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(54) Title: FURIN INHIBITORS FOR TREATING CORONAVIRUS INFECTIONS

(57) Abstract: Provided herein are methods, pharmaceutical compositions, and kits for treating and/or preventing a viral infection resulting from a coronaviridae family virus in a subject in need thereof, comprising administering to the subject a compound of Formula (I), or a pharmaceutical composition comprising a compound of Formula (I). Further provided herein are methods for inhibiting the viral entry into a cell of a coronaviridae family virus (e.g., alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1)) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I) as described herein. Also provided are pharmaceutical compositions and kits comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of a viral infection resulting from a coronaviridae family virus in a subject in need thereof.

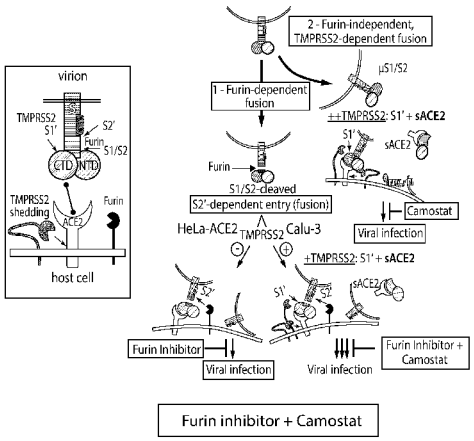
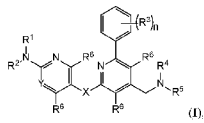


Figure 1



(I)

[Continued on next page]

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TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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FURIN INHIBITORS FOR TREATING CORONAVIRUS INFECTIONS

RELATED APPLICATIONS

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. provisional applications, U.S.S.N. 63/004,365, filed April 2, 2020, U.S.S.N. 63/013,382, filed April 21, 2020, and U.S.S.N. 63/156,058, filed March 3, 2021, which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] The human genome encodes more than 550 proteases. These molecular scissors play important roles in essentially all physiological processes. Proteolytic cleavage is certainly one of the most important post-translational modifications, generating a plethora of bioactive proteins and peptides with key roles in cell proliferation, immunity and inflammation. Not surprisingly, mutations in proteases and/or aberrant protease activity are associated with numerous pathological processes including cancer, cardiovascular disorders, and autoimmune diseases (Chakraborti S, Dhalla NS. *Pathophysiological Aspects of Proteases*. Berlin, Germany: Springer, 2017). Intriguingly, also many viral pathogens exploit cellular proteases for the proteolytic processing and maturation of their own proteins. Similarly, activation of bacterial toxins frequently requires cleavage by proteases of the infected or intoxicated host.

[0003] In recent years, modulation of protease activity has therefore emerged as a potential therapeutic approach in a variety of infectious and noninfectious diseases. One particularly promising target for therapeutic intervention is the cellular protease furin. This protease most likely cleaves and activates more than 150 mammalian, viral, and bacterial substrates (Tian S, Huang Q, Fang Y et al. FurinDB: a database of 20-residue furin cleavage site motifs, substrates and their associated drugs. *Int J Mol Sci* 2011; 12: 1060–1065.) Among them are viral envelope glycoproteins and bacterial toxins, as well as cellular factors that promote tumor development and growth if they are hyperactivated.

[0004] Furin is a member of the evolutionarily ancient family of proprotein convertases. Their similarity with bacterial subtilisin and yeast kexin proteases has led to the abbreviation PCSK (proprotein convertase subtilisin/kexin type). Humans encode nine members of this protease family (PCSK1–9), with PCSK3 representing furin. PCSKs are well known for their ability to activate other cellular proteins. The proteolytic conversion of inactive precursor proteins into bioactive molecules has already been described in the 1960s (Steiner DF,

Cunningham D, Spigelman L et al. Insulin biosynthesis: evidence for a precursor. *Science* 1967; 157: 697–700). However, it took more than 20 years until furin was identified as the first mammalian proprotein convertase (van de Ven WJ, Voorberg J, Fontijn R et al Furin is a subtilisin-like proprotein processing enzyme in higher eukaryotes. *Mol Biol Rep* 1990; 14: 265–275). To date, more than 200 cellular substrates of PCSKs have been described, including hormones, receptors, growth factors and adhesion molecules.

[0005] A potent peptidic furin inhibitor was identified by incorporating a reactive chloromethyl ketone (CMK) moiety (WO 2009/023306 A2; Garten W, Hallenberger S, Ortmann D, Schafer W, Vey M, Angliker H, et al. *Biochimie* **1994**, *76(3-4)*, 217-225). This non-selective CMK peptide (Decanoyl-Arg-Val-Lys-Arg-CMK) engages the active site of furin at the catalytic Ser368 residue to give a tetrahedral hemiketal that irreversibly alkylates the His194 residue. This well-known irreversible protease inhibition mechanism of a halomethylketone provides very high and durable potency, however also can account for non-selective protease inhibition, particularly against other PCSK family members. Furin plays a diverse biological role in health and diseases with high unmet medical need. Therefore, potent and selective small molecule furin inhibitors with drug-like properties are desirable as an attractive approach to provide therapeutic benefit in many diseases, such as infectious diseases.

SUMMARY OF THE INVENTION

[0006] Infectious diseases may be spread from one person to another and are caused by pathogenic microorganisms such as bacteria, viruses, parasites, or fungi. Pathogenicity is the ability of a microbial agent to cause disease and virulence is the degree to which an organism is pathogenic. In order for viruses to enter host cells and replicate, the envelope glycoproteins must be proteolytically activated (Nakayama K. *Biochem. J.* **1997**, *327(3)*, 625-635). The processing of envelope glycoproteins may in some cases impact viral pathogenicity (Nakayama K. *Biochem. J.* **1997**, *327(3)*, 625-635). The glycoprotein precursors of many virulent viruses, such as human immunodeficiency virus (HIV), avian influenza virus, measles virus, respiratory syncytial virus (RSV), Ebola virus, anthrax, and Zika virus (ZIKV), are cleaved at a site marked by a consensus sequence consistent with furin recognition (Thomas G. *Nat. Rev. Mol. Cell. Biol.* **2002**, *3(10)*, 753-766; 2, 36-38). The cleavage of HIV glycoprotein160 and infectious virus production are blocked when the furin inhibitor α1-PDX is expressed in cells (Nakayama K. *Biochem. J.* **1997**, *327(3)*, 625-635). It

is thus conceivable for the therapeutic use of furin inhibitor in a pandemic situation or biological warfare.

[0007] Provided herein are methods, pharmaceutical compositions, and kits for treating a viral infection resulting from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) comprising administering to the subject a therapeutically effective amount of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**) as described herein.

[0008] Further provided herein are methods, pharmaceutical compositions, and kits for preventing a viral infection resulting from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus), comprising administering to the subject a prophylactically effective amount of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**) as described herein.

[0009] In some aspects, the methods disclosed herein further comprise administering to a subject in need thereof an additional pharmaceutical agent (e.g., an antiviral, antibacterial, anti-inflammatory).

[0010] In another aspect, the present disclosure provides methods, pharmaceutical compositions, and kits for decreasing the viral infectivity of a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) in a subject, the method comprising administering to the subject an effective amount of a compound of Formula (**I**), or pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising Formula (**I**) as described herein.

[0011] In another aspect, the pharmaceutical compositions and kits useful in the present disclosure comprise a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, as described herein, and optionally a pharmaceutically acceptable excipient.

[0012] In another aspect, the pharmaceutical compositions and kits useful in the present disclosure comprise a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, as described herein, and optionally an additional pharmaceutical agent (e.g., an antiviral, antibacterial, anti-inflammatory, an antifibrotic agent).

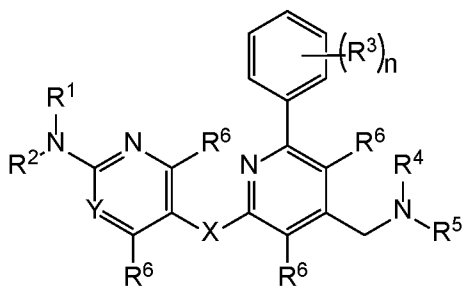
[0013] In yet another aspect, the present invention provides compounds of Formula (**I**), and pharmaceutical compositions thereof, for use in the treatment of a viral infection resulting from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) in a subject in need thereof.

[0014] In yet another aspect, the present invention provides compounds of Formula (**I**), and pharmaceutical compositions thereof, for use in the prevention of a viral infection resulting from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) in a subject in need thereof.

[0015] In another aspect, the present disclosure provides uses of compounds of Formula (**I**), and pharmaceutical compositions thereof, in the manufacture of a medicament for treating viral infection from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1) , a deltacoronavirus, a gammacoronavirus) in a subject in need thereof.

[0016] In another aspect, the present disclosure provides uses of compounds of Formula (**I**), and pharmaceutical compositions thereof, in the manufacture of a medicament for preventing viral infection from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) in a subject in need thereof.

