, J = 3.01 Hz and J = 0.96 Hz, 1H), 7.20 (d, J = 3.00 Hz, 1H), 7.40 (d, J = 9.03 Hz, 2H).

[00382] Preparation of 2-(4-isopropyl-thiazol-2-yl)-6-methoxy-4-(4-methoxy-benzyloxy)-8-methyl-quinoline **222f**. Compound **219** (100 mg, 0.29 mmol), compound **221f** (242 mg, 0.35 mmol), and potassium carbonate (48 mg, 0.35 mmol) in degassed anhydrous DMF were stirred under microwave radiations at 80°C for 1 hr. Solvent was removed under reduced pressure and the crude material was purified by chromatography on silica gel (Petroleum ether/DCM) to yield compound **222f** as yellow powder in 63% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 3H), 1.42 (s, 3H), 2.80 (s, 3H), 3.17-3.24 (m, 1H), 3.85 (s, 3H), 3.89 (s, 3H), 5.31 (s, 2H), 6.99 (d, J = 9.10 Hz, 2H), 7.00 (s, 1H), 7.21 (m, 1H), 7.31 (d, J = 2.93 Hz, 1H), 7.49 (d, J = 9.10 Hz, 2H), 7.79 (s, 1H).

[00383] Preparation of 4-hydroxy-[2-(4-isopropyl-thiazol-2-yl)]-6-methoxy-8-methyl-quinoline **218f**. Compound **222f** (1.23 g, 2.82 mmol), cesium trichloride (1.58 g, 4.23 mmol), and sodium iodide (423 mg, 2.82 mmol) in ACN (26 mL) were stirred at 85 °C for 1 hr. The mixture was then filtered through celite and the solvent was evaporated. The brown solid obtained was suspended in water, pH was adjusted at 5 with 1N HCl. The mixture was extracted with DCM, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by chromatography on silica gel (petroleum ether/DCM) to yield compound **218f** as a brown solid in 55 % yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.40 (d, J = 6.91 Hz, 6H), 2.80 (s, 3H), 3.17-3.24 (m, 1H), 3.89 (s, 3H), 7.00 (s, 1H), 7.21 (m, 1H), 7.55 (s, 1H), 7.79 (s, 1H), 9.56 (brs, 1H).

Example 2

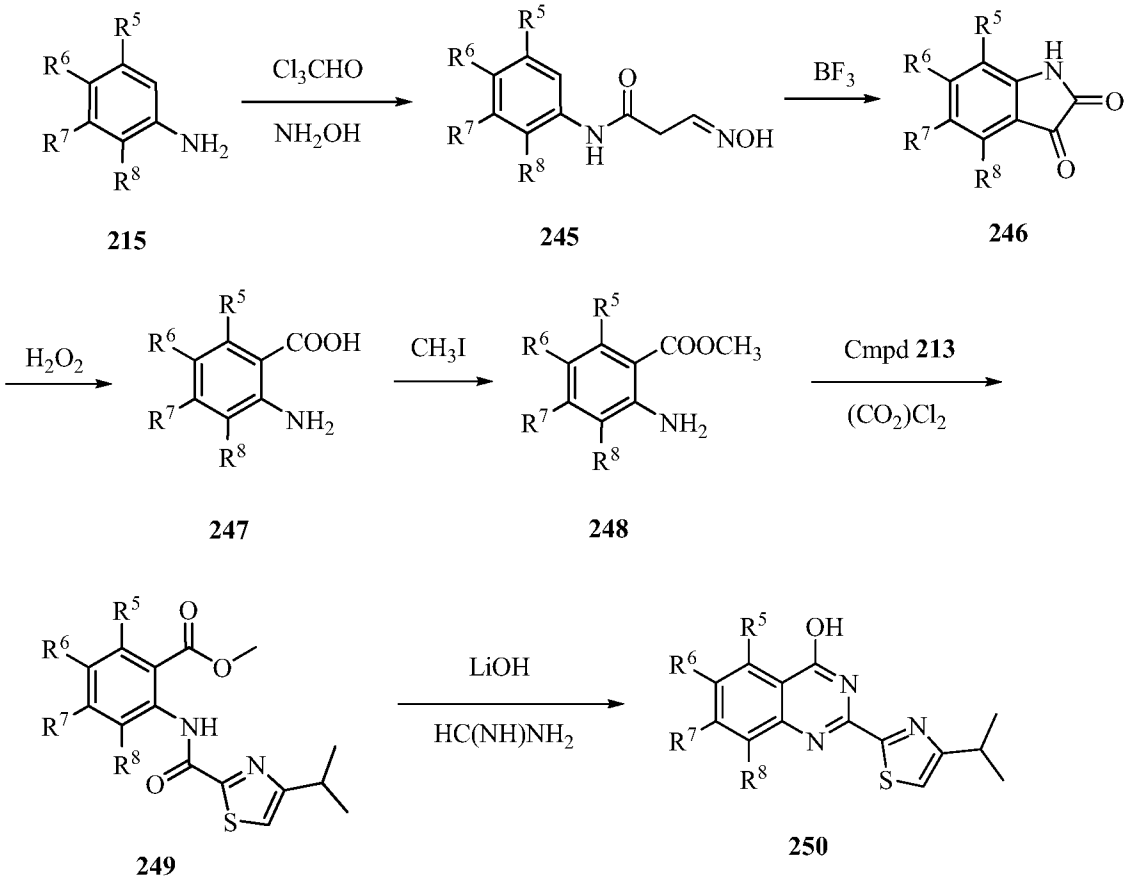
Preparation of 2-(4-isopropylthiazol-2-yl)-substituted quinolin-4-ols **250**



250a: R^5 = H, R^6 = H, R^7 = OCH_3, R^8 = H
250b: R^5 = H, R^6 = H, R^7 = OCH_3, R^8 = CH_3
250c: R^5 = H, R^6 = H, R^7 = OCH_3, R^8 = F
250d: R^5 = H, R^6 = H, R^7 = OCH_3, R^8 = Cl
250e: R^5 = OCH_3, $R^{6'}$ = H, R^7 = OCH_3, R^8 = H
250f: R^5 = H, R^6 = OCH_3, R^7 = H, R^8 = CH_3
250g: R^5 = H, R^6 = OCH_3, R^7 = Cl, R^8 = H
250h: R^5 = H, R^6 = H, R^7 = OCH_3, R^8 = Br

[00384] The syntheses of compounds **250** are shown in Scheme 6, where R^5, R^6, R^7, and R^8 in compounds **215** and **245** to **249** are each as defined in compounds **250**.

Scheme 6



[00385] Preparation of *N*-(2-chloro-3-methoxyphenyl)-2-hydroxyimino-acetamide **245d**. To a stirred solution of sodium sulfate (58.5 g, 412 mmol) in water (100 mL) was added a solution of chloralhydrate (9.36 g, 56.6 mmol) in water (120 mL). Chloroanisidine **215d** (10g, 51.5 mmol) was added followed by 37% HCl (20 mL). A solution of hydroxylamine (50% in water, 4.7 mL, 154.5 mmol) in 50 mL was then added and the reaction mixture was refluxed for 90 min. The suspended solid was filtered off, and washed with water and ether. Organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield compound **245d** as a brown solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 3.86 (s, 3H), 6.98 (d, J = 8.07 Hz, 1H), 7.31 (t, J = 8.07 Hz, 1H), 7.61 (d, J = 8.07 Hz, 1H), 7.66 (s, 1H), 9.43 (s, 1H), 12.43 (s, 1H).

[00386] Preparation of 7-chloro-6-methoxy-1H-indole-2,3-dione **246d**. Compound **245d** (10.46 g, 45.74 mmol) was added portionwise to $BF_3 \cdot Et_2O$ at 40 °C. The mixture was then heated at 90°C for 3 hrs. After cooling down to room temperature, the reaction mixture was poured into crushed ice and extracted with EtOAc. Organics were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by chromatography on silica gel (petroleum ether/EtOAc). The compound obtained was recrystallized from EtOH to yield compound **246d** as a brown solid in 63% yield. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 3.96 (s, 3H), 6.79 (d, J =9.10 Hz, 1H), 7.52 (d, J =9.10 Hz, 1H), 11.40 (s, 1H).

[00387] Preparation of 2-amino-3-chloro-4-methoxy benzoic acid **247d**. A suspension of compound **246d** (6.03 g, 28.52 mmol), NaOH (1.25 g, 31.37 mmol), and NaCl (3.49 g, 59.89 mmol) in water (60 mL) was stirred at room temperature for 30 min and was then ice-cooled. H_2O_2 was added dropwise. The mixture was stirred at 0 °C for 20 min and at room temperature for 3 hrs. The reaction mixture was quenched with glacial AcOH, filtered, and washed with water. The solid obtained was dissolved in DCM, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by chromatography on silica gel (DCM/MeOH) to yield compound **247d** as an orange solid in 36% yield. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 3.85 (s, 3H), 6.41 (d, J = 9.05 Hz, 1H), 6.77 (brs, 2H), 7.74 (d, J = 9.05 Hz, 1H), 12.7 (brs, 1H).

[00388] Preparation of 2-amino-3-chloro-4-methoxy benzoic acid methyl ester **248d**. To a stirred solution of compound **247d** (1.9 g, 9.6 mmol) in dry DMF (25 mL) was added K_2CO_3 (1.32 g, 9.6 mmol) at room temperature. The reaction mixture was stirred for 30 min and methyl iodide (0.77 mL, 12.4 mmol) was added. After 2 hrs at room temperature, 5%

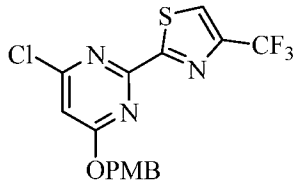
aqueous citric acid was added. The mixture was extracted with EtOAc. Organics were washed with water, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by chromatography on silica gel (petroleum ether/EtOAc) to yield compound **248d** as beige soild in 50% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.79 (s, 3H), 3.86 (s, 3H), 6.23 (d, J = 9.03 Hz, 1H), 7.75 (d, J= 9.03 Hz, 1H).

[00389] Preparation of methyl 3-chloro-2-(4-isopropylthiazole-2-carboxamido)-4-methoxybenzoate **249d**. To a stirred solution of compound **213** (758 mg, 4.28 mmol) in dry DCM was added oxalyl chloride (720 µL, 8.56 mmol) and few drops of DMF at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 2 hrs. The mixture was filtered, concentrated under reduced pressure, and dissolved in dioxane (3 mL). Compound **248d** (770 mg, 3.56 mmol) in dioxane (6 mL) was then added. The reaction mixture was stirred at room temperature for 16 hrs. Solvent was evaporated. Water was added to the mixture. The reaction mixture was extracted with EtOAc. Organics were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by chromatography on silica gel (petroleum ether/EtOAc) to yield compound **249d** as a pale yellow solid in 92% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.19 (d, J = 6.63 Hz, 6H), 3.09-3.16 (m, 1H), 3.79 (s, 3H), 3.91 (s, 3H), 6.82 (d, J = 9.02 Hz, 1H), 7.19 (s, 1H), 7.82 (d, J = 9.02 Hz, 1H), 9.97 (s, 1H).

[00390] Preparation of 8-chloro-2-(4-isopropyl-thiazol-2-yl)-7-methoxy-quinazolin-4-ol **250d**. To a stirred solution of compound **249d** (1.32 g, 3.58 mmol) in EtOH/H_2O (1/1, 10 mL) was added LiOH (10.3 mg, 4.29 mmol). The reaction mixture was stirred at 60 °C for 2 hrs. An aqueous solution of citric acid (5%) was added and the mixture was extracted with EtOAc. Organic were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was stirred with formamidine (26 mL) at 150 °C for 4 hrs, and the mixture was allowed to cool down to room temperature overnight. The mixture was poured into water, and extracted with DCM. Organics were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by chromatography on silica gel (petroleum ether/EtOAc) to yield compound **250d** as beige solid in 58% yield. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 1.32 (d, J = 6.71 Hz, 6H), 3.09-3.15 (m, 1H), 4.01 (s, 3H), 7.42 (d, J = 9.03 Hz, 1H), 7.67 (s, 1H), 8.11 (d, J = 9.03 Hz, 1H), 12.42 (s, 1H).

Example 3

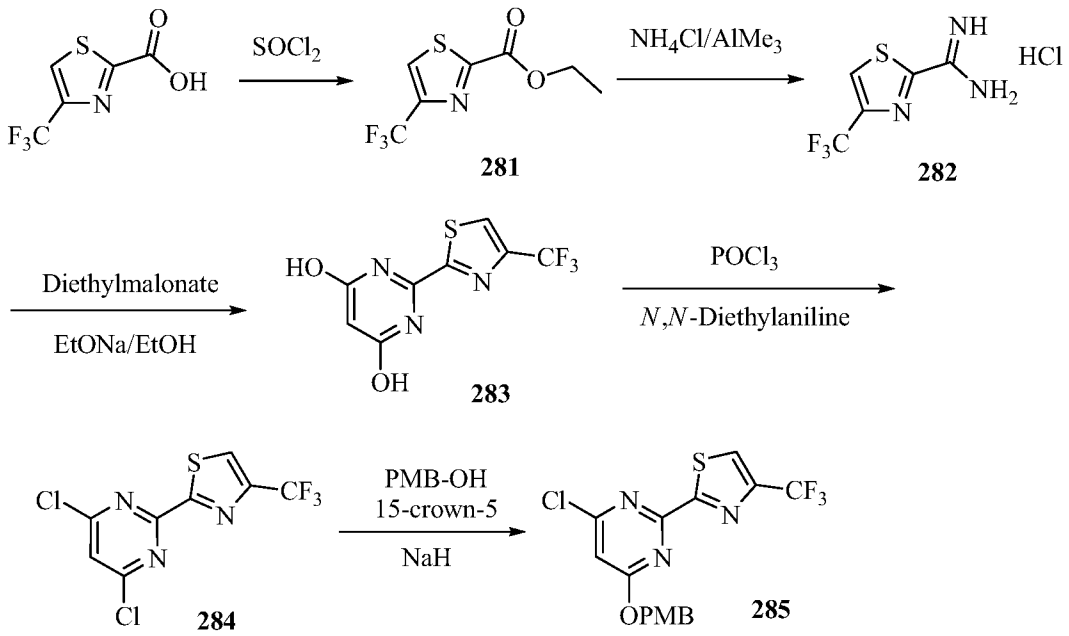
Preparation of (4-chloro-6-(4-methoxy-benzyloxy)-2-(4-trifluoromethyl-thiazol-2-yl) pyrimidine **285**



285

[00391] The synthesis of compound **285** is shown in Scheme 7.

Scheme 7



[00392] Preparation of 4-trifluoromethylthiazole-2-carboxylic acid ethyl ester **281**. To a stirred solution of 4-trifluoromethylthiazole-2-carboxylic acid (98 g, 1 eq.) in EtOH (600 mL) was added dropwise $SOCl_2$ (36 mL, 1 eq.). The mixture was stirred at 40 °C for 8 hrs and then at room temperature for 16 hrs. The reaction mixture was concentrated under reduced pressure and the residue was redissolved in DCM. Organics were washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield compound **281** as a brown solid in 96% yield. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45 (t, J = 7.14 Hz, 3H), 4.49-4.54 (q, J = 7.10 Hz, 2H), 8.02 (s, 1H).

[00393] Preparation of 4-trifluoromethylthiazole-2-carboxamidine hydrochloric acid **282**. To a suspension of NH_4Cl (19.8 g, 5 eq.) in toluene (250 mL) was added $AlMe_3$ in toluene (2 M, 185 mL, 5 eq.) dropwise at 0 °C. The mixture was stirred at room temperature for 1 hr. A solution of compound **281** (16.8 g, 1 eq.) in toluene (250 mL) was then slowly added and the reaction mixture was stirred at 80 °C for 16 hrs. After cooling at 0 °C, MeOH was added and the precipitate obtained was removed by filtration. The filtrate was concentrated under reduced pressure, dissolved in DCM/MeOH mixture, the precipitate obtained was removed by filtration. The filtrate was concentrated under reduced pressure and crystallized from DCM to yield compound **282** as a beige solid in 100% yield. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.44 (s, 1H).

[00394] Preparation of 2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4,6-diol **283**. To a stirred solution of NaOEt (32 g, 5 eq.) in EtOH (200 mL) was slowly added compound **282** (22 g, 1 eq.). The reaction mixture was stirred at room temperature for 30 min and diethyl malonate (11.5 mL, 0.8 eq.) was then added. The suspension was refluxed for 24 hrs. The solvent was removed under reduced pressure. The residue was suspended in H_2O (200 mL) and acidified to pH 5 with 2 N aqueous HCl. The resulting solid was filtered, washed with water, and dried under reduced pressure to yield compound **283** as a brown solid in 98% yield. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.77 (s, 1H), 8.68 (s, 1H).

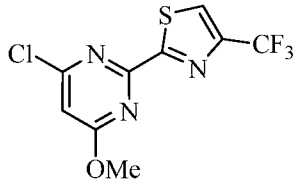
[00395] Preparation of 4,6-dichloro-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **284**. To a solution of compound **283** (14.41 g, 1 eq.) in $POCl_3$ (100 mL) was added dropwise *N*,*N*-diethylaniline (15 mL, 1.7 eq.) at 0 °C. The resulting mixture was stirred at 100 °C for 1 hr. $POCl_3$ was then removed under reduced pressure. Ice was added to the residue and the mixture was extracted with DCM. The combined organic layers were washed sequentially with H_2O, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was solubilised in DCM, pentane was added. The solid obtained was removed by filtration and organics were concentrated under reduced pressure to yield compound **284** as an orange solid in 68% yield. MS (ESI, EI^+): *m/z* =300 (MH^+).

[00396] Preparation of 4-chloro-6-(4-methoxy-benzyloxy)-2-(4-trifluoromethyl-thiazol-2-yl) pyrimidine **285**. NaH (60% in oil) (1.49 g, 1 eq.) was added portionwise to a stirred solution of compound **284** (11.2 g, 1 eq.) and 4-methoxybenzyl alcohol (5.15 g, 1 eq.). The reaction mixture was stirred at 0 °C for 1 hr and saturated $NaHCO_3$ solution was added. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under

reduced pressure. The residue obtained was triturated in pentane to yield compound **285** as a beige solid in 89% yield. MS (ESI, EI^+): *m/z* =402 (MH^+).

Example 4

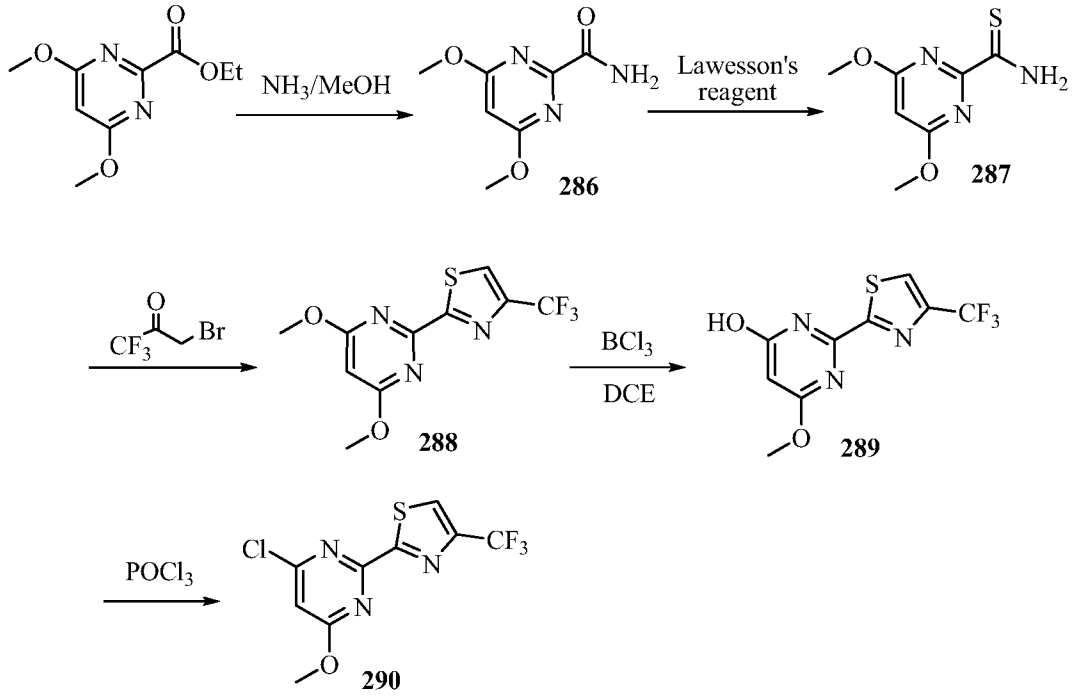
Preparation of 4-chloro-6-methoxy-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **290**



290

[00397] The synthesis of compound **290** is shown in Scheme 8.