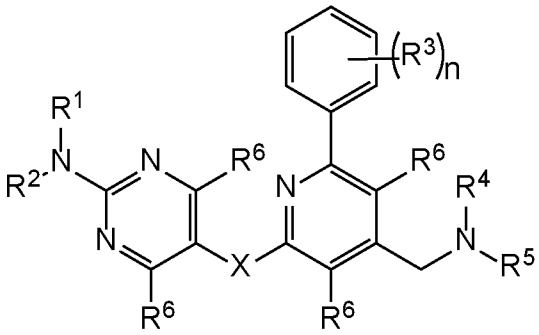
[0017] In certain embodiments, the compounds useful in the present disclosure are of the Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt thereof.

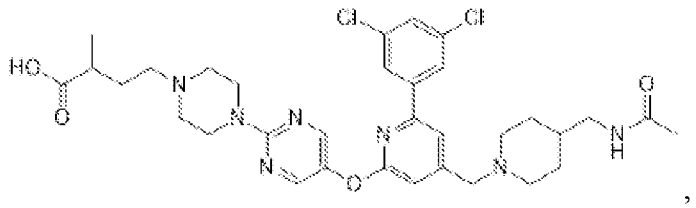
[0018] In certain embodiments, the compound of Formula (**I**) is of the Formula (**II**):



(**II**),

or a pharmaceutically acceptable salt thereof, wherein:

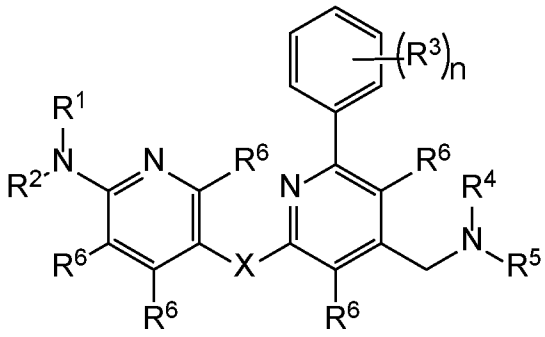
[0019] In certain embodiments, the compound of Formula (**II**) useful in the present disclosure is of the formula (Table 1, #192):



,

or a pharmaceutically acceptable salt thereof.

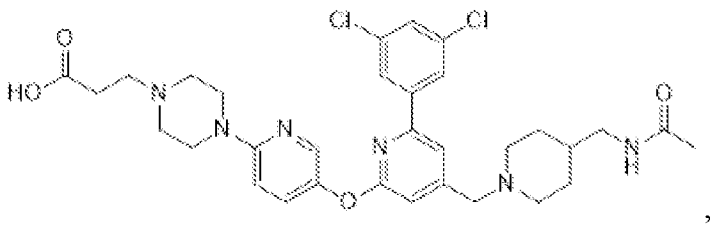
[0020] In certain embodiments, the compound of Formula (**I**) is of the Formula (**III**):



(**III**),

or a pharmaceutically acceptable salt thereof.

[0021] In certain embodiments, the compound of Formula (**III**) useful in the present disclosure is of the formula (Table 2, #219):



,

or a pharmaceutically acceptable salt thereof.

[0022] Another aspect of the present disclosure relates to kits comprising a container with a compound of Formula (**I**), or a pharmaceutical composition comprising a compound of

Formula (**I**), as described herein. The kits described herein may include a single dose or multiple doses of the compound or pharmaceutical composition. The kits may be useful in a method of the disclosure. In certain embodiments, the kit further includes an additional pharmaceutical agent. In certain embodiments, the kit further includes instructions for using the compound or pharmaceutical composition. A kit described herein may also include information (e.g. prescribing information) as required by a regulatory agency, such as the U.S. Food and Drug Administration (FDA).

[0023] The details of certain embodiments of the disclosure are set forth in the Detailed Description of Certain Embodiments, as described below. Other features, objects, and advantages of the disclosure will be apparent from the Definitions, Examples, Figures, and Claims.

DEFINITIONS

[0024] Terms are used within their ordinary and accepted meanings. The following definitions are meant to clarify, but not limit, the terms defined herein.

[0025] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999;Michael B. Smith, *March's Advanced Organic Chemistry*, 7th Edition, John Wiley & Sons, Inc., New York, 2013; Richard C. Larock, *Comprehensive Organic Transformations*, John Wiley & Sons, Inc., New York, 2018; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0026] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, e.g., enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen

et al., Tetrahedron 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, S.H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). This disclosure also encompasses compounds as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0027] In a formula, the bond ~~~ is a single bond, the dashed line --- is a single bond or absent, and the bond ═══ or ═══ is a single or double bond.

[0028] Unless otherwise provided, a formula includes compounds that do not include isotopically enriched atoms and also compounds that include isotopically enriched atoms. Compounds that include isotopically enriched atoms may be useful, for example, as analytical tools and/or probes in biological assays.

[0029] When a range of values ("range") is listed, it is intended to encompass each value and sub-range within the range. A range is inclusive of the values at the two ends of the range unless otherwise provided. For example "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[0030] The term "aliphatic" refers to alkyl, alkenyl, alkynyl, and carbocyclic groups. Likewise, the term "heteroaliphatic" refers to heteroalkyl, heteroalkenyl, heteroalkynyl, and heterocyclic groups. The term "alkyl" refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms ("C_{1-20} alkyl"). In some embodiments, an alkyl group has 1 to 12 carbon atoms ("C_{1-12} alkyl"). In some embodiments, an alkyl group has 1 to 10 carbon atoms ("C_{1-10} alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("C_{1-9} alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("C_{1-8} alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("C_{1-7} alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C_{1-6} alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("C_{1-5} alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("C_{1-4} alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C_{1-3} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C_{2-6} alkyl"). Examples of C_{1-6} alkyl groups include methyl (C_1), ethyl (C_2), propyl (C_3) (e.g., n-propyl, isopropyl), butyl (C_4) (e.g., n-butyl, tert-butyl, sec-butyl, isobutyl), pentyl (C_5) (e.g., n-pentyl, 3-pentanyl, amyl, neopentyl, 3-methyl-2-butanyl, tert-amyl), and hexyl (C_6) (e.g., n-hexyl). Additional examples of alkyl groups include n-heptyl (C_7), n-octyl (C_8), n-dodecyl

(C_{12}), and the like. Unless otherwise specified, each instance of an alkyl group is independently unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents (e.g., halogen, such as F). In certain embodiments, the alkyl group is an unsubstituted C_{1-12} alkyl (such as unsubstituted C_{1-6} alkyl, e.g., $-CH_3$ (Me), unsubstituted ethyl (Et), unsubstituted propyl (Pr, e.g., unsubstituted n-propyl (n-Pr), unsubstituted isopropyl (i-Pr)), unsubstituted butyl (Bu, e.g., unsubstituted n-butyl (n-Bu), unsubstituted tert-butyl (tert-Bu or t-Bu), unsubstituted sec-butyl (sec-Bu or s-Bu), unsubstituted isobutyl (i-Bu)). In certain embodiments, the alkyl group is a substituted C_{1-12} alkyl (such as substituted C_{1-6} alkyl, e.g., $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, or benzyl (Bn)).

[0031] "Alkoxy" refers to a group containing an alkyl radical, attached through an oxygen linking atom. The term "(C_1-C_4)alkoxy" refers to a straight- or branched-chain hydrocarbon radical having at least 1 and up to 4 carbon atoms attached through an oxygen linking atom. Exemplary "(C_1-C_4)alkoxy" groups include, without limitation, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *s*-butoxy, isobutoxy, and *t*-butoxy.

[0032] When the term "alkyl" is used in combination with other substituent groups, such as "halo(C_1-C_6)alkyl", "(C_3-C_6)cycloalkyl(C_1-C_4)alkyl-", or "(C_1-C_4)alkoxy(C_2-C_4)alkyl-", the term "alkyl" is intended to encompass a divalent straight or branched-chain hydrocarbon radical, wherein the point of attachment is through the alkyl moiety. The term "halo(C_1-C_6)alkyl" is intended to mean a radical having one or more halogen atoms, which may be the same or different, at one or more carbon atoms of an alkyl moiety containing from 1 to 6 carbon atoms, which is a straight or branched-chain carbon radical. Examples of "halo(C_1-C_6)alkyl" groups include, but are not limited to, $-CH_2F$ (fluoromethyl), $-CHF_2$ (difluoromethyl), $-CF_3$ (trifluoromethyl), $-CCl_3$ (trichloromethyl), 1,1-difluoroethyl, 2-fluoro-2-methylpropyl, 2,2-difluoropropyl, 2,2,2-trifluoroethyl, and hexafluoroisopropyl. Examples of "(C_3-C_6)cycloalkyl(C_1-C_4)alkyl-" groups include, but are not limited to, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclobutylethyl, cyclopentylethyl, and cyclohexylethyl. Examples of "(C_1-C_4)alkoxy(C_2-C_4)alkyl-" groups include, but are not limited to, methoxyethyl, methoxyisopropyl, ethoxyethyl, ethoxyisopropyl, isopropoxyethyl, isopropoxyisopropyl, *t*-butoxyethyl, and *t*-butoxyisopropyl.