Scheme 8



[00398] Preparation of 4,6-dimethoxy-pyrimidin-2-carboxylic amide **286**. Ethyl-4,6-dimethoxy-pyrimidin-2-carboxylate (25 g, 1 eq.) in NH_3/MeOH (7 M, 15 mL) was irradiated in a microwave reactor at 100 °C for 15 min. The solution was concentrated *in vacuo* to yield compound **286** as a beige solid in 100% yield. MS (ESI, EI^+): *m/z* =184 (MH^+).

[00399] Preparation of 4,6-dimethoxy-pyrimidin-2-carbothioic acid amide **287**. To a stirred solution of compound **286** (21.86 g, 1 eq.) in dry THF (200 mL) was added Lawesson's reagent (29 g, 0.6 eq.) under nitrogen. The mixture was then stirred at 90 °C for

1 hr and then concentrated *in vacuo*. The residue obtained was triturated in a DCM/diisopropyl ether mixture to yield compound **287** as an orange solid in 72% yield. MS (ESI, EI^+): *m/z* =200 (MH^+).

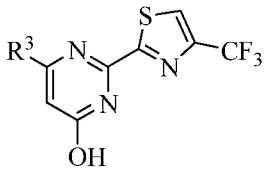
[00400] Preparation of 4,6-dimethoxy-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **288**. To a solution of compound **287** (14 g, 1 eq.) in EtOH (140 mL) was added 3-bromo-1,1,1-trifluoroacetone (8.8 mL, 1.2 eq.). The mixture was stirred at 90 °C for 16 hrs and concentrated *in vacuo*. DCM (20 mL) and water (20 mL) were added. Organics were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and flushed on a silica gel column with 5% MeOH/DCM to yield compound **288** as a beige compound in 12% yield. MS (ESI, EI^+): *m/z* =292 (MH^+).

[00401] Preparation of 6-hydroxy-4-methoxy-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **289**. To a solution of compound **288** (460 mg, 1 eq.) in DCE (10 mL) was added BCl_3 (3.16 mL, 2 eq.). The mixture was stirred at 60 °C for 16 hrs. Water and DCM were then added. Organics were separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was triturated in a DCM/pentane mixture to yield compound **289** as a beige solid in 38% yield. MS (ESI, EI^+): *m/z* =278 (MH^+).

[00402] Preparation of 4-chloro-6-methoxy-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **290**. To a stirred solution of compound **289** (2.38 g, 1 eq.) in $POCl_3$ (7.2 mL) was added *N*,*N*-diethylaniline (2.17 g, 1.7 eq.). The mixture was stirred at 110 °C for 16 hrs. The reaction was cooled down to room temperature and poured dropwise into an ice/water mixture. The aqueous solution was extracted with DCM. Organics were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by silica gel chromatography to yield compound **290** as an orange solid in 45% yield. MS (ESI, EI^+): *m/z* =296 (MH^+).

Example 5

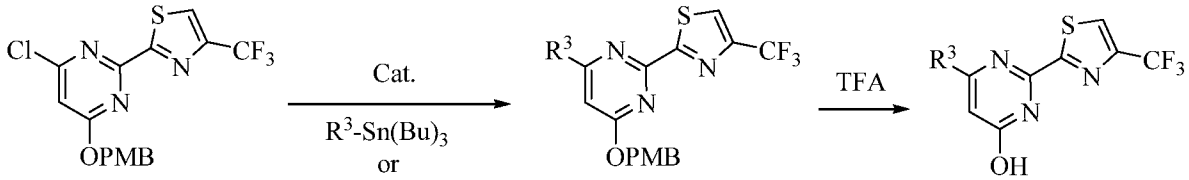
Preparation of 6-substituted-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidines **A1** to **AG1**



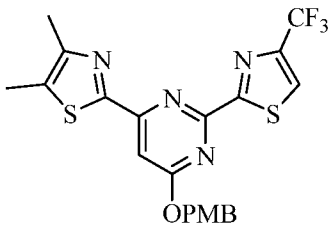
A1 to AG1

[00403] The syntheses of pyrimidines **A1** to **AG1** are shown in Scheme 9, wherein each R^3 is as defined herein.

Scheme 9



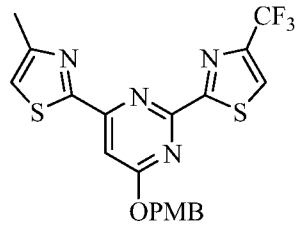
[00404] Preparation of 6-(4,5-dimethyl-thiazol-2-yl)-4-(4-methoxy-benzyloxy)-2-(4-trifluoromethylthiazol-2-yl)-pyrimidine **A**.



A

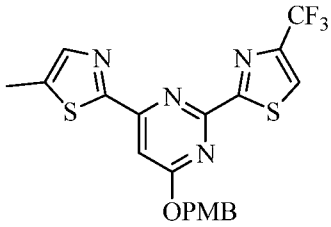
[00405] Compound **285** (800 mg), K_2CO_3 (331 mg, 1.2 eq.), $PdCl_2(PPh_3)_2$ (140 mg, 10%), and 4,5-dimethyl-2-(tributylstannyl)thiazole (965 mg, 1.2 eq.) in DMF (8 mL) were irradiated at 100 °C for 1 hr. The reaction mixture was concentrated under reduced pressure. Water and DCM were then added. Organics were separated, concentrated under reduced pressure, and purified by chromatography on silica gel (petroleum ether/EtOAc) to yield compound **A** as a yellow-brown oil in 92% yield. MS (ESI, EI^+): *m/z* =479 (MH^+).

[00406] Compounds **B** to **I** were synthesized according to the procedure as described for compound **A**.



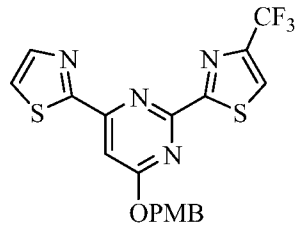
B

[00407] 4-(4-Methoxy-benzyloxy)-6-(4-methylthiazol-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **B** was synthesized from 4-methyl-2-(tributylstannyl)thiazole (931 mg, 1.2 eq.) as a pale yellow powder in 87% yield. MS (ESI, EI^+): *m/z* = 465 (MH^+).



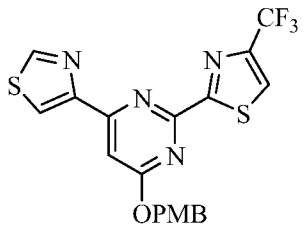
C

[00408] 4-(4-Methoxy-benzyloxy)-6-(5-methylthiazol-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **C** was synthesized from 5-methyl-2-(tributylstannyl)thiazole (931 mg, 1.2 eq.) as a pale yellow powder in 39% yield. MS (ESI, EI+): *m/z* = 465 (MH^+).



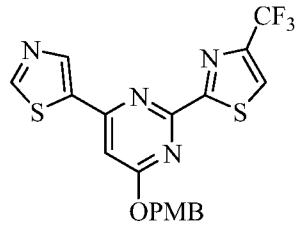
D

[00409] 4-(4-Methoxy-benzyloxy)-6-(thiazol-2-yl)-2-(4-trifluoromethylthiazol-2-yl)-pyrimidine **D** was synthesized from 2-(tributylstannyl)thiazole (898 mg, 1.2 eq.) as a pale yellow powder in 79% yield. MS (ESI, EI^+): *m/z* = 451 (MH^+).



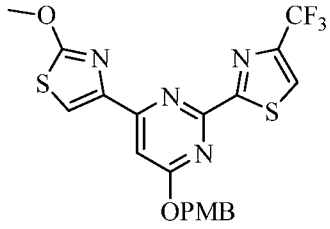
E

[00410] 4-(4-Methoxy-benzyloxy)-6-(thiazol-4-yl)-2-(4-trifluoromethylthiazol-2-yl)-pyrimidine **E** was synthesized from 4-(tributylstannyl)thiazole (898 mg, 1.2 eq.) as a pale yellow powder in 77% yield. MS (ESI, EI^+): *m/z* = 451 (MH^+).



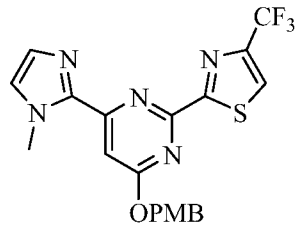
F

[00411] 4-(4-Methoxy-benzyloxy)-6-(thiazol-5-yl)-2-(4-trifluoromethylthiazol-2-yl)-pyrimidine **F** was synthesized from 5-(tributylstannyl)thiazole (898 mg, 1.2 eq.) as a pale yellow powder in 31% yield. MS (ESI, EI^+): *m/z* = 451 (MH^+).



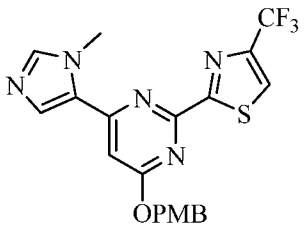
G

[00412] 4-(4-Methoxy-benzyloxy)-6-(2-methoxy-thiazol-4-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **G** was synthesized from 2-methoxy-4-(tributylstannyl)thiazole (970 mg, 1.2 eq.) as a pale yellow powder in 64% yield. MS (ESI, EI^+): *m/z* = 481 (MH^+).



H

[00413] 4-(4-Methoxy-benzyloxy)-6-(1-methyl-imidazol-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **H** was synthesized from 1-methyl -2-(tributylstannyl)imidazole (890 mg, 1.2 eq.) as a pale yellow powder in 30% yield. MS (ESI, EI^+): *m/z* = 448 (MH^+).

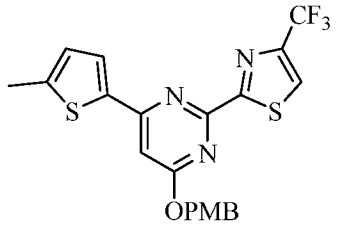


I

[00414] 4-(4-Methoxy-benzyloxy)-6-(1-methyl-imidazol-5-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **I**. Compound **I** was synthesized from 1-methyl-5-(tributylstannyl)-imidazole (890 mg, 1.2 eq.) as a pale yellow powder in 100% yield. MS (ESI, EI^+): *m/z* =

448 (MH^+).

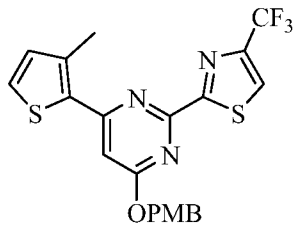
[00415] Preparation of 4-(4-methoxy-benzyloxy)-6-(5-methyl-thiophen-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **J**.



J

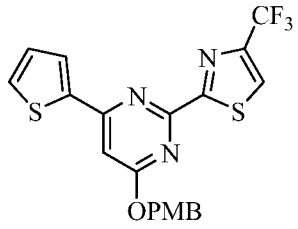
[00416] A mixture of compound **14** (800 mg, 1 eq.), 5-methylthiophene-2-boronic acid (423 mg, 1.5 eq.), $Pd(OAc)_2$ (7 mg, 1.5 mol%), PPh_3 (16 mg, 3 mol%), and Na_2CO_3 (422 mg, 2 eq.) in dioxane (8 mL) and water (1 mL) was irradiated at 120 °C for 30 min. The reaction mixture was then vigorously stirred for 10 min in DCM (30 mL) and water (30 mL). Layers were separated and organics were evaporated to yield compound **J** as an orange solid in 95% yield. MS (ESI, EI^+): *m/z* = 464 (MH^+).

[00417] Compounds **L** to **AG** were synthesized according to the procedure as described for compound **J**.



L

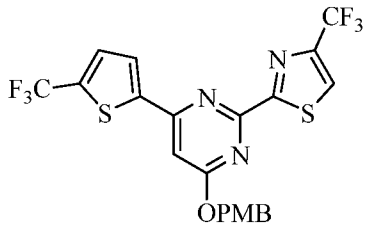
[00418] 4-(4-Methoxy-benzyloxy)-6-(3-methyl-thiophen-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **L** was synthesized from 3-methylthiophene-2-boronic acid (423 mg, 1.5 eq.) as a yellow solid in 95% yield. MS (ESI, EI^+): *m/z* = 464 (MH^+).



M

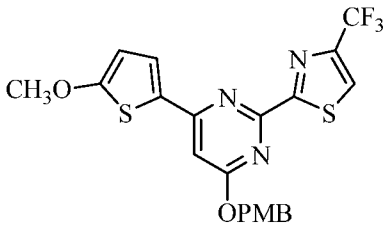
[00419] 4-(4-Methoxy-benzyloxy)-6-(thiophen-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **M** was synthesized from thiophene-2-boronic acid (509 mg, 1.5 eq.) as a

yellow solid in 92% yield. MS (ESI, EI^+): *m/z* = 450 (MH^+).



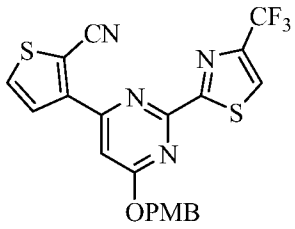
N

[00420] 4-(4-Methoxy-benzyloxy)-6-(5-trifluoromethyl-thiophen-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **N** was synthesized from 5-trifluoromethyl-thiophene-2-boronic acid pinacol ester (830 mg, 1.5 eq.) as a yellow solid in 87% yield. MS (ESI, EI^+): *m/z* = 518 (MH^+).



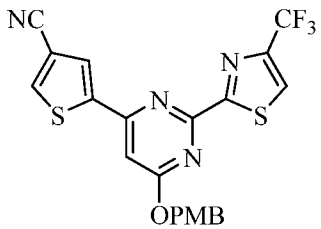
O

[00421] 4-(4-Methoxy-benzyloxy)-6-(5-methoxy-thiophen-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **O** was synthesized from 5-methoxy-thiophene-2-boronic acid pinacol ester (716 mg, 1.5 eq.) as an orange solid in 69% yield. MS (ESI, EI^+): *m/z* = 480 (MH^+).



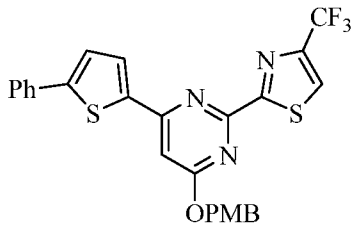
P

[00422] 4-(4-Methoxy-benzyloxy)-6-(2-cyano-thiophen-3-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **P** was synthesized from 2-cyano-thiophene-3-boronic acid pinacol ester (702 mg, 1.5 eq.) as a white foam in 83% yield. MS (ESI, EI^+): *m/z* = 497 $(M+Na)^+$.



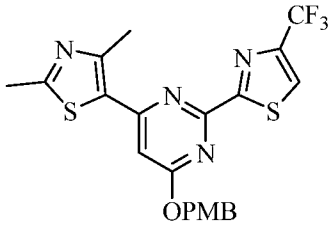
Q

[00423] 4-(4-Methoxy-benzyloxy)-6-(4-cyano-thiophen-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **Q** was synthesized from 4-cyano-thiophene-2-boronic acid pinacol ester (702 mg, 1.5 eq.) as a yellow foam in 85% yield. MS (ESI, EI^+): *m/z* = 497 $(M+Na)^+$.



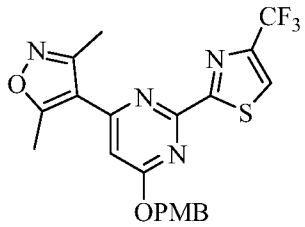
S

[00424] 4-(4-Methoxy-benzyloxy)-6-(5-phenyl-thiophen-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **S** was synthesized from 5-phenyl-thiophene-2-boronic acid (609 mg, 1.5 eq.) as a dark green gum in 68% yield. MS (ESI, EI^+): *m/z* = 526 (MH^+).



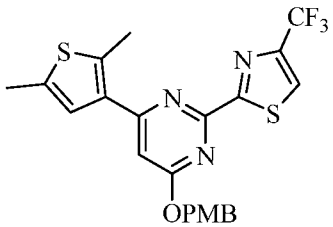
T

[00425] 4-(4-Methoxy-benzyloxy)-6-(2,4-dimethyl-thiazol-5-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **T** was synthesized from 2,4-dimethyl-thiazol-5-boronic acid pinacol ester (739 mg, 1.5 eq.) as a yellow solid in 98% yield. MS (ESI, EI^+): *m/z* = 479 (MH^+).



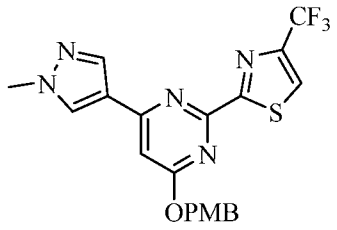
U

[00426] 4-(4-Methoxy-benzyloxy)-6-(3,5-dimethylisoxazol-4-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **U** was synthesized from 3,5-dimethylisoxazol-4-boronic acid (435 mg, 1.5 eq.) as a yellow solid in 57% yield. MS (ESI, EI^+): *m/z* = 463 (MH^+).



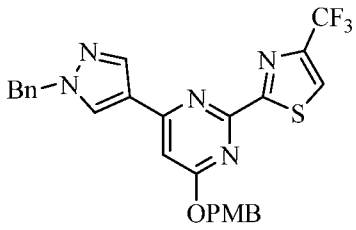
V

[00427] 4-(4-Methoxy-benzyloxy)-6-(2,5-dimethylthiophen-3-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **V** was synthesized from 2,5-dimethylthiophen-3-boronic acid (468 mg, 1.5 eq.) as a beige solid in 100% yield. MS (ESI, EI^+): *m/z* = 448 (MH^+).



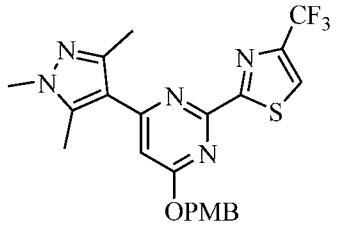
W

[00428] 4-(4-Methoxy-benzyloxy)-6-(1-methyl-pyrazol-4-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **W** was synthesized from 1-methyl-pyrazole-4-boronic acid (500 mg, 1 eq.) as a brown solid in 92% yield. MS (ESI, EI^+): *m/z* = 448 (MH^+).



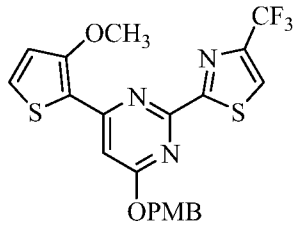
X

[00429] 4-(4-Methoxy-benzyloxy)-6-(1-benzyl-pyrazol-4-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **X** was synthesized from 1-benzyl-pyrazole-4-boronic acid (460 mg, 1 eq.) as a beige solid in 76% yield. MS (ESI, EI^+): *m/z* =524 (MH^+).



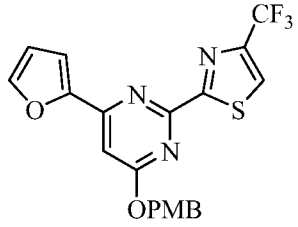
Y

[00430] 4-(4-Methoxy-benzyloxy)-6-(1,3,5-trimethylpyrazol-4-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **Y** was synthesized from 1,3,5-trimethylpyrazole-4-boronic acid (456 mg, 1 eq.) as a beige solid in 56% yield. MS (ESI, EI^+): *m/z* =476 (MH^+).



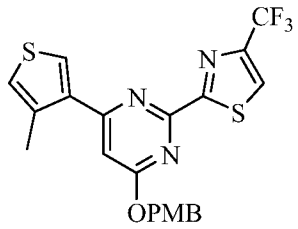
Z

[00431] 4-(4-Methoxy-benzyloxy)-6-(3-methoxy-thiophen-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **Z** was synthesized from 3-methoxythiophene-2-boronic acid (720 mg, 1 eq.) as a yellow solid in 76% yield. MS (ESI, EI^+): *m/z* = 480 (MH^+).



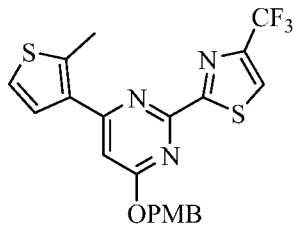
AA

[00432] 4-(4-Methoxy-benzyloxy)-6-(furan-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **AA** was synthesized from furan-2-boronic acid (750 mg, 1 eq.) as a beige solid in 92% yield. MS (ESI, EI^+): *m/z* =434 (MH^+).



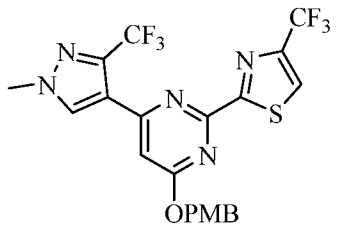
AB

[00433] 4-(4-Methoxy-benzyloxy)-6-(4-methyl-thiophen-3-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **AB** was synthesized from 3-methyl-thiophen-4-boronic acid (426 mg, 1 eq.) as a yellow solid in 90% yield**.** MS (ESI, EI^+): *m/z* = 464 (MH^+).



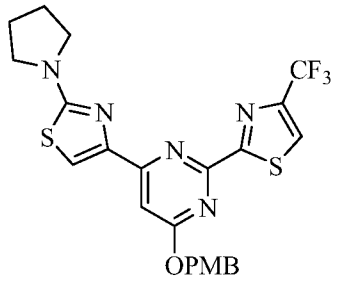
AC

[00434] 4-(4-Methoxy-benzyloxy)-6-(2-methyl-thiophen-3-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **AC** was synthesized from 2-methyl-thiophen-3-boronic acid (672 mg, 1 eq.) as a brown solid in 89% yield**.** MS (ESI, EI^+): *m/z* =464 (MH^+).



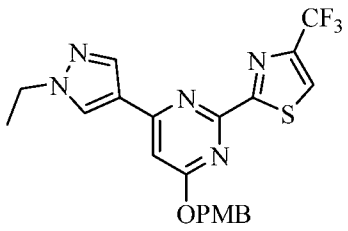
AD

[00435] 4-(4-Methoxy-benzyloxy)-6-(1-methyl-3-trifluoromethyl-pyrazol-4-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **AD** was synthesized from 1-methyl-3-trifluoromethyl-pyrazol-4-yl-boronic acid pinacol ester (414 mg, 1 eq.) as a beige solid in 66% yield. MS (ESI, EI^+): *m/z* =516 (MH^+).



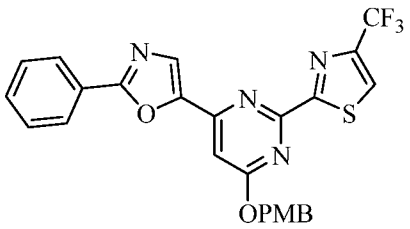
AE

[00436] 4-(4-Methoxy-benzyloxy)-6-(2-pyrrolidin-1-yl-thiazol-4-yl)-2-(4-trifluoromethylthiazol-2-yl)-pyrimidine **AE** was synthesized from 2-pyrrolidin-1-yl-thiazol-4-boronic acid pinacol ester (420 mg, 1 eq.) as a yellow solid in 89% yield. MS (ESI, EI^+): *m/z* =520 (MH^+).



AF

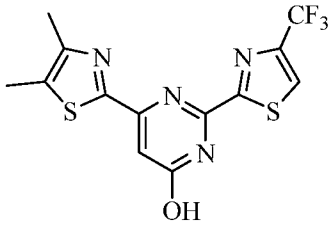
[00437] 4-(4-Methoxy-benzyloxy)-6-(1-ethyl-pyrazol-4-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **AF** was synthesized from 1-ethyl-pyrazole-4-boronic acid pinacol ester (333 mg, 1 eq.) as a beige solid in 96% yield. MS (ESI, EI^+): *m/z* =462 (MH^+).



AG

[00438] 4-(4-Methoxy-benzyloxy)-6-(2-phenyl-oxazol-5-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **AG** was synthesized from 2-phenyl-oxazol-5-boronic acid (407 mg, 1 eq.) as a white solid in 68% yield. MS (ESI, EI^+): *m/z* =511 (MH^+).

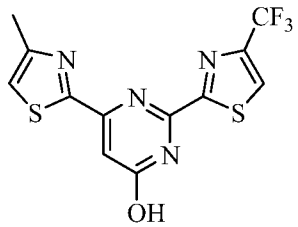
[00439] Preparation of 6-(4,5-dimethyl-thiazol-2-yl)- 2-(4-trifluoromethylthiazol-2-yl)-pyrimidin-4-ol **A1**.



A1

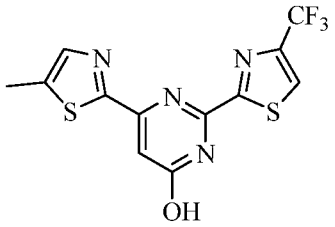
[00440] A solution of compound **A** (881 mg, 1 eq.) in TFA (2 mL) was stirred at room temperature for 2 hrs. DCM was added and the mixture was concentrated under reduced pressure. DCM was added to the residue followed by diisopropylether. The solid obtained was collected by filtration to yield compound **A1** as a beige solid in 96% yield. MS (ESI, EI^+): *m/z* =359 (MH^+).

[00441] Compounds **B1** to **AG1** were synthesized according to the procedure as described for compound **A1**.



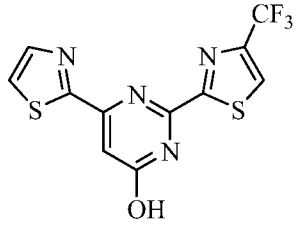
B1

[00442] 6-(4-Methylthiazol-2-yl)-2-(4-trifluoromethylthiazol-2-yl)-pyrimidin-4-ol **B1** was synthesized from compound **B** (807 mg, 1 eq.) as a pale yellow powder in 91% yield. MS (ESI, EI^+): *m/z* = 345 (MH^+).



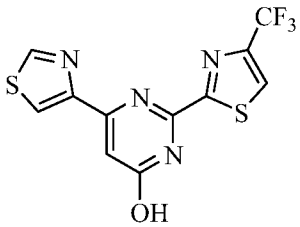
C1

[00443] 6-(5-Methylthiazol-2-yl)-2-(4-trifluoromethylthiazol-2-yl)-pyrimidin-4-ol **C1** was synthesized from compound **C** (363 mg, 1 eq.) as a pale yellow powder in 98% yield. MS (ESI, EI^+): *m/z* = 345 (MH^+).



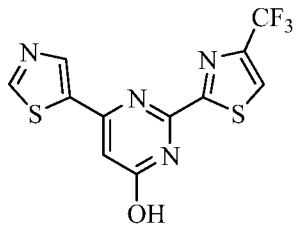
D1

[00444] 6-(Thiazol-2-yl)-2-(4-trifluoromethylthiazol-2-yl)-pyrimidin-4-ol **D1** was synthesized from compound **D** (715 mg, 1 eq.) as a pale yellow powder in 100% yield. MS (ESI, EI^+): *m/z* = 331 (MH^+).



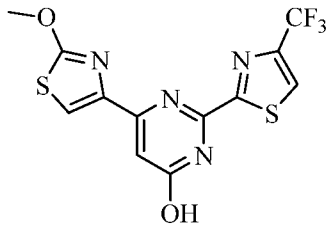
E1

[00445] 6-(Thiazol-4-yl)-2-(4-trifluoromethylthiazol-2-yl)-pyrimidin-4-ol **E1** was synthesized from compound **E** (695 mg, 1 eq.) as a pale yellow powder in 100% yield. MS (ESI, EI^+): *m/z* = 331 (MH^+).



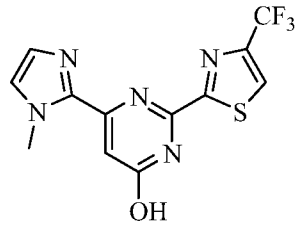
F1

[00446] 6-(Thiazol-5-yl)-2-(4-trifluoromethylthiazol-2-yl)-pyrimidin-4-ol **F1** was synthesized from compound **F** (280 mg, 1 eq.) as a pale yellow powder in 95% yield. MS (ESI, EI^+): *m/z* = 331 (MH^+).



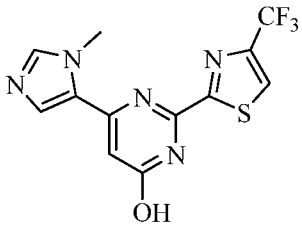
G1

[00447] 6-(2-Methoxy-thiazol-4-yl)-2-(4-trifluoromethylthiazol-2-yl)-pyrimidin-4-ol **G1** was synthesized from compound **G** (611 mg, 1 eq.) as a pale yellow powder in 97% yield. MS (ESI, EI^+): *m/z* = 361 (MH^+).



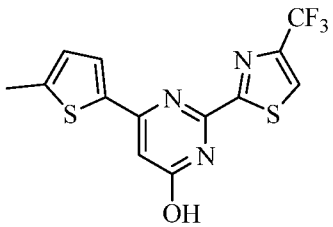
H1

[00448] 6-(1-Methyl-imidazol-2-yl)-2-(4-trifluoromethylthiazol-2-yl)-pyrimidin-4-ol **H1** was synthesized from compound **H** (270 mg, 1 eq.) as a pale yellow powder in 100% yield. MS (ESI, EI^+): *m/z* = 328 (MH^+).



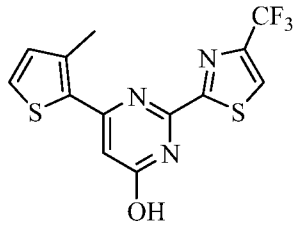
I1

[00449] 6-(1-Methyl-imidazol-5-yl)-2-(4-trifluoromethylthiazol-2-yl)-pyrimidin-4-ol **I1** was synthesized from compound **I** (915 mg, 1 eq.) as a pale yellow powder in 100% yield. MS (ESI, EI^+): *m/z* =328 (MH^+).



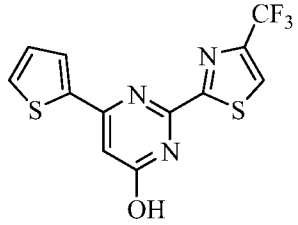
J1

[00450] 6-(5-Methyl-thiophen-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **J1** was synthesized from compound **J** (307 mg, 1 eq.) as white solid in 80% yield. MS (ESI, EI^+): *m/z* = 344 (MH^+).



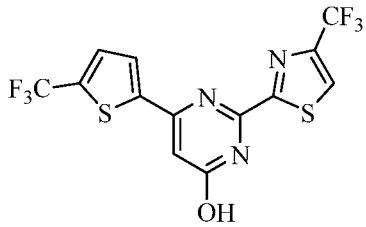
L1

[00451] 6-(3-Methyl-thiophen-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **L1** was synthesized from compound **L** (880 mg, 1 eq.) as a yellow solid in 83% yield. MS (ESI, EI^+): *m/z* = 344 (MH^+).



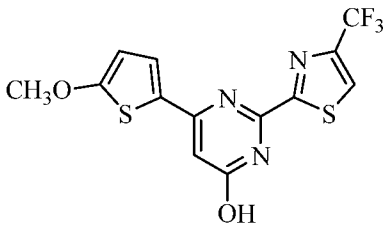
M1

[00452] 6-(Thiophen-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **M1** was synthesized from compound **M** (821 mg, 1 eq.) as a yellow solid in 96% yield. MS (ESI, EI^+): *m/z* = 330 (MH^+).



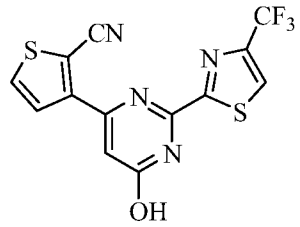
N1

[00453] 6-(5-Trifluoromethyl-thiophen-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **N1** was synthesized from compound **N** (900 mg, 1 eq.) as a yellow solid in 100% yield. MS (ESI, EI^+): *m/z* = 398 (MH^+).



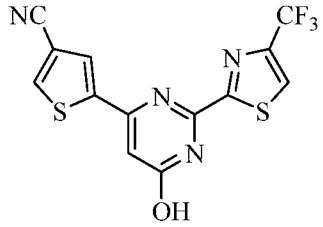
O1

[00454] 6-(5-Methoxy-thiophen-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **O1** was synthesized from compound **O** (657 mg, 1 eq.) as yellow solid in 94% yield. MS (ESI, EI^+): *m/z* = 360 (MH^+).



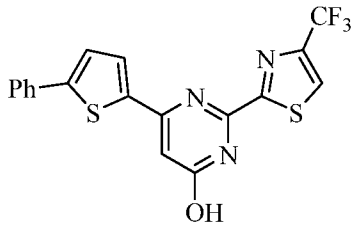
P1

[00455] 6-(2-Cyano-thiophen-3-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **P1** was synthesized from compound **P** (781 mg, 1 eq.) as a white solid in 100% yield. MS (ESI, EI^+): *m/z* = 355 (MH^+).



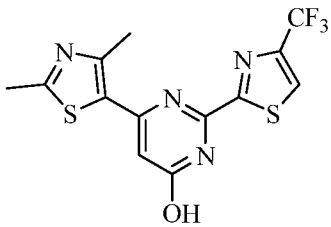
Q1

[00456] 6-(4-Cyano-thiophen-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **Q1** was synthesized from compound **Q** (807 mg, 1 eq.) as a white solid in 94% yield. MS (ESI, EI^+): *m/z* = 355 (MH^+).



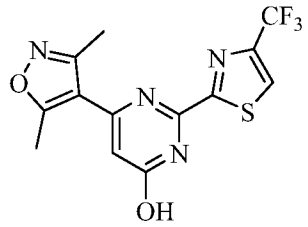
S1

[00457] 6-(5-Phenyl-thiophen-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **S1** was synthesized from compound **S** (719 mg, 1 eq.) as a green solid in 76% yield. MS (ESI, EI^+): *m/z* = 406 (MH^+).



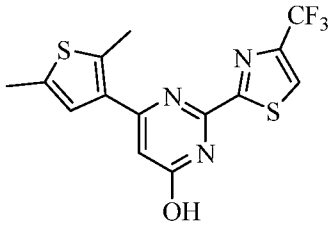
T1

[00458] 6-(2,4-Dimethyl-thiazol-5-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **T1** was synthesized from compound **T** (685 mg, 1 eq.) as a cream solid in 100% yield. MS (ESI, EI^+): *m/z* = 360 (MH^+).



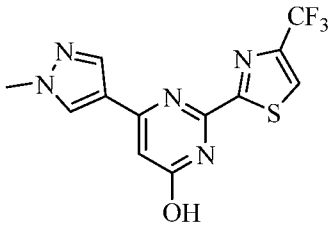
U1

[00459] 6-(3,5-Dimethylisoxazol-4-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **U1** was synthesized from compound **U** (224 mg, 1 eq.) as a white solid in 92% yield. MS (ESI, EI^+): *m/z* = 343 (MH^+).



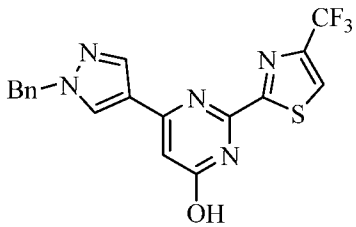
V1

[00460] 6-(2,5-Dimethylthiophen-3-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **V1** was synthesized from compound **V** (970 mg, 1 eq.) as a beige solid in 46% yield. MS (ESI, EI^+): *m/z* = 358 (MH^+).



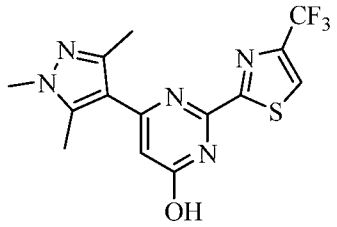
W1

[00461] 6-(1-Methyl-pyrazol-4-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **W1** was synthesized from compound **W** (826 mg, 1 eq.) as a brown solid in 85% yield. MS (ESI, EI^+): *m/z* =328 (MH^+).



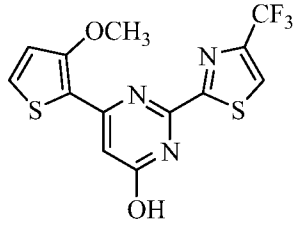
X1

[00462] 6-(1-Benzyl-pyrazol-4-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **X1** was synthesized from compound **X** (867 mg, 1 eq.) as a beige solid in 100% yield. MS (ESI, EI^+): *m/z* =404 (MH^+).



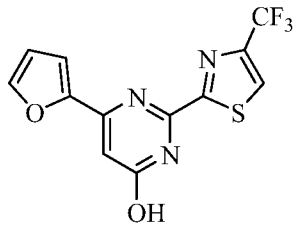
Y1

[00463] 6-(1,3,5-Trimethyl-pyrazol-4-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **Y1** was synthesized from compound **Y** (489 mg, 1 eq.) as a white solid in 100% yield. MS (ESI, EI^+): *m/z* =356 (MH^+).



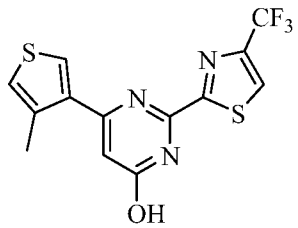
Z1

[00464] 6-(3-Methoxy-thiophen-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **Z1** was synthesized from compound **Z** (744 mg, 1 eq.) as a white solid in 80% yield. MS (ESI, EI^+): *m/z* =360 (MH^+).



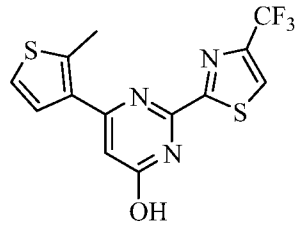
AA1

[00465] 6-(Furan-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **AA1** was synthesized from compound **AA** (791 mg, 1 eq.) as a beige solid in 85% yield. MS (ESI, EI^+): *m/z* =314 *(*MH^+).



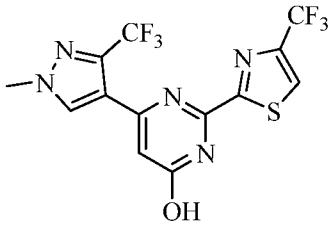
AB1

[00466] 6-(4-Methyl-thiophen-3-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **AB1** was synthesized from compound **AB** (831 mg, 1 eq.) as a beige solid in 67% yield. MS (ESI, EI^+): *m/z* =344(MH^+).



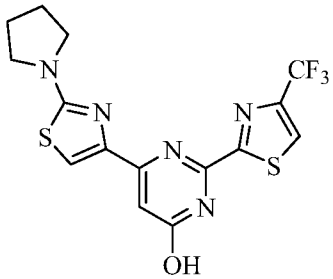
AC1

[00467] 6-(2-Methyl-thiophen-3-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **AC1** was synthesized from compound **AC** (827 mg, 1 eq.) as a brown solid in 67% yield. MS (ESI, EI^+): *m/z* =344(MH^+).



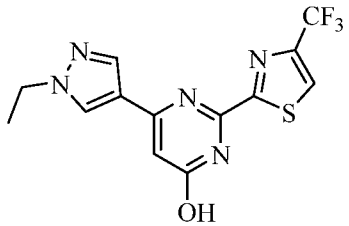
AD1

[00468] 6-(1-Methyl-3-trifluoromethyl-pyrazol-4-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **AD1** was synthesized from compound **AD** (342 mg, 1 eq.) as a beige solid in 100% yield. MS (ESI, EI^+): *m/z* =396(MH^+).



AE1

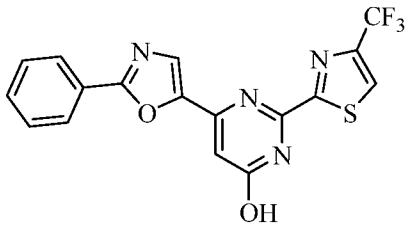
[00469] 6-(2-Pyrrolidin-1-yl-thiazol-4-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **AE1** was synthesized from compound **AE** (464 mg, 1 eq.) as a yellow solid in 87% yield. MS (ESI, EI^+): *m/z* =400(MH^+).



AF1

[00470] 6-(1-Ethyl-pyrazol-4-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **AF1** was synthesized from compound **AF** (442 mg, 1 eq.) as a beige solid in 93% yield. MS

(ESI, EI^+): *m/z* =342(MH^+).

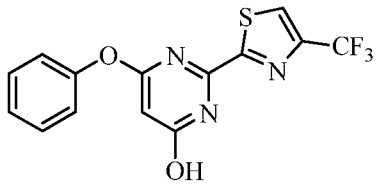


AG1

[00471] 6-(2-Phenyl-oxazol-5-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **AG1** was synthesized from compound **AG** (346 mg, 1 eq.) as a white solid in 100% yield. MS (ESI, EI^+): *m/z* =391(MH^+).