[0033] The term "haloalkyl" is a substituted alkyl group, wherein one or more of the –H atoms are independently replaced by a halogen, e.g., fluoro, bromo, chloro, or iodo. "Perhaloalkyl" is a subset of haloalkyl, and refers to an alkyl group wherein all of the –H atoms are independently replaced by a halogen, e.g., fluoro, bromo, chloro, or iodo. In some

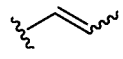
embodiments, the haloalkyl moiety has 1 to 20 carbon atoms ("C_{1-20} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 10 carbon atoms ("C_{1-10} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 9 carbon atoms ("C_{1-9} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 8 carbon atoms ("C_{1-8} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 7 carbon atoms ("C_{1-7} haloalkyl").In some embodiments, the haloalkyl moiety has 1 to 6 carbon atoms ("C_{1-6} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 5 carbon atoms ("C_{1-5} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 4 carbon atoms ("C_{1-4} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 3 carbon atoms ("C_{1-3} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 2 carbon atoms ("C_{1-2} haloalkyl"). In some embodiments, all of the haloalkyl –H atoms are independently replaced with fluoro to provide a "perfluoroalkyl" group. In some embodiments, all of the haloalkyl –H atoms are independently replaced with chloro to provide a "perchloroalkyl" group. Examples of haloalkyl groups include $-CHF_2$, $-CH_2F$, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, and the like.

[0034] The term "heteroalkyl" refers to an alkyl group, which further includes at least one heteroatom (e.g., 1, 2, 3, or 4 heteroatoms), such as oxygen, nitrogen, or sulfur within (e.g., inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 20 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-20} alkyl"). In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 12 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-12} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 11 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-11} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 10 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-10} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-9} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-8} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-7} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-6} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon

atoms and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-5} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1or 2 heteroatoms within the parent chain ("heteroC_{1-4} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-3} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-2} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("heteroC_1 alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkyl"). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an "unsubstituted heteroalkyl") or substituted (a "substituted heteroalkyl") with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-12} alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC_{1-12} alkyl.

[0035] The term "alkenyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 1 to 20 carbon atoms and one or more carbon-carbon double bonds (e.g., 1, 2, 3, or 4 double bonds). In some embodiments, an alkenyl group has 1 to 20 carbon atoms ("C_{1-20} alkenyl"). In some embodiments, an alkenyl group has 1 to 12 carbon atoms ("C_{1-12} alkenyl"). In some embodiments, an alkenyl group has 1 to 11 carbon atoms ("C_{1-11} alkenyl"). In some embodiments, an alkenyl group has 1 to 10 carbon atoms ("C_{1-10} alkenyl"). In some embodiments, an alkenyl group has 1 to 9 carbon atoms ("C_{1-9} alkenyl"). In some embodiments, an alkenyl group has 1 to 8 carbon atoms ("C_{1-8} alkenyl"). In some embodiments, an alkenyl group has 1 to 7 carbon atoms ("C_{1-7} alkenyl"). In some embodiments, an alkenyl group has 1 to 6 carbon atoms ("C_{1-6} alkenyl"). In some embodiments, an alkenyl group has 1 to 5 carbon atoms ("C_{1-5} alkenyl"). In some embodiments, an alkenyl group has 1 to 4 carbon atoms ("C_{1-4} alkenyl"). In some embodiments, an alkenyl group has 1 to 3 carbon atoms ("C_{1-3} alkenyl"). In some embodiments, an alkenyl group has 1 to 2 carbon atoms ("C_{1-2} alkenyl"). In some embodiments, an alkenyl group has 1 carbon atom ("C_1 alkenyl"). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl).

[0036] Examples of C_{1-4} alkenyl groups include methylidenyl (C_1), ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{1-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl

include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless otherwise specified, each instance of an alkenyl group is independently unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents. In certain embodiments, the alkenyl group is an unsubstituted C_{1-20} alkenyl. In certain embodiments, the alkenyl group is a substituted C_{1-20} alkenyl. In an alkenyl group, a C=C double bond for which the stereochemistry is not specified (e.g., $-CH=CHCH_3$ or ) may be in the (E)- or (Z)-configuration.

The term "heteroalkenyl" refers to an alkenyl group, which further includes at least one heteroatom (e.g., 1, 2, 3, or 4 heteroatoms) such as oxygen, nitrogen, or sulfur within (e.g., inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkenyl group refers to a group having from 1 to 20 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-20} alkenyl"). In certain embodiments, a heteroalkenyl group refers to a group having from 1 to 12 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-12} alkenyl"). In certain embodiments, a heteroalkenyl group refers to a group having from 1 to 11 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-11} alkenyl"). In certain embodiments, a heteroalkenyl group refers to a group having from 1 to 10 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-10} alkenyl"). In some embodiments, a heteroalkenyl group has 1 to 9 carbon atoms at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-9} alkenyl"). In some embodiments, a heteroalkenyl group has 1 to 8 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-8} alkenyl"). In some embodiments, a heteroalkenyl group has 1 to 7 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-7} alkenyl"). In some embodiments, a heteroalkenyl group has 1to 6 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-6} alkenyl"). In some embodiments, a heteroalkenyl group has 1 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-5} alkenyl"). In some embodiments, a heteroalkenyl group has 1 to 4 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-4} alkenyl"). In some embodiments, a heteroalkenyl group has 1 to 3 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain ("heteroC_{1-3} alkenyl"). In some embodiments, a heteroalkenyl group

has 1 to 2 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain ("heteroC_{1-2} alkenyl"). In some embodiments, a heteroalkenyl group has 1 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-6} alkenyl"). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an "unsubstituted heteroalkenyl") or substituted (a "substituted heteroalkenyl") with one or more substituents. In certain embodiments, the heteroalkenyl group is an unsubstituted heteroC_{1-20} alkenyl. In certain embodiments, the heteroalkenyl group is a substituted heteroC_{1-20} alkenyl.

[0037] The term "alkynyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 1 to 20 carbon atoms and one or more carbon-carbon triple bonds (e.g., 1, 2, 3, or 4 triple bonds) ("C_{1-20} alkynyl"). In some embodiments, an alkynyl group has 1 to 10 carbon atoms ("C_{1-10} alkynyl"). In some embodiments, an alkynyl group has 1 to 9 carbon atoms ("C_{1-9} alkynyl"). In some embodiments, an alkynyl group has 1 to 8 carbon atoms ("C_{1-8} alkynyl"). In some embodiments, an alkynyl group has 1 to 7 carbon atoms ("C_{1-7} alkynyl"). In some embodiments, an alkynyl group has 1 to 6 carbon atoms ("C_{1-6} alkynyl"). In some embodiments, an alkynyl group has 1 to 5 carbon atoms ("C_{1-5} alkynyl"). In some embodiments, an alkynyl group has 1 to 4 carbon atoms ("C_{1-4} alkynyl"). In some embodiments, an alkynyl group has 1 to 3 carbon atoms ("C_{1-3} alkynyl"). In some embodiments, an alkynyl group has 1 to 2 carbon atoms ("C_{1-2} alkynyl"). In some embodiments, an alkynyl group has 1 carbon atom ("C_1 alkynyl"). The one or more carbon-carbon triple bonds can be internal (such as in 2-butynyl) or terminal (such as in 1-butynyl). Examples of C_{1-4} alkynyl groups include, without limitation, methylidynyl (C_1), ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), and the like. Examples of C_{1-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. Unless otherwise specified, each instance of an alkynyl group is independently unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents. In certain embodiments, the alkynyl group is an unsubstituted C_{1-20} alkynyl. In certain embodiments, the alkynyl group is a substituted C_{1-20} alkynyl.

[0038] The term "carbocyclyl" or "carbocyclic" refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms ("C_{3-14} carbocyclyl") and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 14 ring carbon atoms ("C_{3-14} carbocyclyl"). In some embodiments, a carbocyclyl group

has 3 to 13 ring carbon atoms ("C_{3-13} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 12 ring carbon atoms ("C_{3-12} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 11 ring carbon atoms ("C_{3-11} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 7 ring carbon atoms ("C_{3-7} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms ("C_{4-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms ("C_{5-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. Exemplary C_{3-8} carbocyclyl groups include the aforementioned C_{3-10} carbocyclyl groups as well as cycloundecyl (C_{11}), spiro[5.5]undecanyl (C_{11}), cyclododecyl (C_{12}), cyclododecenyl (C_{12}), cyclotridecane (C_{13}), cyclotetradecane (C_{14}), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or polycyclic (e.g., containing a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") or tricyclic system ("tricyclic carbocyclyl")) and can be saturated or can contain one or more carbon-carbon double or triple bonds. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is an unsubstituted C_{3-14} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-14} carbocyclyl.

[0039] In some embodiments, "carbocyclyl" is a non-aromatic, monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms ("C_{3-14} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 4 to 6 ring carbon atoms ("C_{4-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_{5-10} cycloalkyl"). Examples of C_{5-6} cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} cycloalkyl groups include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is an unsubstituted C_{3-14} cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C_{3-14} cycloalkyl. In certain embodiments, the carbocyclyl includes 0, 1, or 2 C=C double bonds in the carbocyclic ring system, as valency permits. Exemplary "(C_3-C_6)cycloalkyl" groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0040] The term "heterocyclyl" or "heterocyclic" refers to a radical of a 3- to 14-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently nitrogen, oxygen, or sulfur ("3–14 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or polycyclic (e.g., a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl") or tricyclic system ("tricyclic heterocyclyl")), and can be saturated or can contain one or more carbon-carbon double or triple bonds. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings.

[0041] "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members

continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is an unsubstituted 4–11 membered heterocyclyl. In certain embodiments, the heterocyclyl group is a substituted 4–11 membered heterocyclyl. In certain embodiments, the heterocyclyl is substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclyl, wherein 1, 2, or 3 atoms in the heterocyclic ring system are independently oxygen, nitrogen, or sulfur, as valency permits.

[0042] In some embodiments, a heterocyclyl group is a 5–10 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently nitrogen, oxygen, or sulfur ("5–10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–8 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently nitrogen, oxygen, or sulfur ("5–8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–6 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently nitrogen, oxygen, or sulfur ("5–6 membered heterocyclyl"). In some embodiments, the 5–6 membered heterocyclyl group has 1–3 ring heteroatoms, such as nitrogen, oxygen, or sulfur. In some embodiments, the 5–6 membered heterocyclyl group has 1–2 ring heteroatoms such as nitrogen, oxygen, or sulfur. In some embodiments, the 5–6 membered heterocyclyl group has 1 ring heteroatom such as nitrogen, oxygen, or sulfur.

[0043] Exemplary 3-membered heterocyclyl groups containing 1 heteroatom include azirdinyl, oxiranyl, and thiiranyl. Exemplary 4-membered heterocyclyl groups containing 1 heteroatom include azetidinyl, oxetanyl, and thietanyl. Exemplary 5-membered heterocyclyl groups containing 1 heteroatom include tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing 2 heteroatoms include dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5-membered heterocyclyl groups containing 3 heteroatoms include triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing 3 heteroatoms include triazinyl. Exemplary 7-membered heterocyclyl groups containing 1 heteroatom include azepanyl,

oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing 1 heteroatom include azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro-1,8-naphthyridinyl, octahydropyrrolo[3,2-b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H-benzo[e][1,4]diazepinyl, 1,4,5,7-tetrahydropyrano[3,4-b]pyrrolyl, 5,6-dihydro-4H-furo[3,2-b]pyrrolyl, 6,7-dihydro-5H-furo[3,2-b]pyranyl, 5,7-dihydro-4H-thieno[2,3-c]pyranyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl, 2,3-dihydrofuro[2,3-b]pyridinyl, 4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridinyl, 4,5,6,7-tetrahydrofuro[3,2-c]pyridinyl, 4,5,6,7-tetrahydrothieno[3,2-b]pyridinyl, 1,2,3,4-tetrahydro-1,6-naphthyridinyl, and the like.

[0044] The term "aryl" refers to a radical of a monocyclic or polycyclic (e.g., bicyclic or tricyclic) 4n+2 aromatic ring system (e.g., having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has 6 ring carbon atoms ("C_6 aryl"; e.g., phenyl). In some embodiments, an aryl group has 10 ring carbon atoms ("C_{10} aryl"; e.g., naphthyl such as 1–naphthyl and 2-naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms ("C_{14} aryl"; e.g., anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Unless otherwise specified, each instance of an aryl group is independently unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is an unsubstituted C_{6-14} aryl. In certain embodiments, the aryl group is a substituted C_{6-14} aryl.

[0045] "Aralkyl" is a subset of "alkyl" and refers to an alkyl group substituted by an aryl group, wherein the point of attachment is on the alkyl moiety.

[0046] The term "heteroaryl" refers to a radical of a 5-14 membered monocyclic or polycyclic (e.g., bicyclic, tricyclic) 4n+2 aromatic ring system (e.g., having 6, 10, or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently nitrogen,

oxygen, or sulfur ("5-14 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused polycyclic (aryl/heteroaryl) ring system. Polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (e.g., indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, e.g., either the ring bearing a heteroatom (e.g., 2-indolyl) or the ring that does not contain a heteroatom (e.g., 5-indolyl). In certain embodiments, the heteroaryl is substituted or unsubstituted, 5- or 6-membered, monocyclic heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur. In certain embodiments, the heteroaryl is substituted or unsubstituted, 9- or 10-membered, bicyclic heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur.

[0047] In some embodiments, a heteroaryl group is a 5-10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently nitrogen, oxygen, or sulfur ("5-10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently nitrogen, oxygen, or sulfur ("5-8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently nitrogen, oxygen, or sulfur ("5-6 membered heteroaryl"). In some embodiments, the 5-6 membered heteroaryl has 1–3 ring heteroatoms nitrogen, oxygen, or sulfur. In some embodiments, the 5-6 membered heteroaryl has 1–2 ring heteroatoms nitrogen, oxygen, or sulfur. In some embodiments, the 5-6 membered heteroaryl has 1 ring heteroatom nitrogen, oxygen, or sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more

substituents. In certain embodiments, the heteroaryl group is an unsubstituted 5-14 membered heteroaryl. In certain embodiments, the heteroaryl group is a substituted 5-14 membered heteroaryl.

[0048] Exemplary 5-membered heteroaryl groups containing 1 heteroatom include pyrrolyl, furanyl, and thiophenyl. Exemplary 5-membered heteroaryl groups containing 2 heteroatoms include imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing 3 heteroatoms include triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing 4 heteroatoms include tetrazolyl. Exemplary 6-membered heteroaryl groups containing 1 heteroatom include pyridinyl. Exemplary 6-membered heteroaryl groups containing 2 heteroatoms include pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing 3 or 4 heteroatoms include triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing 1 heteroatom include azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Exemplary tricyclic heteroaryl groups include phenanthridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl, and phenazinyl.

[0049] "Heteroaralkyl" is a subset of "alkyl" and refers to an alkyl group substituted by a heteroaryl group, wherein the point of attachment is on the alkyl moiety.

[0050] The term "unsaturated bond" refers to a double or triple bond.

[0051] The term "unsaturated" or "partially unsaturated" refers to a moiety that includes at least one double or triple bond.

[0052] The term "saturated" or "fully saturated" refers to a moiety that does not contain a double or triple bond, e.g., the moiety only contains single bonds.

[0053] Affixing the suffix "-ene" to a group indicates the group is a divalent moiety, e.g., alkylene is the divalent moiety of alkyl, alkenylene is the divalent moiety of alkenyl, alkynylene is the divalent moiety of alkynyl, heteroalkylene is the divalent moiety of heteroalkyl, heteroalkenylene is the divalent moiety of heteroalkenyl, heteroalkynylene is the divalent moiety of heteroalkynyl, carbocyclylene is the divalent moiety of carbocyclyl,

heterocyclylene is the divalent moiety of heterocyclyl, arylene is the divalent moiety of aryl, and heteroarylene is the divalent moiety of heteroaryl.

[0054] A group is optionally substituted unless expressly provided otherwise. The term "optionally substituted" refers to being substituted or unsubstituted. In certain embodiments, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups are optionally substituted. "Optionally substituted" refers to a group which may be substituted or unsubstituted (e.g., "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" heteroalkyl, "substituted" or "unsubstituted" heteroalkenyl, "substituted" or "unsubstituted" heteroalkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted" means that at least one –H present on a group is replaced with a permissible substituent, e.g., a substituent which upon substitution results in a stable compound, e.g., a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, and includes any of the substituents described herein that results in the formation of a stable compound. Heteroatoms such as nitrogen may have –H substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety. This disclosure is not intended to be limited in any manner by the exemplary substituents described herein.

[0055] Exemplary carbon atom substituents include halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(R^{bb})_3^+X^-$, $-N(OR^{cc})R^{bb}$, $-SH$, $-SR^{aa}$, $-SSR^{cc}$, $-C(=O)R^{aa}$, $-CO_2H$, $-CHO$, $-C(OR^{cc})_2$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-OC(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, $-OS(=O)R^{aa}$, $-Si(R^{aa})_3$, $-OSi(R^{aa})_3$ $-C(=S)N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$, $-OC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-P(=O)(N(R^{bb})_2)_2$, $-OP(=O)(N(R^{bb})_2)_2$, $-NR^{bb}P(=O)(R^{aa})_2$,