Example 6

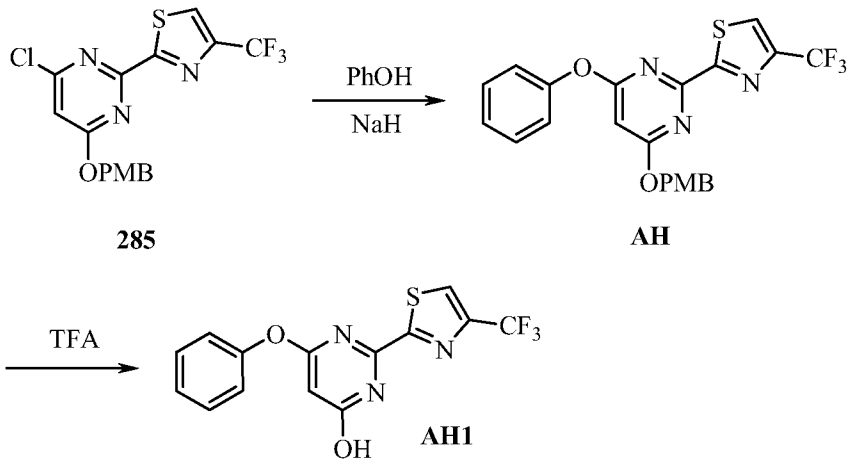
Preparation of 6-phenoxy-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **AH1**



AH1

[00472] The synthesis of compound **AH1** is shown in Scheme 10.

Scheme 10



285 **AH** **AH1**

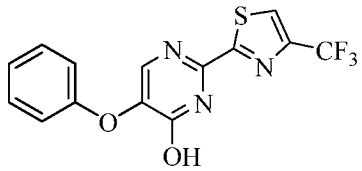
[00473] Preparation of 4-(4-methoxy-benzyloxy)-6-phenoxy-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **AH**. To a stirred solution of compound **285** (246 mg, 1 eq.) in anhydrous DMF (5 mL) was added a solution of phenol (69 mg, 1.2 eq.) and NaH 60% in oil (29 mg, 1.2 eq.) in anhydrous DMF (5 mL). The resulting mixture was stirred at room

temperature for 3 hrs and concentrated under reduced pressure. The crude material was solubilized in EtOAc (10 mL), and washed sequentially with water and brine. Organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield compound **AH** as a beige solid in 100% yield. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.82 (s, 3H), 5.48 (s, 2H), 6.01 (s, 1H), 6.83-6.93 (m, 1H), 7.16-7.31 (m; 4H), 4.43 (m, 4H), 7.90 (s, 1H).

[00474] Preparation of 6-phenoxy-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **AH1**. Compound **AH1** was synthesized from compound **AH** (5 mg, 1 eq.) as beige solid in 60% yield, according to the procedure as described for compound **A1**. MS (ESI, EI^+): *m/z* =340(MH^+).

Example 7

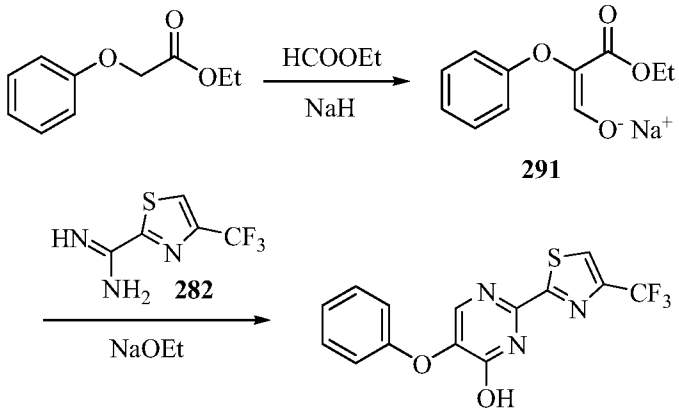
Preparation of 5-phenoxy-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **AI1**



AI1

[00475] The synthesis of compound **AI1** is shown in Scheme 11.

Scheme 11



AI1

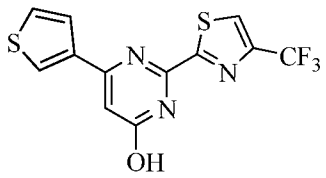
[00476] Preparation of sodium 2-ethoxycarbonyl-2-phenoxyethenolate **291**. To a suspension of NaH (60% in oil) (760 mg, 1.1 eq.) in dry Et_2O (8 mL) was added dropwise a solution of ethyl formate (1.4 mL, 1 eq.) and phenoxy ethyl acetate (2.7 mL, 1 eq.) in 2 mL of Et_2O at 0 °C. The solution was allowed to warm up to room temperature and was stirred for

18 hrs. The suspension obtained was filtered and washed with ether and pentane to yield compound **291** as a white solid in 68% yield. MS (ESI, EI^+): *m/z* =231 ($M+Na^+$).

[00477] Preparation of 5-phenoxy-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **AI1**. To a solution of compound **282** (280 mg, 1 eq.) in dry EtOH (6 mL) was added compound **291** (1.38 g, 5 eq.) under nitrogen, followed by NaOEt (165 mg, 1 eq.). The reaction mixture was stirred at 90 °C for 2 hrs. EtOH was evaporated and a DCM/water mixture was added. Aqueous layer was acidified to pH 5 with aqueous 1N HCl and was extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by chromatography on silica gel (DCM/MeOH) to yield compound **AI1** as a beige oil in 81% yield. MS (ESI, EI^+): *m/z* =340 (MH^+).

Example 8

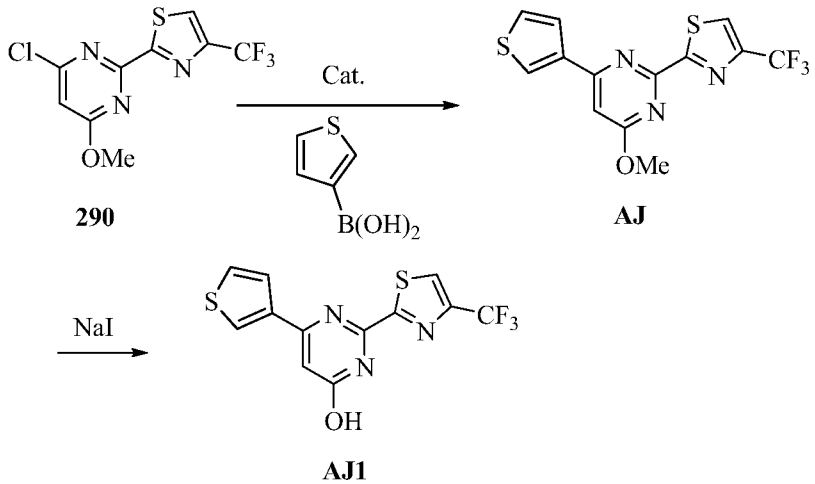
Preparation of 6-(thien-3-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **AJ1**



AJ1

[00478] The synthesis of compound **AJ** is shown in Scheme 12.

Scheme 12



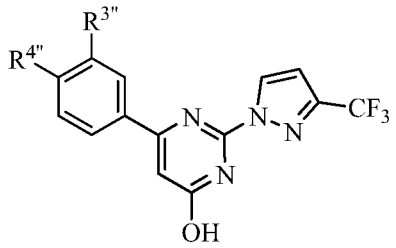
[00479] Preparation of 4-methoxy-6-thien-3-yl-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidine **AJ**. Compound **AJ** was synthesized from thienyl-3-boronic acid (357 mg, 1.5 eq.) and compound **290** as a white solid in 50% yield according to the procedure as described

for compound **J**. MS (ESI, EI^+): *m/z* =344 (MH^+).

[00480] Preparation of 6-(thien-3-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-ol **AJ1**. A mixture of compound **AJ** (320 mg, 1 eq.) and NaI (557 mg, 4 eq.) in ACN (100 mL) was irradiated for 5 min at room temperature. TMS-Cl (470µL, 4 eq.) was then added and the mixture was irradiated at 100 °C for 15 min. The mixture was concentrated under reduced pressure. The residue was solubilized in DCM, and washed sequentially with sodium thiosulfate solution and brine. Organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield compound **AJ1** as a white solid in 100% yield. MS (ESI, EI^+): *m/z* =330 (MH^+).

Example 9

Preparation of substituted pyrimidines **308**



308b: $R^{3"}$= H, $R^{4"}$ = H,
308c: $R^{3"}$= H, $R^{4"}$ = Me
308d: $R^{3"}$= H, $R^{4"}$= OMe
308e: $R^{3"}$= H, $R^{4"}$= Cl
308f: $R^{3"}$= Cl, $R^{4""}$= H
308g: $R^{3"}$= H, $R^{4"}$= F

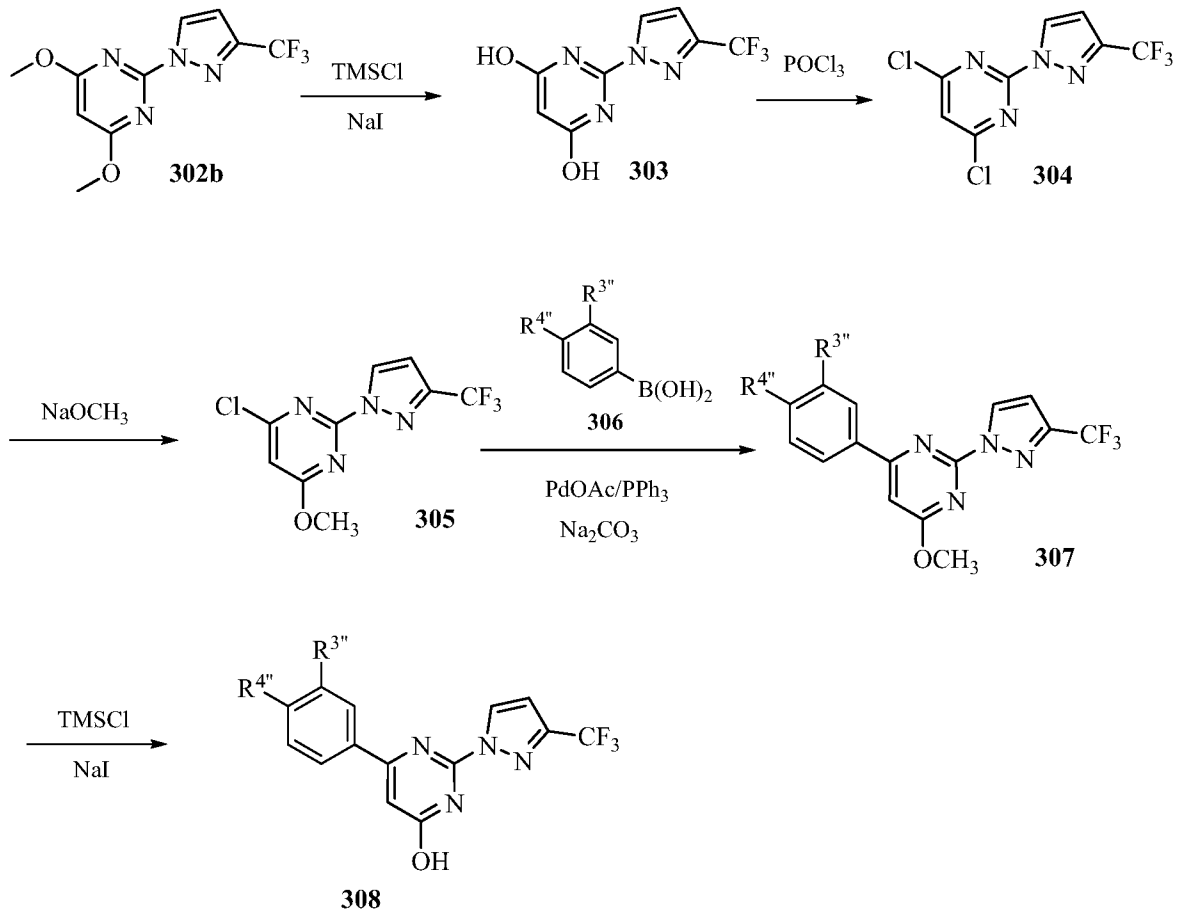
[00481] The syntheses of compounds **308** are shown in Scheme 13.

[00482] Preparation of 4,6-dihydroxy-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **303**. Compound **303** was synthesized from compound **302b** (12.3 g, 90.3 mmol), according to the procedure as described for compound **302a**, as a white solid in 100% yield. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm) 5.80 (s, 1H), 7.00 (d, J = 2.78 Hz, 1H), 8.62 (dd, J = 2.78 Hz and J = 1.00 Hz, 1H); ^{19}F NMR (DMSO-d_6, 376 MHz) δ (ppm) -61.23 (s, 3F).

[00483] Preparation of 4,6-dichloro-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **304**. To compound **303** (8.7 g, 35.15 mmol) were added $POCl_3$ (16.5 mL) and *N*,*N*-diethylaniline (9.56 mL). The resulting mixture was stirred at 110 °C for 2 hrs. The mixture was then cooled down to room temperature and poured dropwise into an ice/water mixture. The precipitate was filtered, washed with water, and dried under reduced pressure to yield

compound **304** as a white solid in 90% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 6.77 (s, 1H), 7.37 (s, 1H), 8.63 (dd, J = 2.78 Hz and J = 1.00 Hz, 1H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm) -62.78 (s, 3F).

Scheme 13

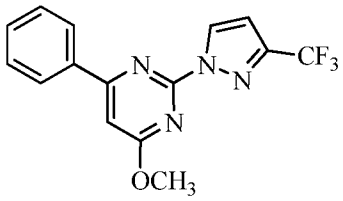


302b **303** **304** **305** **306** **307** **308**

[00484] Preparation of 6-chloro-4-methoxy-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **305**. To a stirred solution of compound **304** (1 g, 3.53 mmol) in MeOH (10 mL) at 0°C was added NaOMe (760 µL) dropwise. The mixture was stirred at room temperature for 2 hrs. Methanol was evaporated. The residue was dissolved in DCM, washed sequentially with water and brine. Organics were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by silica gel chromatography to yield compound **305** as a white solid in 68% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.11 (s, 3H), 6.71-6.72 (m, 2H), 8.58 (dd, J = 2.78 Hz and J = 1.00 Hz, 1H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm) -62.54 (s, 3F).

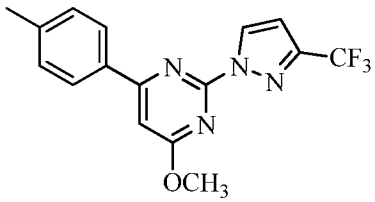
[00485] Preparation of 4-methoxy-6-phenyl-2-(3-trifluoromethyl-pyrazol-1-yl)-

pyrimidine **307b**.



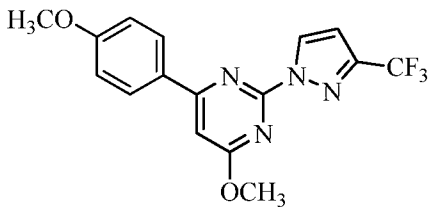
307b

[00486] To a solution of compound **305** (670 mg, 2.4 mmol) in dry THF (11 mL) were added phenyl boronic acid **306b** (439 mg, 3.6 mmol), palladium acetate (7 mg, 0.03 mmol), triphenyl phosphine (16 mg, 0.06 mmol), and sodium carbonate (4.8 mg). The mixture was stirred at 60 °C for 3 hrs. The solution was then cooled down to room temperature. Water and TBDME were added. Organics were washed with water, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by silica gel chromatography to yield compound **307b** as a white solid in 95% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.11 (s, 3H), 6.71-6.72 (m, 2H), 7.54-8.05 (m, 5H), 8.58 (dd, J = 2.78 Hz and J = 1.00 Hz, 1H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm) -62.45 (s, 3F).



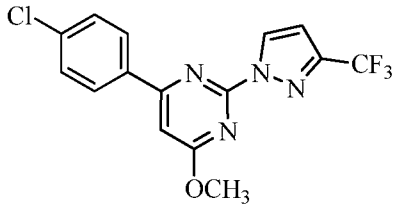
307c

[00487] 4-Methoxy-6-(4-methyl-phenyl)-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **307c** was synthesized from compound **305** (1 g, 3.59 mmol) and (4-methyl-phenyl)-boronic acid **306c** (732 mg, 5.39 mmol), according to the procedure as described for compound **307b**, as a white solid in 75% yield. MS (ESI, EI$^+$): m/z = 335 (MH$^+$).



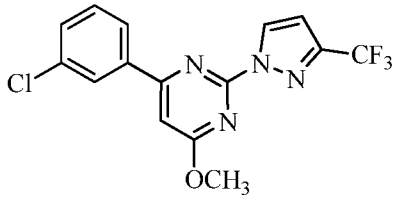
307d

[00488] 4-Methoxy-6-(4-methoxy-phenyl)-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **307d** was synthesized from compound **305** (1 g, 3.59 mmol) and (4-methoxy-phenyl)-boronic acid **306d** (819 mg, 5.39 mmol), according to the procedure as described for compound **307b**, as a beige solid in 55% yield. MS (ESI, EI$^+$): m/z = 351 (MH$^+$).



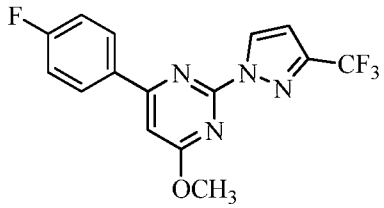
307e

[00489] 4-Methoxy-6-(4-chloro-phenyl)-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **307e** was synthesized from compound **305** (1 g, 3.59 mmol) and (4-chloro-phenyl)-boronic acid **306e** (842 mg, 5.39 mmol), according to the procedure as described for compound **307b**, was a beige solid in 45% yield. MS (ESI, EI^+): *m/z* = 355 (MH^+).



307f

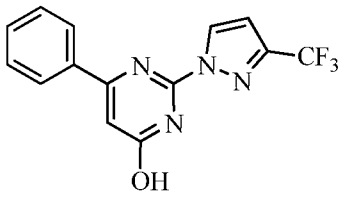
[00490] 4-Methoxy-6-(3-chloro-phenyl)-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **307f** was synthesized from compound **305** (1 g, 3.59 mmol) and (3-chloro-phenyl)-boronic acid **306f** (842 mg, 5.39 mmol), according to the procedure as described for compound **307b** as a beige solid in 45% yield. MS (ESI, EI^+): *m/z* = 355 (MH^+).



307g

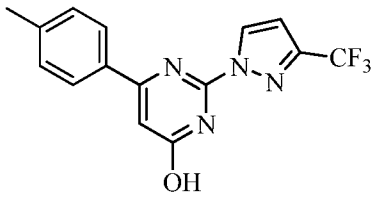
[00491] 4-Methoxy-6-(4-fluoro-phenyl)-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **307g** was synthesized from compound **100** (760 mg, 3.18 mmol) and compound **27a** (650 mg, 4.78 mmol) following the procedure as described for compound **307b**, as a yellow solid in 100% yield. MS (ESI, EI^+): *m/z* = 339 (MH^+).

[00492] Preparation of 4-hydroxy-6-phenyl-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **308b**.



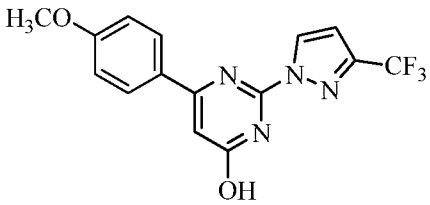
308b

[00493] Compound **308b** was synthesized from compound **307b** (720 mg, 2.25 mmol), according to the procedure as described for compound **308a**, as a white solid in 20% yield. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 7.06 (d, J = 2.65 Hz, 1H), 7.26 (s, 1H), 7.51-7.56 (m, 3H), 8.24-8.27 (m, 2H), 8.99 (dd, J = 2.70 Hz and J = 0.97 Hz, 1H).



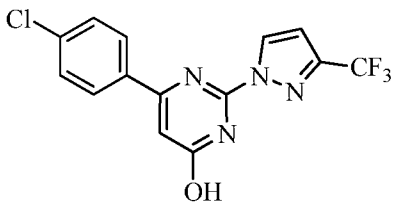
308c

[00494] 4-Hydroxy-6-(4-methyl-phenyl)-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **308c** was synthesized from compound **307c**, according to the procedure as described for compound **308a**, as a white solid in 50% yield. MS (ESI, EI$^+$): m/z = 321 (MH^+).



308d

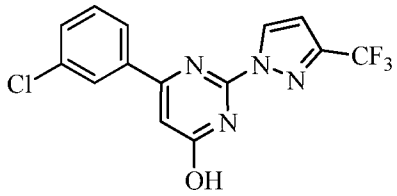
[00495] 4-Hydroxy-6-(4-methoxy-phenyl)-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **308d** was synthesized from compound **307d**, according to the procedure as described for compound **308a**, as a beige solid in 60% yield. MS (ESI, EI$^+$): m/z = 337 (MH^+).



308e

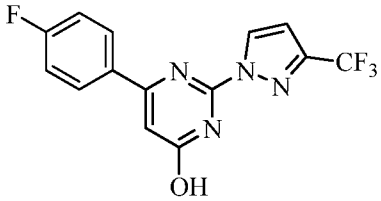
[00496] 4-Hydroxy-6-(4-chloro-phenyl)-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **308e** was synthesized from compound **307e**, according to the procedure as described for

compound **308a**, as a beige solid in 42% yield. MS (ESI, EI^+): *m/z* = 341 (MH^+).



308f

[00497] 4-Hydroxy-6-(3-chloro-phenyl)-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **308f** was synthesized from compound **307f**, according to the procedure as described for compound **308a**, as a beige solid in 90% yield. MS (ESI, EI^+): *m/z* = 341 (MH^+).

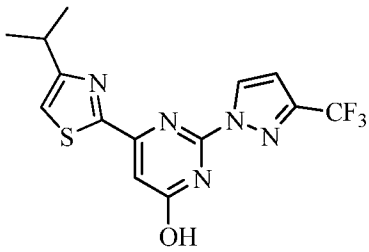


308g

[00498] 4-Hydroxy-6-(4-fluoro-phenyl)-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **308g** was synthesized from compound **307g**, according to the procedure as described for compound **308a**, as a yellow solid in 43% yield. MS (ESI, EI^+): *m/z* = 325 (MH^+).

Example 10

Preparation of 4-hydroxy-6-(4-isopropyl-thiazol-2-yl)-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **308h**



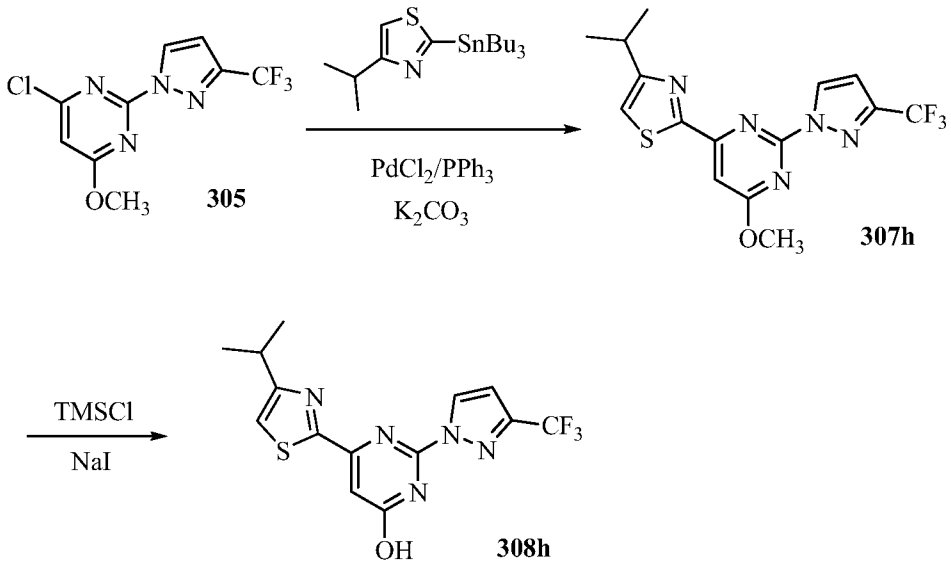
308h

[00499] The synthesis of compound **308h** is shown in Scheme 14.

[00500] Preparation of 4-methoxy-6-(4-isopropyl-thiazol-2-yl)-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **307h**. To a solution of compound **305** (892 mg, 3.2 mmol) in dry DMF (15 mL) were added tributyl(4-isopropyl-thiazole)-stannane **219** (2 g, 4.8 mmol), $PdCl_2(PPh_3)_2$ (224 mg, 0.32 mmol), and potassium carbonate (530 mg, 3.84 mmol). The mixture was stirred at 90 °C for 48 hrs, and the concentrated under reduced pressure. Water

and ethyl acetate were added. Organics were washed with water, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by silica gel chromatography to yield compound **307h** as a beige solid in 76% yield. MS (ESI, EI^+): *m/z* = 370 (MH^+).

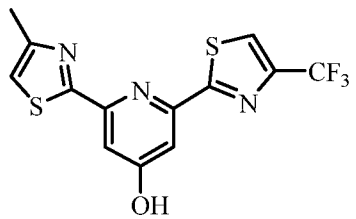
Scheme 14



[00501] Preparation of 4-hydroxy-6-(4-isopropyl-thiazol-2-yl)-2-(3-trifluoromethyl-pyrazol-1-yl)-pyrimidine **308h**. Compound **308h** was synthesized from compound **307h** (900 mg, 2.44 mmol), according to the procedure as described for compound **308a**, as a beige solid in 30% yield. MS (ESI, EI^+): *m/z* = 356 (MH^+).

Example 11

Preparation of 2-(4-methyl-thiazol-2-yl)-6-(4-trifluoromethyl-thiazol-2-yl)-pyridin-4-ol **23**



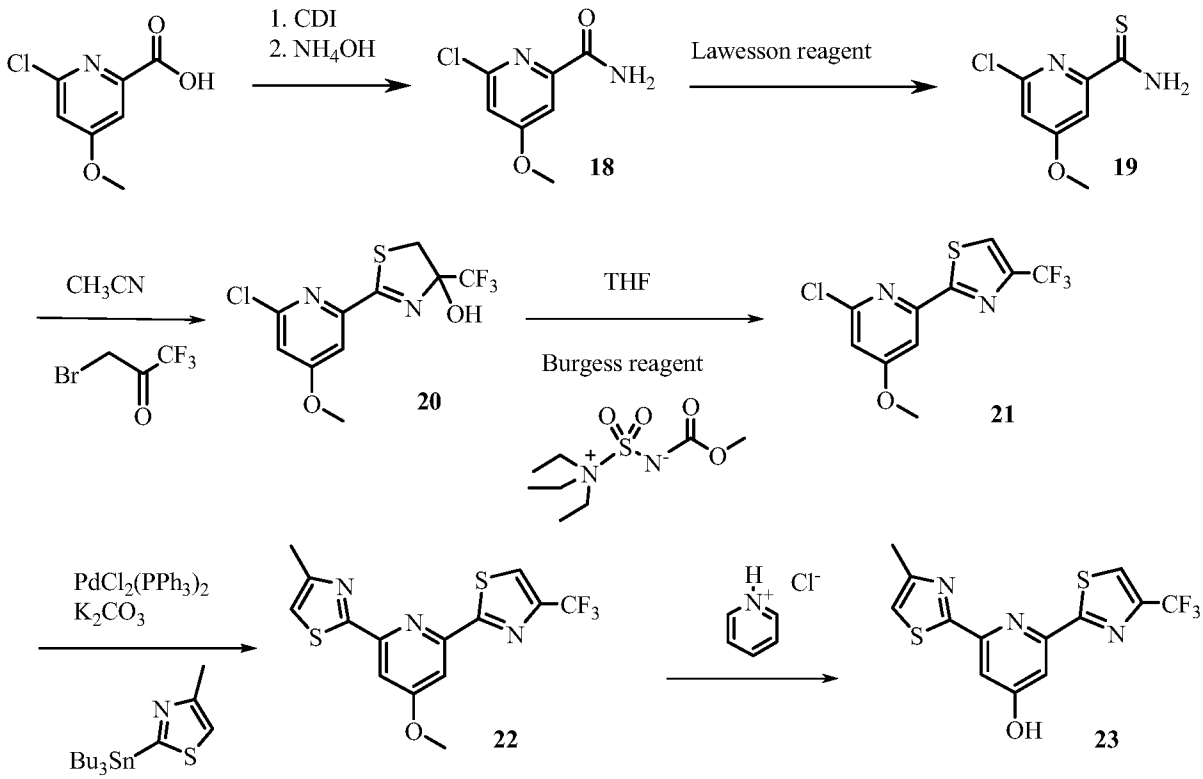
23

[00502] The synthesis of compound **23** is shown in Scheme 15.

[00503] Preparation of 6-chloro-4-methoxy-pyridine-2-carboxylic acid amide **18**. To a solution of 4-methoxy-6-chloro picolinic acid (25 mmol) in anhydrous DMF (48 mL) was added CDI (27.5 mmol) at 0 °C. The reaction mixture was stirred for 5 min in an ice-bath and then stirred at room temperature. After the reaction was completed, NH_4OH (190 mL)

was added and the reaction mixture was stirred at room temperature for 6 hrs. The mixture was partionned between H_2O (200 mL) and DCM (300 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by silica gel chromatography (eluent: DCM/CH_3OH) to give compound **18** as a beige solid in 61% yield. MS (ESI, EI^+): *m/z* = 187.14 (MH^+).

Scheme 15



[00504] Preparation of 6-chloro-4-methoxy-pyridine-2-carbothioic acid amide **19**. To a solution of compound **18** (9 mmol) in THF (30 mL) was added Lawesson reagent (5.4 mmol). The reaction mixture was stirred at 90 °C for 2 hrs. After cooling at room temperature, the solution was concentrated under reduced pressure and the residue was triturated in DCM to give compound **19** as a yellow solid in 71% yield. MS (ESI, EI^+): *m/z* = 203 (MH^+).

[00505] Preparation of 2-(6-chloro-4-methoxy-pyridin-2-yl)-4-trifluoromethyl-4,5-dihydro-thiazol-4-ol **20**. To a solution of compound **19** (7.4 mmol) in acetonitrile (35 mL) was added 3-bromo-1,1,1-trifluoro-1-propan-2-one (8.14 mmol). The reaction mixture was stirred at 90 °C for 1 hr. The solution was concentrated under reduced pressure. DCM and a saturated solution of $NaHCO_3$ were added. The layers were separated and the organic layer

was concentrated under reduced pressure. The crude was purified by silica gel chromatography (eluent: DCM) to give compound **20** in 95% yield. MS (ESI, EI^+): *m/z* = 313 (MH^+).

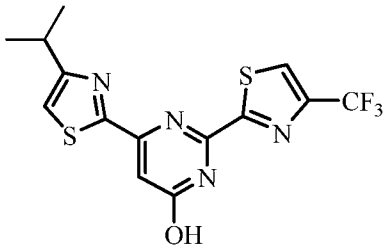
[00506] Preparation of 2-chloro-4-methoxy-6-(4-trifluoromethyl-thiazol-2-yl)-pyridine **21**. To a solution of compound **20** (8.67 mmol) in THF (30 mL) was added Burgess Reagent (9.5 mmol). The reaction mixture was stirred at 60 °C for 30 min. The solution was concentrated *in vacuo* and H_2O and DCM were added. The layers were separated and the organic layer was concentrated. The crude was purified by silica gel chromatography (eluent: petroleum ether/DCM 50 to 100%) to give compound **21** as a beige solid in 48% yield. MS (ESI, EI^+): *m/z* = 294.87 (MH^+).

[00507] Preparation of 4-methoxy-2-(4-methyl-thiazol-2-yl)-6-(4-trifluoromethyl-thiazol-2-yl)-pyridine **22**. To a solution of compound **21** (4.17 mmol) in DMF (15 mL) were added 4 - methyl-2-(tributylstannyl)thiazole (5 mmol), dichlorobis(triphenylphosphine) palladium (II) chloride (0.417 mmol), and K_2CO_3 (5 mmol). The reaction mixture was stirred at 110 °C under microwave irradiations for 1 hr. The solution was concentrated *in vacuo* and H_2O and DCM were added. The layers were separated and the organic layer was concentrated. The crude was purified by silica gel chromatography (eluent: DCM) to give compound **22** in quantitative yield. MS (ESI, EI^+): *m/z* = 357.87 (MH^+).

[00508] Preparation of 2-(4-methyl-thiazol-2-yl)-6-(4-trifluoromethyl-thiazol-2-yl)-pyridin-4-ol **23**. A mixture of compound **22** (1.68 mmol) and pyridinium chloride (5g/mmol) was heated at 200 °C with stirring. After 30 min, the reaction mixture was cooled down to room temperature and H_2O was added. The solid was collected, washed with H_2O, and dried to give compound **23** as a grey solid in 72% yield. MS (ESI, EI^+): *m/z* = 343.85 (MH^+

Example 12

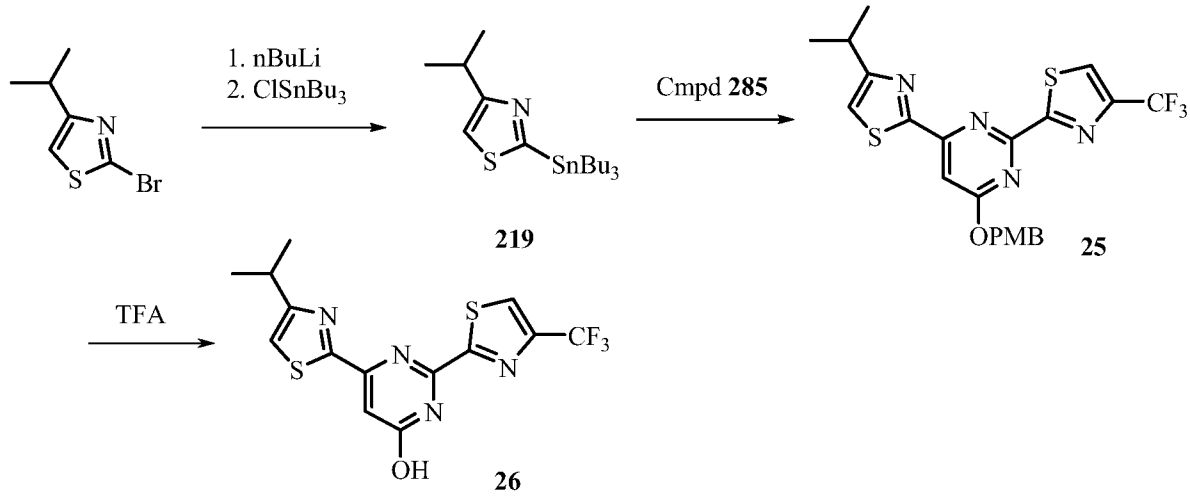
Preparation of 6-(4-isopropylthiazol-2-yl)-2-(4-(trifluoromethyl)thiazol-2-yl)-pyrimidin-4-ol **26**



26

[00509] The synthesis of compound **26** is shown in Scheme 16.

Scheme 16



219 **25** **26**

[00510] Preparation of 4-isopropyl-2-(tributylstannyl)thiazole **219**. To a stirred solution of 2-bromo-4-isopropyl-thiazole (6.79 mmol) in anhydrous Et_2O (30 mL) under nitrogen at -78 °C was added dropwise nBuLi (7.47 mmol). The reaction was stirred for 30 min and the temperature reached to -40 °C. The reaction mixture was cooled down to -78°C and tri-*n*-butyltinchloride (8.15 mmol) was added slowly. The reaction mixture was allowed to warm up to room temperature and stirred during 36 hrs. Et_2O was added and the reaction was quenched with saturated NH_4Cl. The organic layer was washed with saturated NH_4Cl and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give compound **219** as a pale yellow oil in quantitative yield.

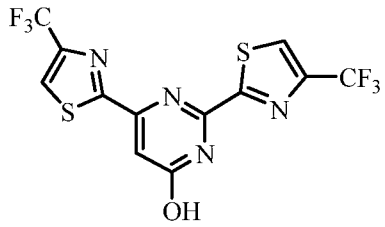
[00511] Preparation of 4-isopropyl-2-(6-(4-methoxybenzyloxy)-2-(4-

(trifluoromethyl)thiazol-2-yl)pyrimidin-4-yl)thiazole **25**. Compound **25** was synthesized from compound **285** (1.87 mmol) and compound **219** (2.43 mmol) as described for compound **22** at a temperature of 110 °C. DCM was added and the mixture was washed sequentially with saturated NH_4Cl and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified two times by silica gel chromatography (eluent: petroleum ether/EtOAc 5 to 10% and petroleum ether/DCM 20 to 60%) to give compound **25** as a colorless oil in 31% yield.

[00512] Preparation of 6-(4-isopropylthiazol-2-yl)-2-(4-(trifluoromethyl)thiazol-2-yl)pyrimidin-4-ol **26**. Compound **26** was synthesized from compound **25** (1.17 mmol) as described for compound **A1** to give compound **26** as a beige powder in quantitative yield.

Example 13

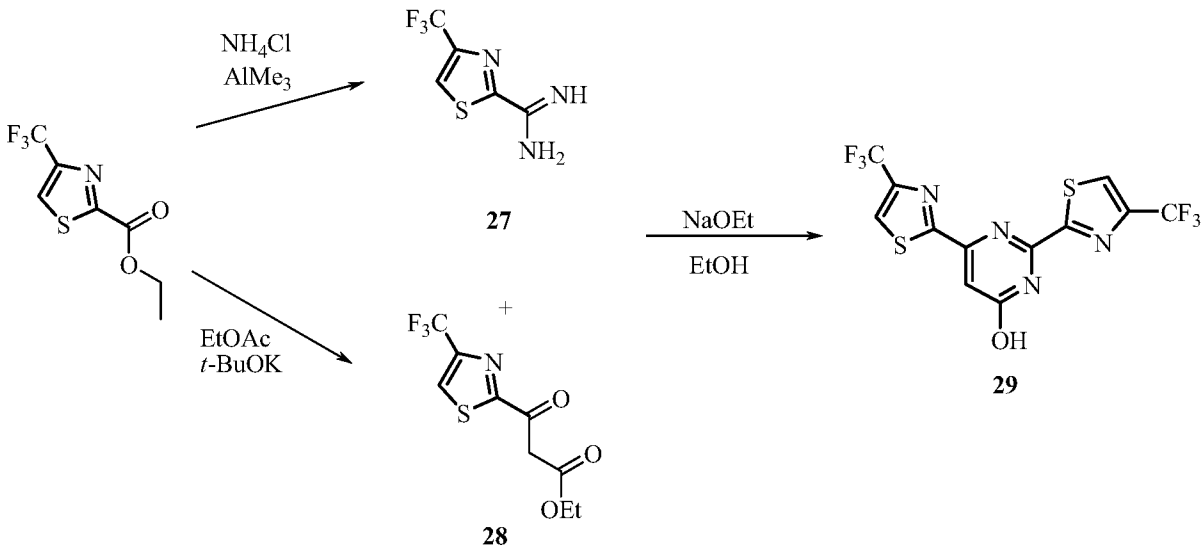
Preparation of 2,6-bis(4-(trifluoromethyl)thiazol-2-yl)pyrimidin-4-ol **29**



29

[00513] The synthesis of compound **29** is shown in Scheme 17.

Scheme 17



[00514] Preparation of 4-(trifluoromethyl)thiazole-2-carboximidamide **27**. To a

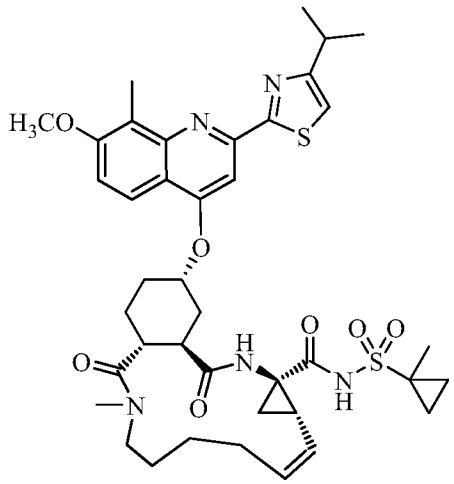
solution of NH_4Cl (66.61 mmol) in toluene (45 ml) was added dropwise $AlMe_3$ (2M in toluene) (66.61 mmol) under nitrogen at 0 °C. The mixture was stirred at room temperature during 1 hr. A solution of 4-trifluoromethylthiazole-2-carboxylic acid ethylester (13.32 mmol) in toluene (45 mL) was slowly added and the reaction mixture was stirred at 80 °C overnight. After cooling to 0 °C, MeOH was added slowly and the precipitate was removed by filtration. The filtrate was concentrated and the residue dissolved in a mixture of DCM/MeOH. The formed precipitate was removed by filtration and the filtrate was concentrated. The remaining residue was crystallized in DCM to give compound **27** as a beige solid in 88% yield. MS (ESI, EI^+): *m/z* = 195.9 (MH^+).