$-NR^{bb}P(=O)(OR^{cc})_2$, $-NR^{bb}P(=O)(N(R^{bb})_2)_2$, $-P(R^{cc})_2$, $-P(OR^{cc})_2$, $-P(R^{cc})_3^+X^-$, $-P(OR^{cc})_3^+X^-$, $-P(R^{cc})_4$, $-P(OR^{cc})_4$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3^+X^-$, $-OP(OR^{cc})_2$, $-OP(OR^{cc})_3^+X^-$, $-OP(R^{cc})_4$, $-OP(OR^{cc})_4$, $-B(R^{aa})_2$, $-B(OR^{cc})_2$, $-BR^{aa}(OR^{cc})$, C_{1-20} alkyl, C_{1-20} perhaloalkyl, C_{1-20} alkenyl, C_{1-20} alkynyl, heteroC_{1-20} alkyl, heteroC_{1-20} alkenyl, heteroC_{1-20} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; wherein X^- is a counterion; or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$; each instance of R^{aa} is, independently, C_{1-20} alkyl, C_{1-20} perhaloalkyl, C_{1-20} alkenyl, C_{1-20} alkynyl, heteroC_{1-20} alkyl, heteroC_{1-20}alkenyl, heteroC_{1-20}alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, or 5-14 membered heteroaryl; or optionally, two R^{aa} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; each instance of R^{bb} is independently –H, $-OH$, $-OR^{aa}$, $-N(R^{cc})_2$, $-CN$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)(N(R^{cc})_2)_2$, C_{1-20} alkyl, C_{1-20} perhaloalkyl, C_{1-20} alkenyl, C_{1-20} alkynyl, heteroC_{1-20}alkyl, heteroC_{1-20}alkenyl, heteroC_{1-20}alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, or 5-14 membered heteroaryl; or optionally two R^{bb} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{cc} is, independently, –H, C_{1-20} alkyl, C_{1-20} perhaloalkyl, C_{1-20} alkenyl, C_{1-20} alkynyl, heteroC_{1-20} alkyl, heteroC_{1-20} alkenyl, heteroC_{1-20} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, or 5-14 membered heteroaryl; or optionally two R^{cc} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is independently halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{ee}$, $-ON(R^{ff})_2$, $-N(R^{ff})_2$, $-N(R^{ff})_3^+X^-$, $-N(OR^{ee})R^{ff}$, $-SH$, $-SR^{ee}$, $-SSR^{ee}$, $-C(=O)R^{ee}$,

$-CO_2H$, $-CO_2R^{ee}$, $-OC(=O)R^{ee}$, $-OCO_2R^{ee}$, $-C(=O)N(R^{ff})_2$, $-OC(=O)N(R^{ff})_2$, $-NR^{ff}C(=O)R^{ee}$, $-NR^{ff}CO_2R^{ee}$, $-NR^{ff}C(=O)N(R^{ff})_2$, $-C(=NR^{ff})OR^{ee}$, $-OC(=NR^{ff})R^{ee}$, $-OC(=NR^{ff})OR^{ee}$, $-C(=NR^{ff})N(R^{ff})_2$, $-OC(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}SO_2R^{ee}$, $-SO_2N(R^{ff})_2$, $-SO_2R^{ee}$, $-SO_2OR^{ee}$, $-OSO_2R^{ee}$, $-S(=O)R^{ee}$, $-Si(R^{ee})_3$, $-OSi(R^{ee})_3$, $-C(=S)N(R^{ff})_2$, $-C(=O)SR^{ee}$, $-C(=S)SR^{ee}$, $-SC(=S)SR^{ee}$, $-P(=O)(OR^{ee})_2$, $-P(=O)(R^{ee})_2$, $-OP(=O)(R^{ee})_2$, $-OP(=O)(OR^{ee})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, heteroC_{1-10}alkyl, heteroC_{1-10}alkenyl, heteroC_{1-10}alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl, or 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S; wherein X^- is a counterion; each instance of R^{ee} is, independently, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{1-10} alkenyl, heteroC_{1-10} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, or 3-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; each instance of R^{ff} is independently –H, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{1-10} alkenyl, heteroC_{1-10} alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl or 5-10 membered heteroaryl; or optionally two R^{ff} groups are joined to form a 3-10 membered heterocyclyl or 5-10 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; each instance of R^{gg} is independently halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OC_{1-6}$ alkyl, $-ON(C_{1-6}$ alkyl$)_2$, $-N(C_{1-6}$ alkyl$)_2$, $-N(C_{1-6}$ alkyl$)_3^+X^-$, $-NH(C_{1-6}$ alkyl$)_2^+X^-$, $-NH_2(C_{1-6}$ alkyl$)^+X^-$, $-NH_3^+X^-$, $-N(OC_{1-6}$ alkyl$)(C_{1-6}$ alkyl$)$, $-N(OH)(C_{1-6}$ alkyl$)$, $-NH(OH)$, $-SH$, $-SC_{1-6}$ alkyl, $-SS(C_{1-6}$ alkyl$)$, $-C(=O)(C_{1-6}$ alkyl$)$, $-CO_2H$, $-CO_2(C_{1-6}$ alkyl$)$, $-OC(=O)(C_{1-6}$ alkyl$)$, $-OCO_2(C_{1-6}$ alkyl$)$, $-C(=O)NH_2$, $-C(=O)N(C_{1-6}$ alkyl$)_2$, $-OC(=O)NH(C_{1-6}$ alkyl$)$, $-NHC(=O)($ C_{1-6} alkyl$)$, $-N(C_{1-6}$ alkyl$)C(=O)($ C_{1-6} alkyl$)$, $-NHCO_2(C_{1-6}$ alkyl$)$, $-NHC(=O)N(C_{1-6}$ alkyl$)_2$, $-NHC(=O)NH(C_{1-6}$ alkyl$)$, $-NHC(=O)NH_2$, $-C(=NH)O(C_{1-6}$ alkyl$)$, $-OC(=NH)(C_{1-6}$ alkyl$)$, $-OC(=NH)OC_{1-6}$ alkyl, $-C(=NH)N(C_{1-6}$ alkyl$)_2$, $-C(=NH)NH(C_{1-6}$ alkyl$)$, $-C(=NH)NH_2$, $-OC(=NH)N(C_{1-6}$ alkyl$)_2$, $-OC(NH)NH(C_{1-6}$ alkyl$)$, $-OC(NH)NH_2$, $-NHC(NH)N(C_{1-6}$ alkyl$)_2$, $-NHC(=NH)NH_2$, $-NHSO_2(C_{1-6}$ alkyl$)$, $-SO_2N(C_{1-6}$ alkyl$)_2$, $-SO_2NH(C_{1-6}$ alkyl$)$, $-SO_2NH_2$, $-SO_2C_{1-6}$ alkyl, $-SO_2OC_{1-6}$ alkyl, $-OSO_2C_{1-6}$ alkyl, $-SOC_{1-6}$ alkyl, $-Si(C_{1-6}$ alkyl$)_3$, $-OSi(C_{1-6}$ alkyl$)_3$ $-C(=S)N(C_{1-6}$ alkyl$)_2$,

C(=S)NH(C_{1-6} alkyl), C(=S)NH_2, −C(=O)S(C_{1-6} alkyl), −C(=S)SC_{1-6} alkyl, −SC(=S)SC_{1-6} alkyl, −P(=O)(OC_{1-6} alkyl)$_2$, −P(=O)(C_{1-6} alkyl)$_2$, −OP(=O)(C_{1-6} alkyl)$_2$, −OP(=O)(OC_{1-6} alkyl)$_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{1-10} alkenyl, heteroC_{1-10} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, or 5-10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; and each X^- is a counterion.

[0056] In certain embodiments, the carbon atom substituents are independently halogen, substituted (e.g., substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, –CN, –SCN, $–NO_2$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, or $-NR^{bb}C(=O)N(R^{bb})_2$. In certain embodiments, the carbon atom substituents are independently halogen, substituted (e.g., substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, –CN, –SCN, $–NO_2$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, or $-NR^{bb}C(=O)N(R^{bb})_2$, wherein R^{aa} is –H, substituted (e.g., substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, an oxygen protecting group (e.g., silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, t-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl) when attached to an oxygen atom, or a sulfur protecting group (e.g., acetamidomethyl, t-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl) when attached to a sulfur atom; and each Rbb is independently –H, substituted (e.g., substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, or a nitrogen protecting group (e.g., Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts). In certain embodiments, the carbon atom substituents are independently halogen, substituted (e.g., substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, –CN, –SCN, or $–NO_2$. In certain embodiments, the carbon atom substituents are independently halogen, substituted (e.g., substituted with one or more halogen moieties) or unsubstituted C_{1-10} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, –CN, –SCN, or $–NO_2$, wherein R^{aa} is –H, substituted (e.g., substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, an oxygen protecting group (e.g., silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, t-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl) when attached to an oxygen atom, or a sulfur protecting group (e.g., acetamidomethyl, t-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl) when attached to a sulfur atom; and each Rbb is independently –H, substituted (e.g., substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, or a nitrogen protecting group (e.g., Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[0057] In certain embodiments, the molecular weight of a carbon atom substituent is lower than 250, lower than 200, lower than 150, lower than 100, or lower than 50 g/mol. In certain embodiments, a carbon atom substituent consists of carbon, –H, fluorine, chlorine, bromine, iodine, oxygen, sulfur, nitrogen, and/or silicon atoms. In certain embodiments, a carbon atom substituent consists of carbon, –H, fluorine, chlorine, bromine, iodine, oxygen, sulfur, and/or nitrogen atoms. In certain embodiments, a carbon atom substituent consists of carbon, –H, fluorine, chlorine, bromine, and/or iodine atoms. In certain embodiments, a carbon atom substituent consists of carbon, –H, fluorine, and/or chlorine atoms.

[0058] The term "halo" or "halogen" refers to fluorine (fluoro, −F), chlorine (chloro, −Cl), bromine (bromo, −Br), or iodine (iodo, −I).

[0059] The term "hydroxyl" or "hydroxy" refers to the group −OH. The term "substituted hydroxyl" or "substituted hydroxyl," by extension, refers to a hydroxyl group wherein the oxygen atom directly attached to the parent molecule is substituted with a group other than –H, and includes groups $-OR^{aa}$, $-ON(R^{bb})_2$, $-OC(=O)SR^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})N(R^{bb})_2$, $-OS(=O)R^{aa}$, $-OSO_2R^{aa}$, $-OSi(R^{aa})_3$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3^+X^-$, $-OP(OR^{cc})_2$, $-OP(OR^{cc})_3^+X^-$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, or $-OP(=O)(N(R^{bb}))_2$, wherein X^-, R^{aa}, R^{bb}, and R^{cc} are as defined herein.

"Oxo" represents a double-bonded oxygen moiety; for example, if attached directly to a carbon atom forms a carbonyl moiety (C=O).

[0060] The term "amino" refers to the group $-NH_2$. The term "substituted amino," by extension, refers to a monosubstituted amino, a disubstituted amino, or a trisubstituted amino. In certain embodiments, the "substituted amino" is a monosubstituted amino or a disubstituted amino group.

[0061] The term "monosubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with one –H and one group other than –H, and includes $-NH(R^{bb})$, $-NHC(=O)R^{aa}$, $-NHCO_2R^{aa}$, $-NHC(=O)N(R^{bb})_2$, $-NHC(=NR^{bb})N(R^{bb})_2$, $-NHSO_2R^{aa}$, $-NHP(=O)(OR^{cc})_2$, or $-NHP(=O)(N(R^{bb})_2)_2$, wherein R^{aa}, R^{bb} and R^{cc} are as defined herein, and wherein R^{bb} of the group $-NH(R^{bb})$ is not –H.

[0062] The term "disubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with two groups other than –H, and includes groups $-N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}SO_2R^{aa}$, $-NR^{bb}P(=O)(OR^{cc})_2$, or $-NR^{bb}P(=O)(N(R^{bb})_2)_2$,

wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein, with the proviso that the nitrogen atom directly attached to the parent molecule is not substituted with –H.

[0063] The term "trisubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with three groups, and includes $-N(R^{bb})_3$ or $-N(R^{bb})_3^+X^-$, wherein R^{bb} and X^- are as defined herein.

[0064] The term "sulfonyl" refers to–$SO_2N(R^{bb})_2$, –SO_2R^{aa}, or –SO_2OR^{aa}, wherein R^{aa} and R^{bb} are as defined herein.

[0065] The term "sulfinyl" refers to the group –$S(=O)R^{aa}$, wherein R^{aa} is as defined herein.

[0066] The term "acyl" refers to a group having the general formula $-C(=O)R^{X1}$, $-C(=O)OR^{X1}$, $-C(=O)-O-C(=O)R^{X1}$, $-C(=O)SR^{X1}$, $-C(=O)N(R^{X1})_2$, $-C(=S)R^{X1}$, $-C(=S)N(R^{X1})_2$, and $-C(=S)S(R^{X1})$, $-C(=NR^{X1})R^{X1}$, $-C(=NR^{X1})OR^{X1}$, $-C(=NR^{X1})SR^{X1}$, or $-C(=NR^{X1})N(R^{X1})_2$, wherein R^{X1} is –H; halogen; substituted or unsubstituted hydroxyl; substituted or unsubstituted thiol; substituted or unsubstituted amino; substituted or unsubstituted acyl, cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkyl; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, mono- or di- aliphaticamino, mono- or di- heteroaliphaticamino, mono- or di- alkylamino, mono- or di- heteroalkylamino, mono- or di-arylamino, or mono- or di-heteroarylamino; or two R^{X1} groups taken together form a 5- to 6-membered heterocyclic ring. Exemplary acyl groups include aldehydes (−CHO), carboxylic acids ($-CO_2H$), ketones, acyl halides, esters, amides, imines, carbonates, carbamates, and ureas. Acyl substituents include, but are not limited to, any of the substituents described herein, that result in the formation of a stable moiety (e.g., aliphatic, alkyl, alkenyl, alkynyl, heteroaliphatic, heterocyclic, aryl, heteroaryl, acyl, oxo, imino, thiooxo, cyano, isocyano, amino, azido, nitro, hydroxyl, thiol, halo, aliphaticamino, heteroaliphaticamino, alkylamino, heteroalkylamino, arylamino, heteroarylamino, alkylaryl, arylalkyl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, acyloxy, and the like, each of which may or may not be further substituted).

[0067] The term "carbonyl" refers to a group wherein the carbon directly attached to the parent molecule is sp^2 hybridized, and is substituted with an oxygen, nitrogen or sulfur atom, e.g., ketones ($-C(=O)R^{aa}$), carboxylic acids ($-CO_2H$), aldehydes (–CHO), esters ($-CO_2R^{aa}$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$), amides ($-C(=O)N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-C(=S)N(R^{bb})_2$), or imines ($-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$), $-C(=NR^{bb})N(R^{bb})_2$), wherein R^{aa} and R^{bb} are as defined herein.

[0068] As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) that occur and event(s) that do not occur.

[0069] The terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a "pathological condition" (e.g., an infectious disease, or one or more signs or symptoms thereof) as described herein. In some embodiments, treatment may be administered after one or more signs or symptoms have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease or condition. In certain embodiments, treatment may be administered after a suspected exposure has occurred. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[0070] The term "prevent," "preventing," or "prevention" refers to a prophylactic treatment of a subject who is not and/or was not with a disease but is at risk of developing the disease or who was with a disease, is not with the disease, but is at risk of regression of the disease. In certain embodiments, the subject is at a higher risk of developing the disease or at a higher risk of regression of the disease than an average healthy member of a population. In certain embodiments, a prophylactic treatment may be administered after a suspected exposure has occurred to prevent viral infection. In some embodiments, a prophylactic treatment may be administered after a suspected exposure has occurred to lessen the severity of symptoms of the viral infection.

[0071] As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought, for instance, by a researcher or clinician.
The term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment,

healing, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function. For use in therapy, therapeutically effective amounts of a compound of Formula (**I**), as well as salts thereof, may be administered as the raw chemical. For use in therapy, therapeutically effective amounts of a compound of Formula (I-a), as well as salts thereof, may be administered as the raw chemical. Additionally, the active ingredient may be presented as a pharmaceutical composition.

[0072] The term "inhibition," "inhibiting," "inhibit," or "inhibitor" refer to the ability of a compound to reduce, slow, halt, or prevent activity of a particular biological process (e.g., furin activity, viral infectivity, viral entry into a cell, viral replication, toxin activation and/or activity) in a subject relative to vehicle.

[0073] A "subject" to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, e.g., a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle–aged adult, or senior adult)). In certain embodiments, the animal is a mammal. The animal may be a male or female and at any stage of development. In certain embodiments, the subject may have previously tested positive for infection from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus). In certain embodiments, the subject may have previously tested negative for infection from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus). In certain embodiments, the subject may be displaying symptoms of infection from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus), e.g., fever, cough, shortness of breath, tightness in the chest, loss of smell, loss of taste, diarrhea, and/or body aches. In certain embodiments, the subject may be not displaying any symptoms of infection from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus).

[0074] The terms "administer," "administering," or "administration," refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing a compound, or a pharmaceutical composition thereof to a subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0075] *Figure 1* shows a model for the processing of S-protein and its blockade by furin and TMPRSS2 inhibitors. Viral infection is favored by the presence of a furin-like sites at S1/S2 and S2'. TMPRSS2 in target cells enhances infection by shedding ACE2 into soluble sACE2 (in bold) and is also enhanced by cleavage of S1 into S1', which forms a secreted complex with sACE2. Optimal blockade of viral infection is achieved by a combination of furin and TMPRSS2 inhibitors. In the absence of a furin-like site at S1/S2 (μS1/S2), high levels of TMPRSS2 can favor infection by cleaving S1 into S1' and shedding ACE2 into soluble sACE2 complexed with S1' (Figure 1-2).

[0076] *Figure 2* shows inhibition of the processing of the pro-(S) protein, which was expressed with a V5 tag, to active (S)-protein by endogenous furin-like enzymes in VeroE6 (African green monkey kidney), BHK21 (Chinese hamster kidney), or A549 (Human pulmonary epithelial) cell lines when Compound 192 or Compound 219 are present at 0.3 μM, 1 μM, or 10 μM, or when decanoyl-RVKR-CMK (RVKR) is present at 50 μM.