[00515] Preparation of ethyl 3-oxo-3-(4-(trifluoromethyl)thiazol-2-yl)propanoate **28**. To a solution of 4-trifluoromethylthiazole-2-carboxylic acid ethylester (8.88 mmol) in toluene (50 mL) were added successively EtOAc (13.32 mmol) and *t*BuOK (17.76 mmol). The resulting mixture was stirred at 100 °C for 1 hr. The solvent was removed by evaporation and water and Et_2O were added. The solution was neutralized with acetic acid. The extract was washed with water and the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give compound **28** as a yellow oil in 45% yield. MS (ESI, EI^-): *m/z* = 266 (MH^-).

[00516] Preparation of 2,6-bis(4-(trifluoromethyl)thiazol-2-yl)pyrimidin-4-ol **29**. To a solution of compound **27** (0.43 mmol) and NaOEt (2.15 mmol) in ethanol (2 mL) was added compound **28** (0.43 mmol). The reaction mixture was stirred at 100 °C overnight. The solvent was evaporated and water and AcOEt were added. The aqueous layer was acidified to pH~4-5 by addition of 2.5M HCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: DCM/MeOH 0 to 5%) to give compound **29** as a beige solid in 11% yield. MS (ESI, EI^-): *m/z* = 396.91 (MH^-).

Example 14

Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid-{18-[7-methoxy-8-methyl-2-(4-trifluoromethyl-thiazol-2-yl)-quinolin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **A101**



A101

[00517] The synthesis of compound **A101** is shown in Scheme 2, where R^B is 2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methyl-quinolin-4-yl.

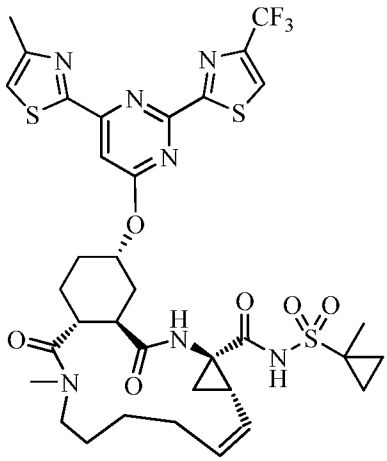
[00518] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-18-[2-(4-isopropyl-thiazol-2-yl)-7-methoxy-8-methyl-quinolin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid methyl ester **15c**. Compound **15c** was synthesized from compound **14** (1.67 mmol) and compound **218b** (1.79 mmol) as described for compound **15a**. After 40 hrs at 70 °C, NMP (10 mL) and K_2CO_3 (0.5 mmol) were added and the reaction mixture was heated at 85 °C for additional 4 hrs. The mixture was cooled down to room temperature and poured on ice bath. The precipitate was filtered, rinsed with water, and purified by silica gel chromatography (eluent: DCM to DCM/EtOAc) to give compound **15c** as a yellow solid in 27% yield. MS (ESI, EI^+): *m/z* = 675.3 (MH^+).

[00519] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-18-[2-(4-isopropyl-thiazol-2-yl)-7-methoxy-8-methyl-quinolin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid **16c**. Compound **16c** was synthesized from compound **15c** (0.445 mmol) as described for compound **16b** with addition of extra LiOH (1.78 mmol) to give compound **16c** as a brown solid in quantitative yield. MS (ESI, EI^+): *m/z* = 661.3 (MH^+).

[00520] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid {18-[2-(4-isopropyl-thiazol-2-yl)-7-methoxy-8-methyl-quinolin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **A101**. Compound **A101** was synthesized from compound **16c** (0.454 mmol) as described for compound **17b**. After the silica gel chromatography, the solid was triturated in ether and the filtrate was purified by preparative TLC to give compound **A101** as a beige solid in 16% yield. MS (ESI, EI^+): *m/z* = 778.3 (MH^+).

Example 15

Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid-{18-[7-methoxy-8-methyl-2-(4-trifluoromethyl-thiazol-2-yl)-quinolin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **C101**



C101

[00521] The synthesis of compound **C101** is shown in Scheme 2, where R^B is 6-(4-methylthiazol-2-yl)-2-(4-trifluoromethylthiazol-2-yl)-pyrimidin-4-yl.

[00522] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-13-methyl-18-[6-(4-methyl-thiazol-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-yloxy]-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid methyl ester **15d**. Compound **15d** was synthesized from compound **14** (1.17 mmol) and compound **B1** (1.25 mmol) as described for compound **15c** with the second heating at 80 °C lasting for 40 hrs to give compound **15d** as a yellow solid in 11% yield. MS (ESI, EI^+): *m/z* = 705.2 (MH^+).

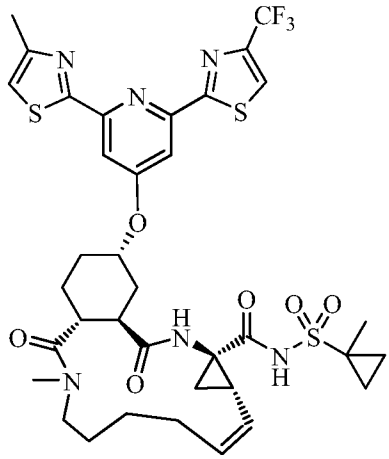
[00523] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-13-methyl-18-[6-(4-methyl-thiazol-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-yloxy]-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid **16d**. Compound **16d** was synthesized

from compound **15d** (0.132 mmol) as described for compound **16c** to give compound **16d** as a yellow solid in 82% yield. MS (ESI, EI^+): *m/z* = 691.2 (MH^+).

[00524] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid {13-methyl-18-[6-(4-methyl-thiazol-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-yloxy]-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **C101**. Compound **C101** was synthesized from compound **16d** (0.108 mmol) as described for compound **A101** to give the compound **C101** as a beige solid in 20% yield. MS (ESI, EI^+): *m/z* = 808.2 (MH^+).

Example 16

Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid {13-methyl-18-[2-(4-methyl-thiazol-2-yl)-6-(4-trifluoromethyl-thiazol-2-yl)-pyridin-4-yloxy]-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **C102**



C102

[00525] The synthesis of compound **C102** is shown in Scheme 2, where R^B is 6-(4-methylthiazol-2-yl)-2-(4-trifluoromethylthiazol-2-yl)-pyridin-4-yl.

[00526] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-13-methyl-18-[2-(4-methyl-thiazol-2-yl)-6-(4-trifluoromethyl-thiazol-2-yl)-pyridin-4-yloxy]-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid methyl ester **15e**. Compound **15e** was synthesized from compound **14** (0.92 mmol) and compound **23** (0.98 mmol) as described for compound **15a** to give compound **15e** as a beige solid in 42% yield. MS (ESI, EI^+): *m/z* = 704.2 (MH^+).

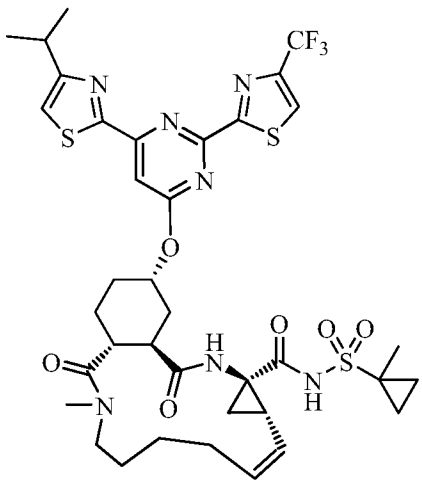
[00527] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-13-methyl-18-[2-(4-methyl-thiazol-2-yl)-

6-(4-trifluoromethyl-thiazol-2-yl)-pyridin-4-yloxy]-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid **16e**. Compound **16e** was synthesized from compound **15e** (0.67 mmol) as described for compound **16b** with reaction time of 60 hrs. The crude was purified by pad of silica (eluent: DCM/MeOH 0 to 10%) to give compound **16e** as a beige solid in 43% yield. MS (ESI, EI^+): *m/z* = 690.2 (MH^+).

[00528] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid {13-methyl-18-[2-(4-methyl-thiazol-2-yl)-6-(4-trifluoromethyl-thiazol-2-yl)-pyridin-4-yloxy]-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **C102**. Compound **C102** was synthesized from compound **16e** (0.145 mmol) as described for compound **17b** with reaction time of 24 hrs. After a second silica gel chromatography, the residue was washed with acetonitrile, filtered, and dried to give compound **C102** as a white solid in 32% yield. MS (ESI, EI^+): *m/z* = 807.2 (MH^+).

Example 17

Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid {18-[6-(4-isopropyl-thiazol-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **C103**



C103

[00529] The synthesis of compound **C103** is shown in Scheme 2, where R^B is 6-(4-isopropyl-thiazol-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-yl.

[00530] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-18-[6-(4-isopropyl-thiazol-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid methyl ester **15f**. Compound **15f** was

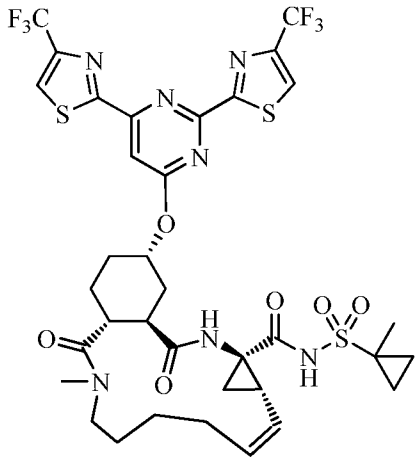
synthesized from compound **14** (0.92 mmol) and compound **26** (0.98 mmol) as described for compound **15c** with reaction time of 20 hrs. The filtrate was extracted with ethyl acetate and ethyl acetate/THF (90/10). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by a filtration on pad of silica (eluent: DCM/EtOAc 0 to 100%) and the obtained oil was precipitated in water and filtered. The two precipitates were purified by silica gel chromatography (eluent: DCM/EtOAc 0 to 100%) to give compound **15f** as a white solid in 37% yield. MS (ESI, EI^+): *m/z* = 733.2 (MH^+).

[00531] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-18-[6-(4-isopropyl-thiazol-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid **16f**. Compound **16f** was synthesized from compound **15f** (0.136 mmol) as described for compound **16b**. After concentration under reduced pressure, the crude was purified by pad of silica (eluent: DCM/MeOH 0 to 15%) to give compound **16f** as a white solid in 75% yield. MS (ESI, EI^+): *m/z* = 719.3 (MH^+).

[00532] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid {18-[6-(4-isopropyl-thiazol-2-yl)-2-(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **C103**. Compound **C103** was synthesized from compound **16f** (0.102 mmol) as described for compound **17b** with reaction time of 90 hrs to give, after two purifications on silica gel chromatography, compound **C103** as a beige solid in 16% yield. MS (ESI, EI^+): *m/z* = 836.3 (MH^+).

Example 18

Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid {18-[2,6-bis(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **C104**



C104

[00533] The synthesis of compound **C104** is shown in Scheme 2, where R^B is 2,6-bis(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-yl.

[00534] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-18-[2,6-bis(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid methyl ester **15j**. Compound **15j** was synthesized from compound **14** (1.09 mmol) and compound **29** (1.42 mmol) as described for compound **15a**. After cooling, EtOAc and water were added. The layers were separated and the organic layer was washed with water and brine, dried, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: petroleum ether/EtOAc 1/1) to give compound **15j** as a beige powder in 37% yield. MS (ESI, EI^+): *m/z* = 759.2 (MH^+).

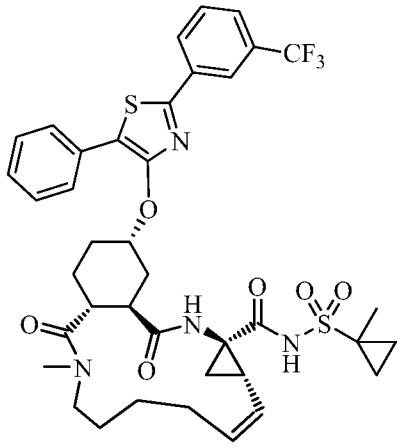
[00535] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-18-[2,6-bis(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid **16j**. Compound **16j** was synthesized from compound **15j** (0.395 mmol) as described for compound **16a** to give compound **16j** as a beige solid in 10% yield. MS (ESI, EI^+): *m/z* = 745 (MH^+).

[00536] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid {18-[2,6-bis(4-trifluoromethyl-thiazol-2-yl)-pyrimidin-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **C104**. Compound **C104** was

synthesized from compound **16j** (0.015 mmol) as described for compound **17a** to give compound **C104** as a yellow solid in 54% yield. MS (ESI, EI^+): *m/z* = 862 (MH^+).

Example 19

Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid{13-methyl-2,14-dioxo-18-[5-phenyl-2-(3-trifluoromethyl-phenyl)-thiazol-4-yloxy]-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **D101**



D101

[00537] The synthesis of compound **D101** is shown in Scheme 2, where R^B is 5-phenyl-2-(3-trifluoromethyl-phenyl)-thiazol-4-yl.

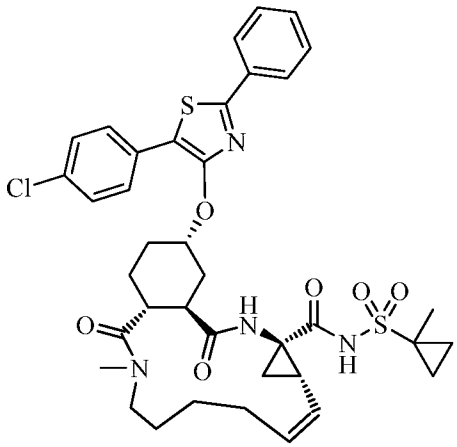
[00538] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-13-methyl-2,14-dioxo-18-[5-phenyl-2-(3-trifluoromethyl-phenyl)-thiazol-4-yloxy]-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid methyl ester **15g**. Compound **15g** was synthesized from compound **14** (0.836 mmol) and 5-phenyl-2-(3-trifluoromethyl-phenyl)-thiazol-4-ol (0.895 mmol) as described for compound **15a** with reaction time of 20 hrs. The reaction mixture was cooled down to room temperature and water was added. The reaction mixture was extracted with ethyl acetate and a mixture of ethyl acetate/THF. The organic layers were combined, dried, filtered, and concentrated under reduced pressure. The crude oil was purified on silica gel chromatography to give compound **15g** as a yellow oil in 64% yield. MS (ESI, EI^+): *m/z* = 682.2 (MH^+).

[00539] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-13-methyl-2,14-dioxo-18-[5-phenyl-2-(3-trifluoromethyl-phenyl)-thiazol-4-yloxy]-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid **16g**. Compound **16g** was synthesized from compound **15g** (0.147 mmol) as described for compound **16b** to give compound **16g** as a yellow solid in quantitative yield. MS (ESI, EI^+): *m/z* = 668.2 (MH^+).

[00540] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid{13-methyl-2,14-dioxo-18-[5-phenyl-2-(3-trifluoromethyl-phenyl)-thiazol-4-yloxy]-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **D101**. Compound **D101** was synthesized from compound **16g** (0.147 mmol) as described for compound **17b** with addition of methyl cyclopropylsulfonamide (0.147 mmol) and DBU (0.147 mmol) to give compound **D101** as a yellow solid in 31% yield. MS (ESI, EI^+): *m/z* = 785.3 (MH^+).

Example 20

Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid{18-[5-(4-chloro-phenyl)-2-phenyl-thiazol-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **D102**



D102

[00541] The synthesis of compound **D102** is shown in Scheme 2, where R^B is 5-(4-chloro-phenyl)-2-phenyl-thiazol-4-yl.

[00542] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-18-[5-(4-chloro-phenyl)-2-phenyl-thiazol-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid methyl ester **15h**. Compound **15h** was synthesized from compound **14** (0.836 mmol) and 2-(4-chlorophenyl)-5-phenyl-1,3-thiazol-4-ol (0.895 mmol) as described for compound **15g** to give, after two purifications on pad of silica (eluent: petroleum ether/EtOAc 0 to 100% and DCM/EtOAc 0 to 100%), compound **15h** as a yellow solid in 61% yield. MS (ESI, EI^+): *m/z* = 648.2 (MH^+).

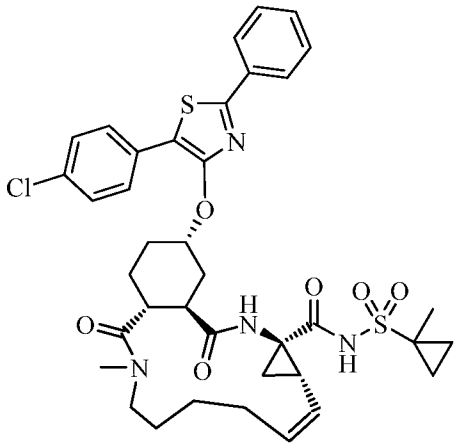
[00543] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-18-[5-(4-chloro-phenyl)-2-phenyl-thiazol-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid **16h**. Compound **16h** was synthesized from compound **15h** (0.185 mmol) as described for

compound **16b** to give compound **16h** as a yellow solid in quantitative yield. MS (ESI, EI^+): *m/z* = 634.2 (MH^+).

[00544] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid{18-[5-(4-chloro-phenyl)-2-phenyl-thiazol-4-yloxy]-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl}-amide **D102**. Compound **D102** was synthesized from compound **16h** (0.185 mmol) as described for compound **17b** with only purification by silica gel chromatography (eluent: DCM/EtOAc 1 to 20%) to give compound **D102** as a yellow solid in 14% yield. MS (ESI, EI^+): *m/z* = 751.2 (MH^+).

Example 21

Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid[18-(2,5-diphenyl-thiazol-4-yloxy)-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl]-amide **D103**



D103

[00545] The synthesis of compound **D103** is shown in Scheme 2, where R^B is 2,5-diphenyl-thiazol-4-yl.

[00546] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-18-(2,5-diphenyl-thiazol-4-yloxy)-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid methyl ester **15i**. Compound **15i** was synthesized from compound **14** (0.836 mmol) and 2,5-diphenyl-1,3-thiazol-4-ol (0.895 mmol) as described for compound **15c** with reaction time of 27 hrs and without addition of more reactants to give compound **15i** as a yellow solid in 56% yield. MS (ESI, EI^+): *m/z* = 614.2 (MH^+).

[00547] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-18-(2,5-diphenyl-thiazol-4-yloxy)-13-

methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carboxylic acid **16i**. Compound **16i** was synthesized from compound **15i** (0.195 mmol) as described for compound **16b** with reaction time of 20 hrs) to give compound **16i** as a yellow solid in quantitative yield. MS (ESI, EI^+): *m/z* = 600.2 (MH^+).

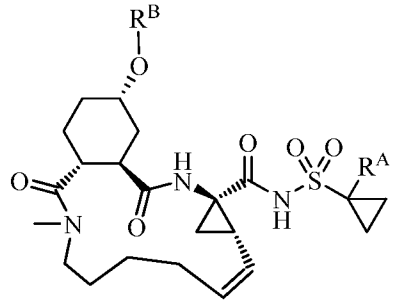
[00548] Preparation of (1*R*,4*R*,6*R*,15*R*,18*S*)-1-methyl-cyclopropanesulfonic acid[18-(2,5-diphenyl-thiazol-4-yloxy)-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.4.0.0]nonadec-7-ene-4-carbonyl]-amide **D103**. Compound **D103** was synthesized from compound **16i** (0.195 mmol) as described for compound **D101**. After the purification on silica gel chromatography, the compound was put again in reaction (0.196 mmol of methyl cyclopropylsulfonamide and 0.196 mmol of DBU) to give, after the same work-up and new purification on silica gel chromatography (eluent: DCM/EtOAc 1 to 10%), compound **D103** as a yellow solid in 24% yield. MS (ESI, EI^+): *m/z* = 717.3 (MH^+).

* * * * *

[00549] The examples set forth above are provided to give those of ordinary skill in the art with a complete disclosure and description of how to make and use the claimed embodiments, and are not intended to limit the scope of what is disclosed herein. Modifications that are obvious to persons of skill in the art are intended to be within the scope of the following claims. All publications, patents, and patent applications cited in this specification are incorporated herein by reference as if each such publication, patent or patent application were specifically and individually indicated to be incorporated herein by reference.