[0077] *Figure 3* shows a schematic representation of the primary structure of proS and its domains and the furin-like S1/S2 site generating the S1- and S2-subunits, as well as the S2' site preceding the fusion peptide (Figure 3A). The signal peptide (SP), N-terminal domain (NTD), receptor binding domain (RBD) to ACE2, the two heptad repeats HR1 and HR2, the transmembrane domain (TM), the cytosolic tail (CT) and the C-terminal V5-tag are indicated. *In vitro* furin and TMPRSS2 cleavage activity against the synthetic peptides is described in Table 1. Each substrate was tested at a final protease concentration of 2 and 100 nM (furin, enlarged box) and 50 nM (TMPRSS2) at pH 6 and 7.5, respectively. *In vitro* furin activity against the V5 tagged proS with the S1/S2 and S2' cleavage site sequence of the spike protein from SARS-CoV-1, SARS-CoV-2, and MERS-CoV was measured (Figure 3B). *In vitro* furin activity against WT and mutated proS proteins carrying substitutions in the furin-like cleavage site S1/S2 SARS-CoV-2 was measured and the results are shown in Figure 3C. TMPRSS2 cleavage at both S1/S2 and S2' was also measured (Figure 3D). S1/S2 site is cleaved only in SARS-1 by TMPRSS2, while in SARS2, TMPESS2 cleaves at S2' at pH6. Western blot analyses were conducted of the processing of WT proS into V5-tagged S2 and S2' by the proprotein convertases furin, PC5A, PACE4, and PC7 following co-transfection of

their cDNAs in HeLa cells (Figure 3E). The migration positions of immature $proS_{im}$, S2 and S2', as well as the actin loading control are marked. V = empty pIRES-EGFP-V5 vector. Western blot analyses were also conducted of HeLa cells following co-transfection with cDNAs coding for either WT S-protein or its double Ala-mutant [R685A + R682A] (μS1/S2) in the absence or presence of cDNAs coding for furin or TMPRSS2 at a ratio of 1:1 (Figure 3F). *The estimated precent cleavages into S1/S2 and S2' are shown, based on the ratio of the V5-immunoreactivity of the cleaved form to the sum of all forms (Figure 3E, 3F). The data are representative of at least three independent experiments.

[0078] *Figure 4* shows comparative processing of proS and its S1/S2 mutants by endogenous proteases in HeLa cells and upon co-expression of furin or TMPRSS2. Hela cells were transiently co-transfected with cDNAs coding for an empty vector (V), including vectors encoding furin, TMPRSS2, and V5 tagged WT spike glycoprotein or its proprotein convertase (PC) cleavage site mutants at positions P4 (R682A), P1 (R685A), and P1' (S686A). At 24 h post-transfection cell lysates were subjected to Western blotting using a V5-mAb (Figure 4A). A Western blot showing the impact of ACE2 on the processing of spike glycoprotein by furin and TMPRSS2 is shown in Figure 4B. The ratio of cDNAs used was S:ACE2:TMPRSS2 = 1:1:2. The percent processing shown under each lane was calculated from the ratio of the V5-imunoreactivity of each protein relative to the total V5-immunoreactivity. The data are representative of at least three independent experiments.

[0079] *Figure 5* shows inhibition of proprotein convertases (PCs) by representative compounds of the disclosure. Figure 5A shows chemical motif of inhibitors. The structure of Compound 93 is shown in Figure 5B. *In vitro* inhibition of the cleavage of the fluorogenic dibasic substrate FAM-QRVRRAVGIDK-TAMRA by each of the proprotein convertases furin, PC5A (PCSK5), PACE4 (PCSK6), and PC7 (PCSK7) is shown in Figure 5C. All experiments were performed in 10 different wells, and the average pIC_{50} (in nM) was calculated. For comparison, the inhibitory pIC_{50} of the furin-like inhibitor RVKR-cmk performed >100 times is presented. Golgi assay: Last column represents the effects of the compounds of this disclosure on U2OS cells expressing each of furin, PC5A, PACE4, and PC7 simultaneously transduced with a BacMam-delivered construct containing a Golgi-targeting sequence followed by a 12-amino acid furin/PCSK cleavage site from Bone Morphogenic Protein 10 (BMP10) and then GFP at the C terminus (GalNAc-T2-GGGGS-DSTARIRR↓NAKG-GGGGS-GFP). Dibasic cleavage releases NAKG-GGGGS-GFP thereby reducing the Golgi-associated fluorescence estimated by imaging. *In vitro* inhibition

of furin by Compounds 93, 192, and 219 (Figure 5D). Furin (2 nM) was incubated with increasing concentration of the compounds, and its enzymatic activity against the synthetic peptides DABSYL/Glu-TNSP**RR**A**R**↓SVAS-EDANS (5 μM) was determined at pH 7.5 (n=3). Furin-inhibitors abrogate endogenous processing of the spike glycoprotein (Figure 5E). Hela cells were transiently transfected with a cDNA encoding an empty vector or with one expressing the spike (S) glycoprotein. Cells were treated 5 h post-transfection with no inhibitor (NT, duplicate) or with the furin-inhibitors at indicated concentrations, or RVKR-cmk at 50 μM. The media were then replaced with fresh ones not containing or containing the inhibitors for an additional 24 h, and finally the cells extracts were analyzed by Western blotting using a mAb-V5. The percent processing shown under each lane was calculated from the ratio of the V5-imunoreactivity of each protein relative to the total V5-immunoreactivity. All data are representative of at least three independent experiments.

[0080] *Figure 6* shows spike-induced cell-to-cell fusion relies on furin cleavage at S1/S2 using a luminescence-based assay HeLa TZM-bl reporter cells stably transfected with an HIV-1-based vector expressing luciferase under the control of the HIV-1 long terminal repeat (LTR), which can be activated by HIV Tat protein.. Cell-to-cell fusion between donor cells (HeLa) expressing the fusogenic SARS-CoV-2 Spike protein along with the HIV trans-activator Tat, and acceptor cells (TZM-bl) that express ACE2 (Figure 6A). Upon fusion, Tat is transferred from donor to acceptor cells, thereby inducing luciferase expression. Donor cells were transfected with vectors expressing either no protein (EV), μS1/S2 , or WT Spike (S) in the absence (NT), or presence of vehicle (DMSO) and the furin-inhibitors RVKR (10 μM), Compound 93, Compound 192, and Compound 219 (300 nM) (Figure 6B). Acceptor cells were transfected with a vector expressing ACE2. After 48 h, cells were co-cultured for 18 h. Luminescence was normalized to the EV value arbitrarily set to 1. Data are presented as mean values ±SD (n=3), One-Way Anova, Dunn-Sidàk multiple comparison test. Donor HeLa cells were co-transfected with vectors (1:1 ratio) expressing WT Spike, μS1/S2 with EV or TMPRSS2 (Figure 6C). Acceptor TZM-bl cells were transfected with ACE2. After 48 h, HeLa and TZM-bl were co-cultured for 18h and luciferase activity measured. The fusion is represented as ratio between the relative luminescence units (RLUs) measured for each condition and the RLU measured in the co-culture between donor cells transfected with EV and ACE2 acceptor cells. Data are presented as mean values ±SD (n=3), One-Way Anova, Bonferroni multiple comparison test. Donor HeLa cells express WT S or μS1/S2. Acceptor TZM-bl cells express EV only, EV + ACE2, EV + TMPRSS2, or ACE2 + TMPRSS2 at a

ratio 1:1 (Figure 6D). The extent of fusion is represented as a ratio between the RLU measured for each condition and the RLU measured in the fusion between HeLa cells expressing EV with respective TZM-bl cells. The bar graph represents the average of 3 experiments performed in triplicates. Data are presented as mean values ±SEM (n=3), Two-Way Anova.

[0081] *Figure 7* shows processing of SARS-CoV-2 S by furin-like convertases is essential for viral entry in human lung epithelial cells but not in model HEK 293 cells stably expressing ACE2 (Figure 7A). Furin cleavage of proS at the S1/S2 site is required for SARS-CoV-2 pseudoviral entry in Calu-3 but not 293T-ACE2. Cells were inoculated with luciferase-expressing HIV particles pseudotyped with SARS-CoV-2 wild-type Spike (WT S) or mutated S (μS1/S2). Each dot represents a different experiment with median luciferase activity calculated from three biological replicates. Three or four experiments were performed for each cell type. Error bars indicate standard deviation (SD). Inhibiting proS processing at S1/S2 by a novel furin-like inhibitor (Compound 93) during pseudovirion packaging prevents viral entry in Calu-3 but not in 293T-ACE2 (Figure 7B). Each dot color depicts a different experiment and shown is mean ± SD of two to three experiments (three biological replicates per experiment). Western blot analysis shows Compound 93 inhibits processing of proS at the S1/S2 site (Figure 7C). Purified pseudovirions and cellular extracts of producing 293T17 cells treated or not with Compound 93 inhibitor were separated on SDS-PAGE gel and analyzed for HIV-1 p24 and V5-tagged S-protein (proSm or cleaved, S2) as indicated.

[0082] *Figure 8* shows furin-like inhibitors and camostat treatment decrease SARS-CoV-2 infection in Calu-3 Cells. Replication kinetics were studied at 12, 24, and 48 h post-infection by plaque assay to determine plaque-forming units (PFUs) of SARS-CoV-2 virus in the supernatant of infected Calu-3 cells treated or not with 1μM Compound 93, 192, and 219 (Figure 8A). A line graph represents results of the triplicate plaque assay results (mean ± SD). The virus titers (expressed as plaque-forming units per milliliter (PFU/ml)) released in the supernatant (24h post-infection) of infected Calu-3 cells treated with indicated concentrations of Compound 93 were determined by plaque assay (mean ± SD of triplicates, *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$) (left panel) (Figure 8B). The selectivity index (SI) of Compound 93 in Calu-3 cells as shown in top right panel was determined by selectivity index relation between IC50 and CC50 (CC_{50}/IC_{50}). The left y axis indicates the inhibition of virus titer (percent) relative to that of the untreated control group (red). The right y axis indicates the cell viability (percent) relative to that of the untreated control group (green). The CC_{50} (50%

cytotoxic concentration), IC_{50} (half maximal inhibitory concentration), and SI (selectivity index) values for each inhibitor are as shown. Representative plaque images of infected Calu-3 cells treated with indicated doses of the compounds are shown in the bottom right panel. Immunoblots for the infected Calu-3 cells (right panel) and viral particles secreted in the supernatant (left panel) with and without treatment with the compounds indicate reduced viral protein levels (Figure 8C). Immunoblots were probed for the full-length (proSm) and cleaved (S2) fragments of viral S protein and nucleocapsid (N) protein as indicated; β-Actin was included as the loading control for the cells. The virus titers (PFU per milliliter) released in the supernatant (24 h post-infection) of infected Calu-3 cells treated with Compound 192 and/or Camostat (Camo) were determined by plaque assay (mean ± SD of duplicates, *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$) (top panel) (Figure 8D). Representative plaque images of infected Calu-3 cells are shown in the bottom panel.