What is claimed is:

1. A compound of Formula I:

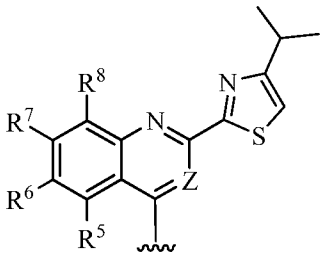


(I)

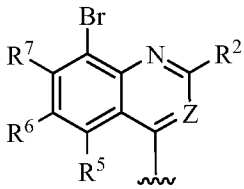
or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein:

R^A is (i) hydrogen or halogen; or (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; and

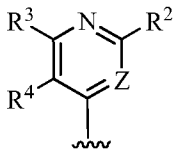
R^B is a moiety selected from (Ia), (Ib), (Ic), and (Id):



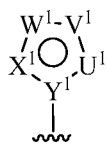
(Ia)



(Ib)



(Ic)



(Id)

wherein:

each Z is independently CR^1 or N;

U^1, V^1, W^1, and X^1 are each independently O, N, S, CR^9, or NR^9;

Y^1 is C or N;

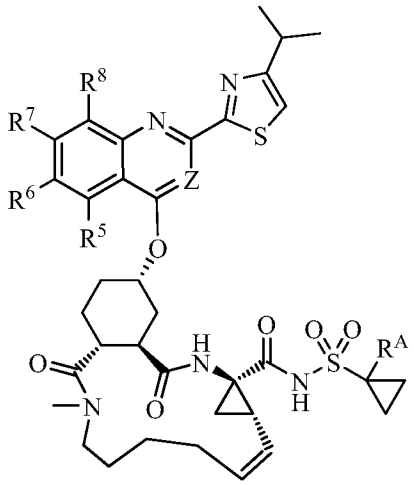
R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are each independently (i) hydrogen, halo, cyano, trifluoromethyl, or nitro; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-P(O)R^{1a}R^{1d}$, $-P(O)(OR^{1a})R^{1d}$, $-P(O)(OR^{1a})(OR^{1d})$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; and

each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or R^{1a} and R^{1c} together with the C and N atoms to which they are attached form heterocyclyl; or R^{1b} and R^{1c} together with the N atom to which they are attached form heterocyclyl;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q, where each Q is independently selected from (a) oxo, cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; and (c) $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^bR^c$, $-C(NR^a)NR^bR^c$, $-OR^a$, $-OC(O)R^a$, $-OC(O)OR^a$, $-OC(O)NR^bR^c$, $-OC(=NR^a)NR^bR^c$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-OS(O)NR^bR^c$, $-OS(O)_2NR^bR^c$, $-NR^bR^c$, $-NR^aC(O)R^d$, $-NR^aC(O)OR^d$, $-NR^aC(O)NR^bR^c$, $-NR^aC(=NR^d)NR^bR^c$, $-NR^aS(O)R^d$, $-NR^aS(O)_2R^d$, $-NR^aS(O)NR^bR^c$, $-NR^aS(O)_2NR^bR^c$, $-P(O)R^aR^d$, $-P(O)(OR^a)R^d$, $-P(O)(OR^a)(OR^d)$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^bR^c$, and $-S(O)_2NR^bR^c$, wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; or (iii) R^b and R^c together with the N atom to which they are attached form heterocyclyl, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a;

wherein each Q^a is independently selected from the group consisting of (a) oxo, cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^fR^g$, $-C(NR^e)NR^fR^g$, $-OR^e$, $-OC(O)R^e$, $-OC(O)OR^e$, $-OC(O)NR^fR^g$, $-OC(=NR^e)NR^fR^g$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^fR^g$, $-OS(O)_2NR^fR^g$, $-NR^fR^g$, $-NR^eC(O)R^h$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^fR^g$, $-NR^eC(=NR^h)NR^fR^g$, $-NR^eS(O)R^h$, $-NR^eS(O)_2R^h$, $-NR^eS(O)NR^fR^g$, $-NR^eS(O)_2NR^fR^g$, $-P(O)R^eR^h$, $-P(O)(OR^e)R^h$, $-P(O)(OR^e)(OR^h)$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^fR^g$, and $-S(O)_2NR^fR^g$; wherein each R^e, R^f, R^g, and R^h is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heterocyclyl.

2. The compound of claim 1, having the structure of Formula IA:



(IA)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

3. The compound of claim 1 or 2, wherein Z is CR^1.

4. The compound of claim 3, wherein Z is CH.

5. The compound of claim 1 or 2, wherein Z is N.

6. The compound of any of claims 1 to 5, wherein R^5 is hydrogen.

7. The compound of any of claims 1 to 6, wherein R^6 is hydrogen.

8. The compound of any of claims 1 to 7, wherein R^7 is $-OR^{1a}$.

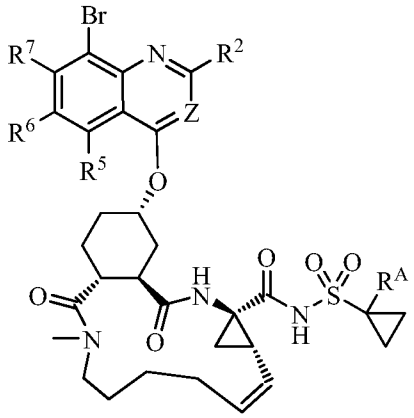
9. The compound of claim 8, wherein R^7 is C_{1-6} alkoxy, optionally substituted with one or more substituents Q.

10. The compound of claim 8, wherein R^7 is methoxy.

11. The compound of any of claims 1 to 10, wherein R^8 is C_{1-6} alkyl, optionally substituted with one or more substituents Q.

12. The compound of claim 11, wherein R^8 is methyl.

13. The compound of claim 1, having the structure of Formula IB:



(IB)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

14. The compound of claim 13, wherein Z is CR^1.

15. The compound of claim 13, wherein Z is CH.

16. The compound of claim 13, wherein Z is N.

17. The compound of any of claims 13 to 16, wherein R^2 is heteroaryl, optionally substituted with one or more substituents Q.

18. The compound of claim 17, wherein R^2 is monocyclic heteroaryl, optionally substituted with one or more substituents Q.

19. The compound of claim 17, wherein R^2 is 5-membered heteroaryl, optionally substituted with one or more substituents Q.

20. The compound of claim 17, wherein R^2 is furanyl, thienyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, thiazolyl, optionally substituted with one or two substituents Q.

21. The compound of claim 17, wherein R^2 is thiazol-2-yl, optionally substituted with one or two substituents Q, and each Q is independently selected from cyano, methyl, ethyl, propyl, isopropyl, trifluoromethyl, ethynyl, phenyl, benzyl, pyrrolidinyl, and methoxy.

22. The compound of claim 17, wherein R^2 is thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, 4-methyl-thiazol-2-yl, 5-methyl-thiazol-2-yl, 4-isopropyl-thiazol-2-yl, 4-trifluoromethyl-

thiazol-2-yl, 2,4-dimethylthiazol-5-yl, 4,5-dimethylthiazol-2-yl, 4-ethynyl-thiazol-2-yl, 2-methoxy-thiazol-4-yl, or 2-pyrrolidin-1-yl-thiazol-4-yl.

23. The compound of any of claims 13 to 22, wherein R^5 is hydrogen.

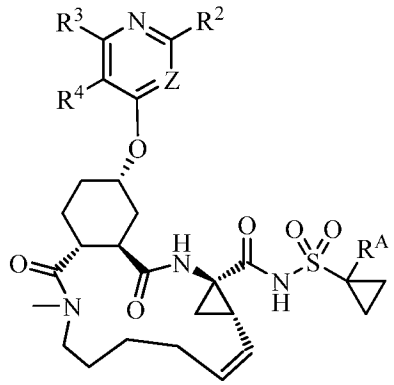
24. The compound of any of claims 13 to 23, wherein R^6 is hydrogen.

25. The compound of any of claims 13 to 24, wherein R^7 is $-OR^{1a}$.

26. The compound of claim 25, wherein R^7 is C_{1-6} alkoxy, optionally substituted with one or more substituents Q.

27. The compound of claim 25, wherein R^7 is methoxy.

28. The compound of claim 1, having the structure of Formula IC:



(IC)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

29. The compound of claim 28, wherein Z is CR^1.

30. The compound of claim 28, wherein Z is CH.

31. The compound of claim 28, wherein Z is N.

32. The compound of any of claims 28 to 31, wherein R^2 is heteroaryl, optionally substituted with one or more substituents Q.

33. The compound of claim 32, wherein R^2 is monocyclic heteroaryl, optionally substituted with one or more substituents Q.

34. The compound of claim 32, wherein R^2 is 5-membered heteroaryl, optionally substituted with one or more substituents Q.

35. The compound of claim 32, wherein R^2 is furanyl, thienyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, thiazolyl, optionally substituted with one or two substituents Q.

36. The compound of claim 32, wherein R^2 is thiazol-2-yl, optionally substituted with one or two substituents Q, and each Q is independently selected from cyano, methyl, ethyl, propyl, isopropyl, trifluoromethyl, ethynyl, phenyl, benzyl, pyrrolidinyl, and methoxy.

37. The compound of claim 32, wherein R^2 is thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, 4-methyl-thiazol-2-yl, 5-methyl-thiazol-2-yl, 4-isopropyl-thiazol-2-yl, 4-trifluoromethyl-thiazol-2-yl, 2,4-dimethylthiazol-5-yl, 4,5-dimethylthiazol-2-yl, 4-ethynyl-thiazol-2-yl, 2-methoxy-thiazol-4-yl, or 2-pyrrolidin-1-yl-thiazol-4-yl.

38. The compound of any of claims 28 to 37, wherein R^3 is C_{6-14} aryl.

39. The compound of claim 38, wherein R^3 is phenyl, optionally substituted with one or more substituents.

40. The compound of claim 38, wherein R^3 is phenyl, optionally substituted with one, two, or three substituents Q, each of which is independently selected from fluoro, chloro, methyl, and methoxy.

41. The compound of claim 38, wherein R^3 is phenyl, fluorophenyl, chlorophenyl, methylphenyl, or methoxyphenyl.

42. The compound of any of claims 28 to 37, wherein R^3 is C_{7-15} aralkyl, optionally substituted with one or more substituents Q.

43. The compound of claim 42, wherein R^3 is benzyl, optionally substituted with one or more substituents.

44. The compound of any of claims 28 to 37, wherein R^3 is heteroaryl, optionally substituted with one or more substituents Q.

45. The compound of claim 44, wherein R^3 is monocyclic heteroaryl, optionally

substituted with one or more substituents Q.

46. The compound of claim 44, wherein R^3 is 5-membered heteroaryl, optionally substituted with one or more substituents Q.

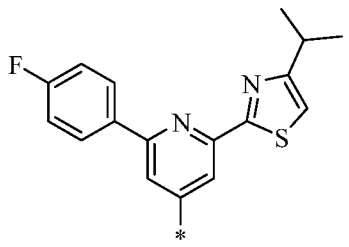
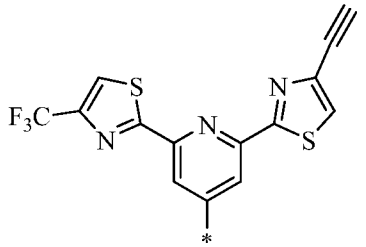
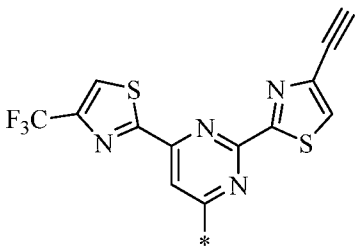
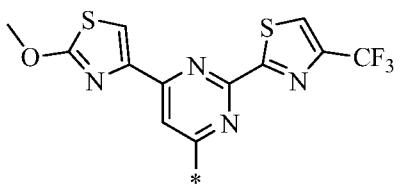
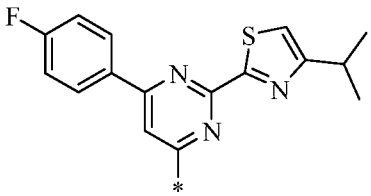
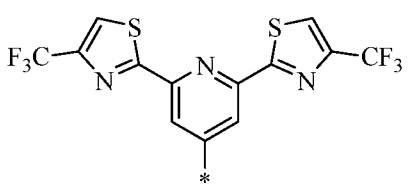
47. The compound of claim 44, wherein R^3 is furanyl, thienyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, thiazolyl, optionally substituted with one or two substituents Q.

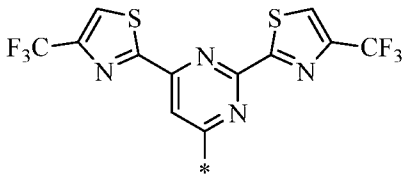
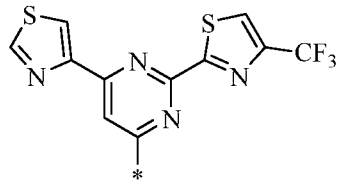
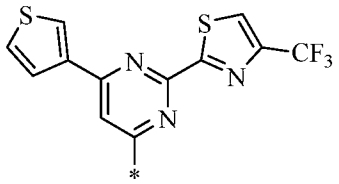
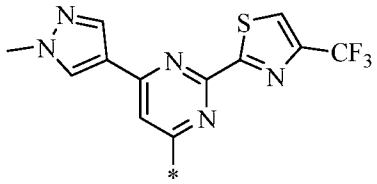
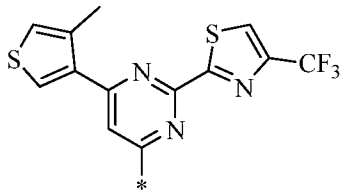
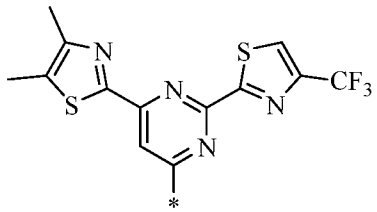
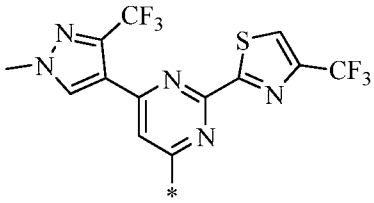
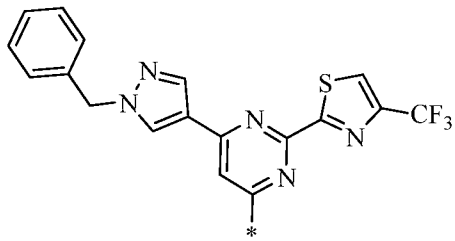
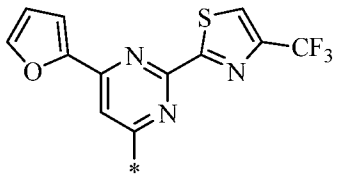
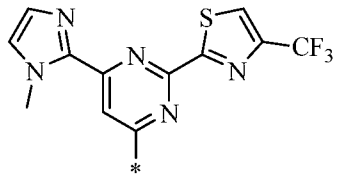
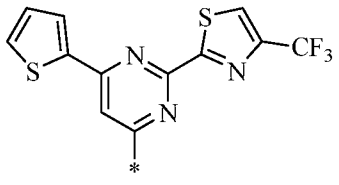
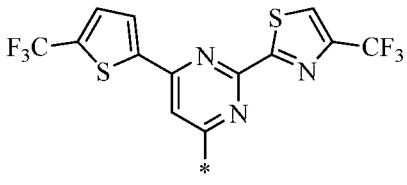
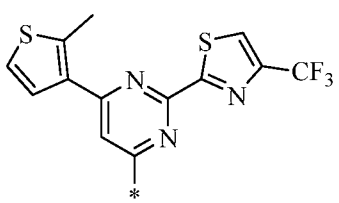
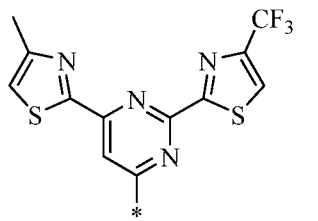
48. The compound of claim 44, wherein R^3 is thiazol-2-yl, optionally substituted with one or two substituents Q, and each Q is independently selected from cyano, methyl, ethyl, propyl, isopropyl, trifluoromethyl, ethynyl, phenyl, benzyl, pyrrolidinyl, and methoxy.

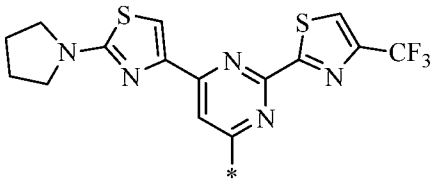
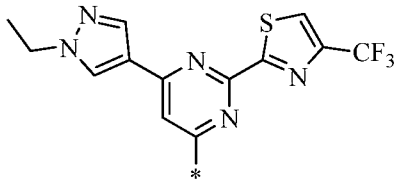
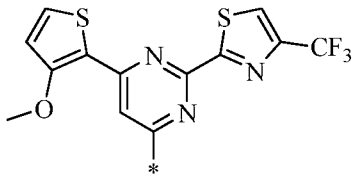
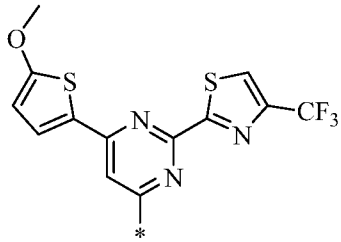
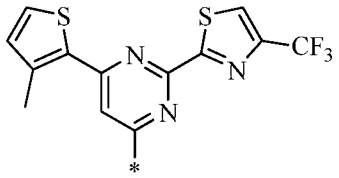
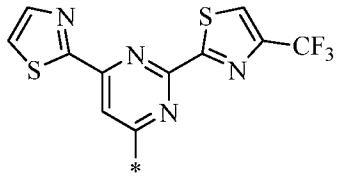
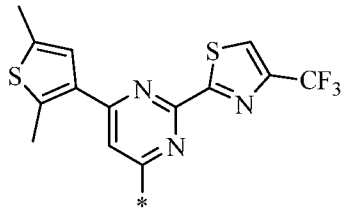
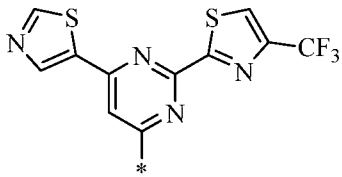
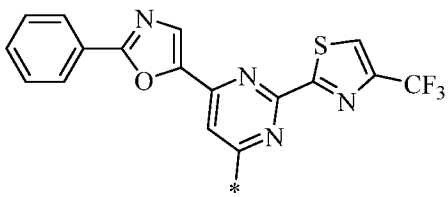
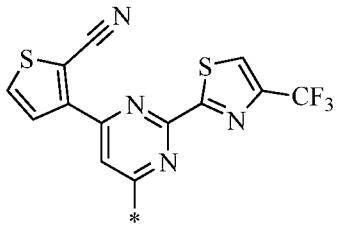
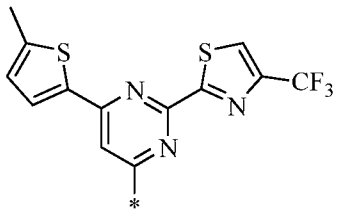
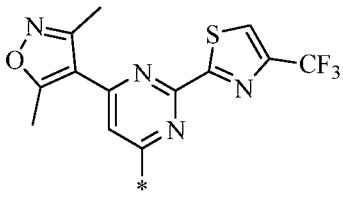
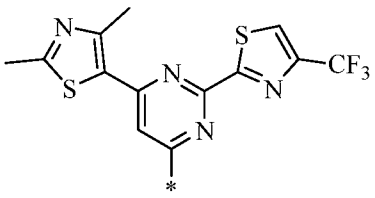
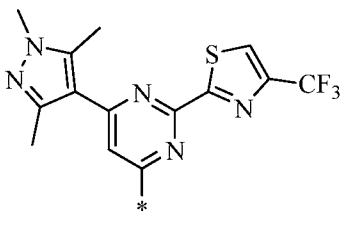
49. The compound of claim 44, wherein R^3 is thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, 4-methyl-thiazol-2-yl, 5-methyl-thiazol-2-yl, 4-isopropyl-thiazol-2-yl, 4-trifluoromethyl-thiazol-2-yl, 2,4-dimethylthiazol-5-yl, 4,5-dimethylthiazol-2-yl, 4-ethynyl-thiazol-2-yl, 2-methoxy-thiazol-4-yl, or 2-pyrrolidin-1-yl-thiazol-4-yl.

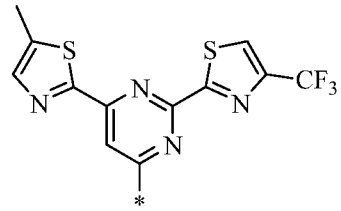
50. The compound of any of claims 28 to 49, wherein R^4 is hydrogen.

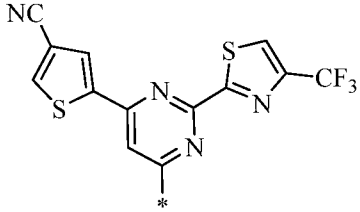
51. The compound of claim 1, wherein R^B is selected from:

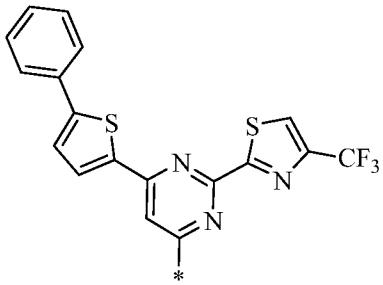

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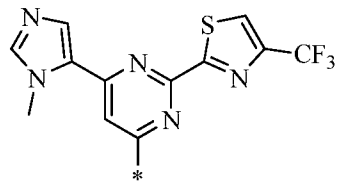

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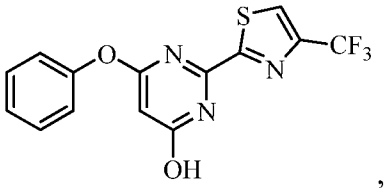

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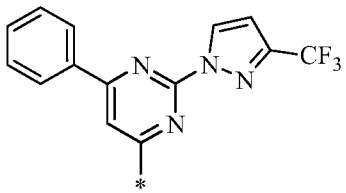

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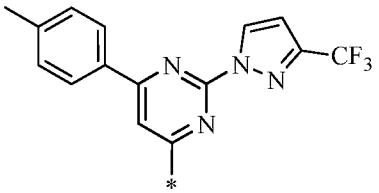

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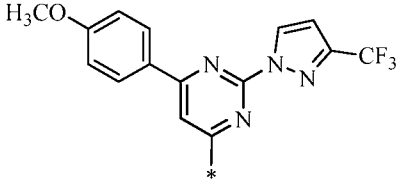

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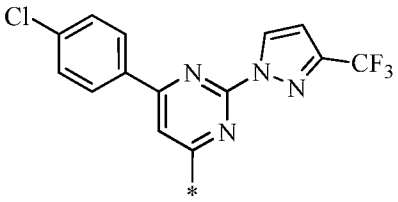

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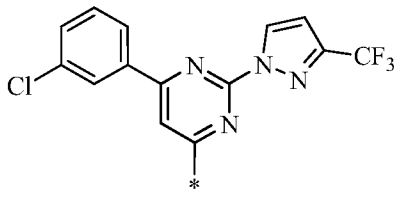

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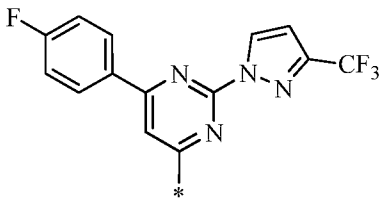

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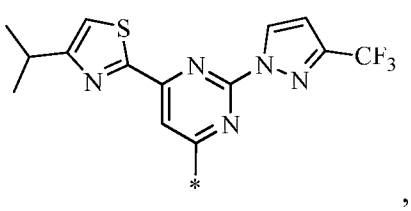

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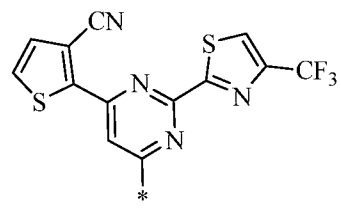

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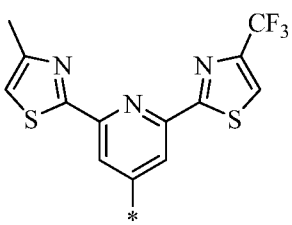

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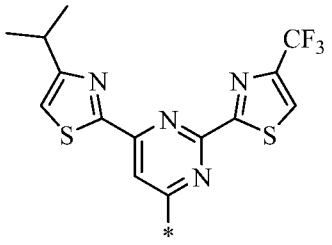

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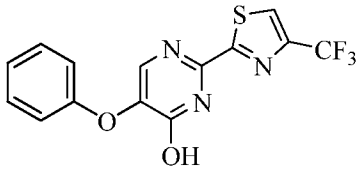

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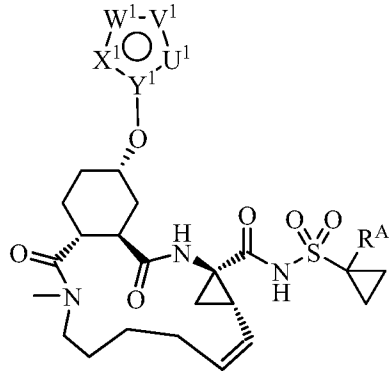
, and



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wherein the symbol * indicates the point of attachment.

52. The compound of claim 1, having the structure of Formula ID:

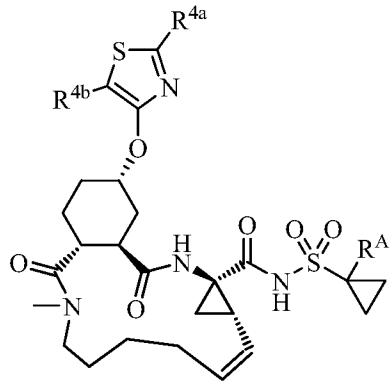


(ID)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

53. The compound of claim 52, wherein the R^B is thiazolyl, optionally substituted with one or more substituents Q.

54. The compound of claim 52, having the structure of Formula IID:



(IID)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein R^{4a} and R^{4b} are each independently (i) hydrogen, halo, cyano, trifluoromethyl, or nitro; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl,

C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-P(O)R^{1a}R^{1d}$, $-P(O)(OR^{1a})R^{1d}$, $-P(O)(OR^{1a})(OR^{1d})$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$.

55. The compound of claim 54, wherein R^{4a} is phenyl, optionally substituted with one or more substituents Q.

56. The compound of claim 54, wherein R^{4a} is phenyl, chlorophenyl, or trifluoromethyl-phenyl.

57. The compound of claim 54, wherein R^{4a} is phenyl, 4-chlorophenyl, or 3-trifluoromethyl-phenyl.

58. The compound of any of claims 54 to 57, wherein R^{4b} is phenyl, optionally substituted with one or more substituents Q.

59. The compound of claim 58, wherein R^{4a} is phenyl, chlorophenyl, or trifluoromethyl-phenyl.

60. The compound of claim 58, wherein R^{4a} is phenyl, 4-chlorophenyl, or 3-trifluoromethyl-phenyl.

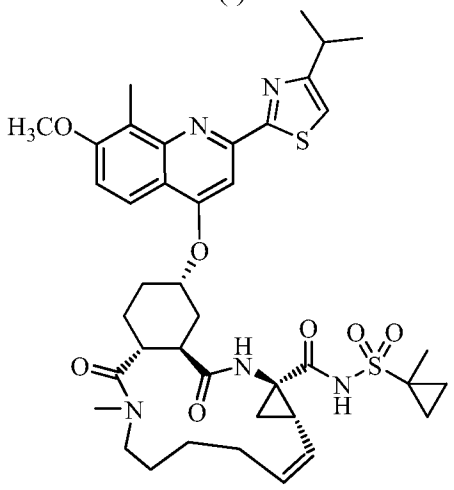
61. The compound of any of claims 1 to 60, wherein R^A is hydrogen.

62. The compound of any of claims 1 to 60, wherein R^A is C_{1-6} alkyl, optionally substituted with one or more substituents Q.

63. The compound of claim 62, wherein R^A is methyl.

64. The compound of claim 1 selected from:

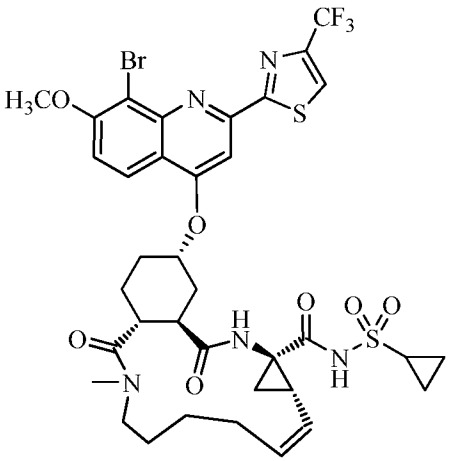
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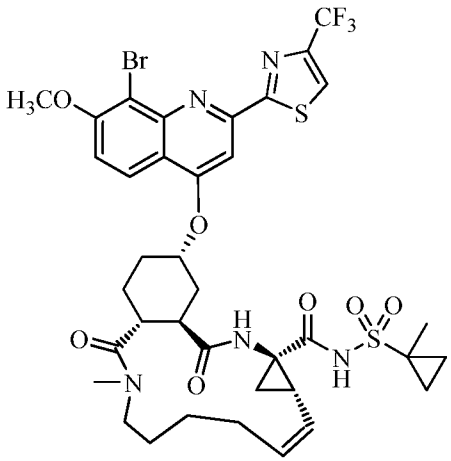
A101

(ii)



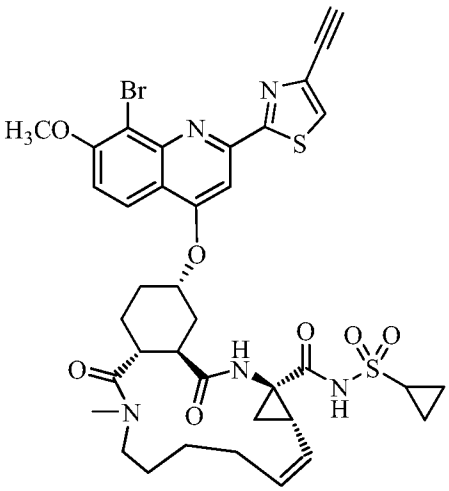
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B101



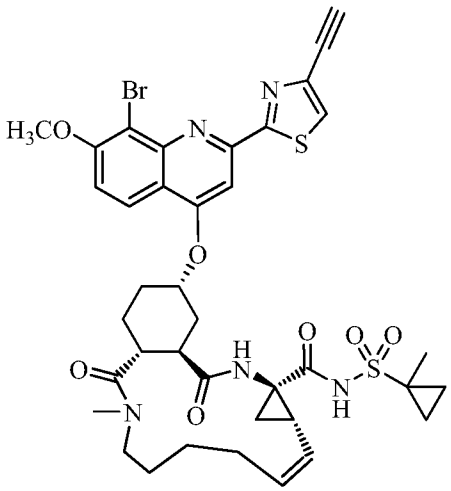
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B102



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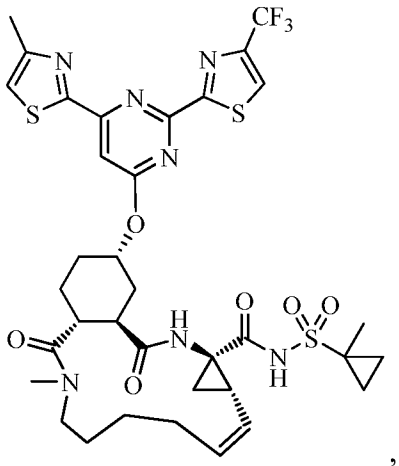
B103



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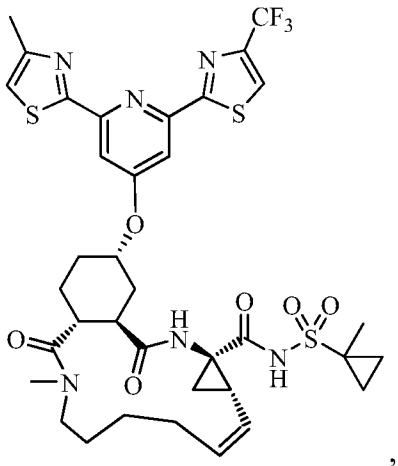
B104

(iii)



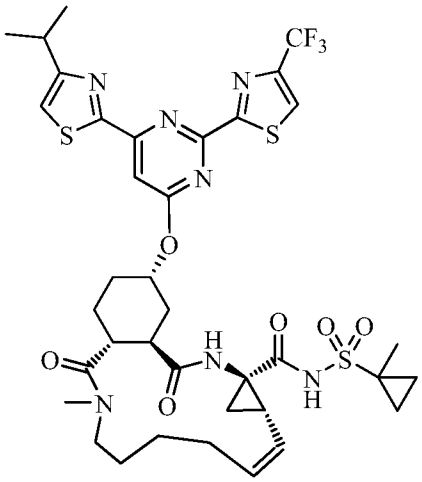
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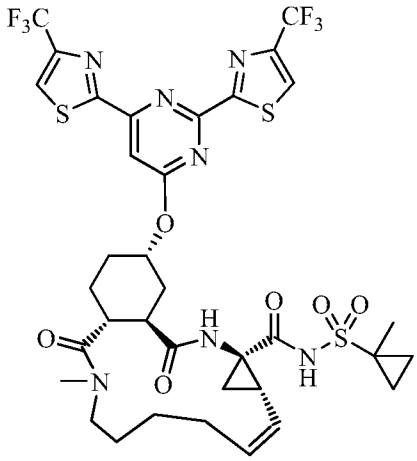
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C103

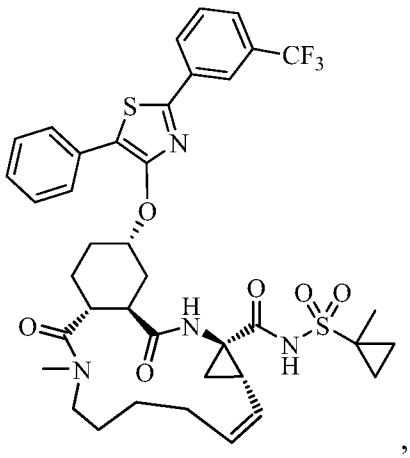
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C104

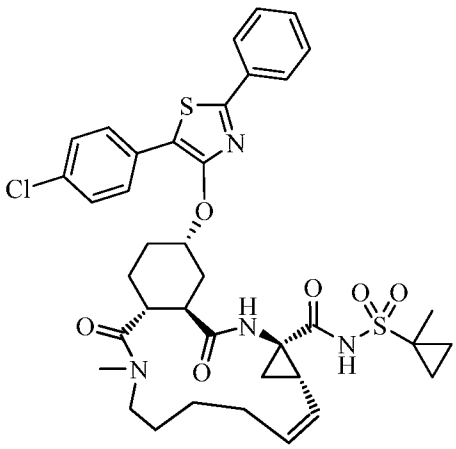
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and (iv)



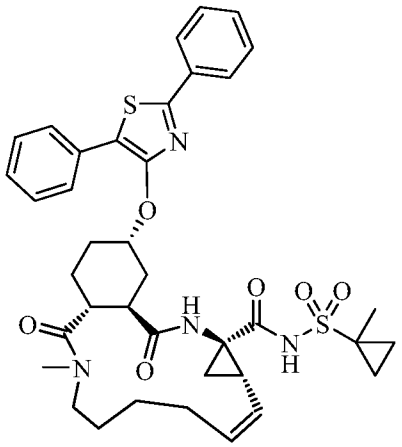
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D102

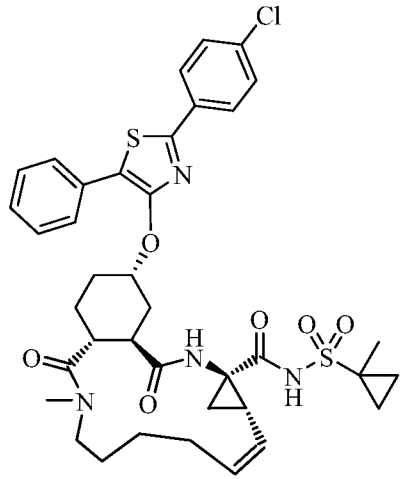
,



D103

,

and



D104

;

and isotopic variants thereof; and pharmaceutically acceptable salts, solvates, and prodrugs thereof.

65. A pharmaceutical composition comprising the compound of any of claims 1 to 64, and one or more pharmaceutically acceptable carriers.

66. The pharmaceutical composition of claim 65, further comprising a second antiviral agent.

67. The pharmaceutical composition of claim 66, wherein the second antiviral agent is selected from the group consisting of an interferon, ribavirin, an interleukin, an NS3 protease inhibitor, a cysteine protease inhibitor, a phenathrenequinone, a thiazolidine, a benzanilide, a helicase inhibitor, a polymerase inhibitor, a nucleotide analogue, a liotoxin, acerulenin, an antisense phosphorothioate oligodeoxynucleotide, an inhibitor of IRES-dependent translation, and a ribozyme.

68. The pharmaceutical composition of claim 66, wherein the second antiviral agent is an interferon.

69. The pharmaceutical composition of claim 68, wherein the interferon is selected from the group consisting of pegylated interferon alpha 2a, interferon alfahcon-1, natural interferon, albuferon, interferon beta-1a, omega interferon, interferon alpha, interferon gamma, interferon tau, interferon delta, and interferon gamma-1b.

70. The pharmaceutical composition of any of claims 65 to 69, wherein the

composition is formulated for single dose administration.

71. The pharmaceutical composition of any of claims 65 to 69, wherein the composition is formulated as oral, parenteral, or intravenous dosage form.

72. The pharmaceutical composition of claim 71, wherein the oral dosage form is a tablet or capsule.

73. The pharmaceutical composition of any of claims 65 to 72, wherein the compound is administered in a dose of about 0.5 milligram to about 1,000 milligram daily.

74. A method for treating or preventing an HCV infection in a subject, which comprises to the subject administering the compound of any of claims 1 to 64.

75. A method of treating, preventing, or ameliorating one or more symptoms of a liver disease or disorder associated with an HCV infection in a subject, comprising administering to the subject the compound of any of claims 1 to 64.

76. The method of claim 75, wherein the method comprises administering to the subject a second antiviral agent, in combination or alternation.

77. The method of claim 76, wherein the second antiviral agent is selected from the group consisting of an interferon, ribavirin, amantadine, an interleukin, a NS3 protease inhibitor, a cysteine protease inhibitor, a phenathrenequinone, a thiazolidine, a benzanilide, a helicase inhibitor, a polymerase inhibitor, a nucleotide analogue, a liotoxin, acerulenin, an antisense phosphorothioate oligodeoxynucleotide, an inhibitor of IRES-dependent translation, and a ribozyme.

78. The method of claim 76, wherein the second antiviral agent is an interferon.

79. The method of claim 78, wherein the interferon is selected from the group consisting of pegylated interferon alpha 2a, interferon alfacon-1, natural interferon, albuferon, interferon beta-1a, omega interferon, interferon alpha, interferon gamma, interferon tau, interferon delta, and interferon gamma-1b.

80. The method of any of claims 74 to 79, wherein the subject is a human.

81. A method for inhibiting replication of a virus in a host, which comprises

contacting the host with the compound of any of claims 1 to 64.

82. The method of claim 81, wherein the host is a human.

83. The method of claim 81, wherein the host is a cell.

84. A method for inhibiting replication of a virus, which comprises contacting the virus with the compound of any of claims 1 to 64.

85. A method for inhibiting the activity of a serine protease, which comprises contacting the protease with the compound of any of claims 1 to 64.

86. The method of claim 85, wherein the serine protease is an HCV NS3 protease.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/024389

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/12 C07D417/14 A61K31/427 A61K31/4436 A61K31/4709
A61K31/506 A61P31/14
ADD.
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)
C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/073195 A2 (MEDIVIR AB [SE]; ROSENQUIST AASA [SE]; THORSTENSSON FREDRIK [SE]; JOHA) 11 August 2005 (2005-08-11)	1-12, 64-86
Y	page 139 - page 144; claims 1-57; examples 104, 111	13-63

X	WO 2008/059046 A1 (TIBOTEC PHARM LTD [IE]; RABOISSON PIERRE JEAN-MARIE BE [BE]; DE KOCK H) 22 May 2008 (2008-05-22)	1
Y	page 72; claims 1-13; compound 7	13-27

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* 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 document 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
11 April 2012	23/04/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sotoca Usina, E

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/024389

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/095999 A1 (TIBOTEC PHARM LTD [IE]; MEDIVIR AB [SE]; RABOISSON PIERRE JEAN-MARIE B) 14 August 2008 (2008-08-14)	1
Y	Compounds 1j, 2f, 3k, 4b, 5, 6h, 7f, 10h, 11, 12, 13f, 14, 15, 16g, 17g, 18h,; page 64 - page 103; claims 1-15; examples 1-25	28-63

X,P	WO 2011/017389 A1 (IDENIX PHARMACEUTICALS INC [US]; PARSY CHRISTOPHE CLAUDE [FR]; ALEXAND) 10 February 2011 (2011-02-10) page 76; claims 1-89; compounds 51, 52	1-86

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Information on patent family members

International application No
PCT/US2012/024389

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Information on patent family members

International application No
PCT/US2012/024389

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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