[0083] *Figure 9* shows endo-F and Endo-H sensitivity of V5-tagged proS and its cleavage products by furin and TMPRSS2 in HeLa cells. Protein extracts from HeLa cells transiently expressing: V5-tagged spike protein alone, wild type (WT) or S1/S2 site mutant (μS1/S2) were treated with Endo-F and Endo-H or mock treated (NT) and analyzed by Western blotting using a V5-mAb (Figure 9A). The spike protein WT alone or in combination with Furin or TMPRSS2 in the absence (NT) or presence of PC inhibitors RVKR (50 μM) or D6R (20 μM) treated in the same way is also shown (Figure 9B). Spike protein ,WT or R905A mutant, in combination with TMPRSS2, were treated with Endo-F and Endo-H or mock treated (NT) and analyzed by Western blotting using a V5-mAb (Figure 9C). Consistently, endogenous and furin overexpression generated S2 fragment, was more pronounced when cells expressed PC inhibitors. TMPRSS2 expressing cells did not generate S2 fragment, nor was the TMPRSS2 cleavage of S impacted by these inhibitors.

[0084] *Figure 10* shows proteomic analysis of S2 and S2'. V5-tagged S-protein was immunoprecipitated from a Hela cell lysate using V5-agarose and subjected to SDS-PAGE electrophoresis. The bands corresponding to S2 and S2' were excised and analyzed by mass spectrometry.

[0085] *Figure 11* shows that the compounds do not affect the generation of S2a and S2b by TMPRSS2. Hela cells were transiently transfected with cDNAs encoding either empty vector, S-protein in the presence or absence of human TMPRSS2, were either not-treated (NT) or treated with the compounds at indicated concentrations. At 48 h post-transfection the cells

were collected, and their protein extracts were analyzed by Western blotting using a mAb-V5.

[0086] *Figure 12* shows TMPRSS2 cleaves proS into ER-retained fragments, sheds ACE2 into a soluble form (sACE2), and cleaves the spike protein S1-subunit into a shorter fragment (S1') that forms a complex with sACE2. Camostat inhibits TMPRSS2 activities on proS, S1, and ACE2. HeLa-ACE2 cells were transiently transfected with empty vector (V) or increasing cDNA ratios of V5-tagged WT spike protein to TMPRSS2 (spike-V5:TMPRSS2) as indicated and 24 h later incubated for an additional 24 h in serum-free media containing 120 μM Camostat (+) or control DMSO (-) (Figure 12A). Immunoblot of the 24 h conditioned media (concentrated 10-fold) was first probed for S1 and S1' using an antibody against S1-subunit (GTX135356), stripped and next probed for sACE2 (ab108252) and mature $TMPRSS2_m$ (14437-1-AP) (upper panel). Cell lysates were immunoblotted for spike protein (V5-mAb), ACE2 (ab108252) and β-Actin (lower panel). HeLa-ACE2 cells were transiently transfected for 48 h with empty vector (V), TMPRSS2, and V5-tagged spike protein (S) alone or in combination with TMPRSS2 (S+TMPRSS2) in a ratio of 1:0.7 (Figure 12B). For each condition, 1 ml of 24h serum free conditioned media was immunoprecipitated with 2 μg goat polyclonal ACE2 antibody (AF933, R&D) and 60 μl TrueBlot anti-goat Ig IP beads (00-8844-25; Rockland) and analyzed by western blot first for S1 and S1' (GTX135356) and next for sACE2 (rabbit MAB; ab108252) (upper right panels). For reference, 50% of the media before immunoprecipitation (concentrated 10-fold) (input) was similarly analyzed (upper left panels). Immunoblots of the cell lysates (spike protein: V5-mAb) are also shown (lower panels).

[0087] *Figure 13* shows TMPRSS2-generates soluble ACE2 (sACE2) and enhances the production of S2' in cells and S1' in media. HeLa cells transfected for 48h with cDNAs coding for the empty vector (V), or V5-tagged spike protein, wild type (WT) or its μS1/S2 mutant, were incubated for the last 24 h with conditioned serum free media of HEK293 cells that were transfected with cDNAs encoding either empty vector (V), TMPRSS2, or full length ACE2 with TMPRSS2 in a 1:1 ratio (Figure 13A). The HeLa cells media (concentrated 5-fold) (upper panel) and cell lysates (lower panel) were analyzed by immunoblotting as indicated. The condition pertaining to incubation of HeLa cells expressing WT spike protein with KEK293 media containing sACE2 and active mature $TMPRSS2_m$ is boxed in. dimer = sometimes observed dimer of proS; *ns = non-specific band. Media (concentrated 8-fold) and cell lysates from HeLa cells co-transfected for 48 h with cDNAs encoding V5-tagged spike protein (WT or μS1/S2) + TMPRSS2 ± ACE2 were analyzed by

Western blotting as indicated (Figure 13B). The ratio of cDNAs used was S:TMPRSS2:ACE2= 1:0.3:0.7. The following antibodies were used: S1 and S1', GTX135356; TMPRSS2m, 14437-1-AP; ACE2, ab108252; S2, S2' and S2a, V5-mAb.

[0088] *Figure 14* shows immunocytochemistry of the co-localization of ACE2 and S-protein or μS1/S2 in HeLa cells. Immunofluorescence of S-protein (S) and μS1/S2 (green) were revealed using the spike S1-antibody GTX632604 in non-permeabilized (NP) conditions or with anti-V5 in permeabilized (P) conditions (Figure 14). ACE2 is labeled in red, and the cell nuclei are stained with DAPI (blue).

[0089] *Figure 15* shows immunofluorescence of S-protein (S) and μS1/S2 (green) in HeLa cells pre-incubated for 5 h before transfection and then for 24 h with 1 mM Compound 192. The confocal localizations were revealed as in Figure 15A. Scale bar = 10 μm. Cells expressing both S protein and ACE2 formed many syncytia associated with reduced cell surface expression of the S protein and even greater reduction of ACE2 (b). Cells expressing both μS1/S2 and ACE2 showed an accumulation of both S and ACE2 inside the cells and at the cell surface (c) however the syncytia formation was very reduced. When cells were preincubated with Compound 192 S-expressing HeLa cells phenocopy cells expressing μS1/S2.

[0090] *Figure 16* shows cell-to-cell fusion assay: correlation between syncytia formation and luciferase activity. The ACE2 expression in TZM-bl allowed fusion with cells expressing S in dose dependent manner (B) Expression of mS1/S2 in donor cells did not enhance the fusion with ACE2 expressing TZM-bl cells. Cell-to-cell fusion between donor cells (HeLa) and acceptor cells (TZM-bl) was evaluated using confocal microscopy (Figure 16A). Hela cell transfected with and empty vector (EV), or expressing HIV-Env, SARS-CoV-2 Spike, or μS1/S2 were placed in co-culture for 18h and the number of syncytia was examined using CellMask™ to probe for the plasma membrane and Dapi to stain the nuclei. Donor cells were transfected with vectors expressing either no protein (EV), Tat, WT Spike (S), Tat and WT Spike (Tat+S), or Tat and HIV-Env (Tat+Env) (Figure 16B). Acceptor cells were transfected with a vector expressing no protein (EV), with ACE2 or directly with Tat as appositive control. After 48 h, cells were co-cultured for 18 h. Luminescence was normalized to the EV value arbitrarily set to 1. Data are presented as mean values ±SD (n=3), and a representative experiment is shown. Donor cells were transfected with increasing amounts of plasmid expressing WT Spike, and acceptor cells were transfected with a vector expressing ACE2 (Figure 16C). After 48 h, cells were co-cultured for 18 h, and prepared for luminescence or microscopy. Correlation between the number of syncytia counted by microscopy (n=10 per

condition), and the luciferase activity was determined, and the correlation coefficient was calculated as shown. R^2=0.87.

[0091] *Figure 17* shows the effects of target cells on TMPRSS2 and soluble ACE2 on cell-to-cell fusion. Donor HeLa cells were transfected with a plasmid vector expressing no protein EV, WT Spike, μS1/S2 or WT-Spike together with soluble ACE2 (hACE2 707X). Acceptor HeLa TZM-bl cells were transfected with a plasmid vector expressing no protein, ACE2 with increasing amount of TMPRSS2 as indicated, or soluble ACE2. Fusion is represented as a ratio between the relative luminescence units (RLU) measured for each condition and the RLU measured in the co-culture between representative donor and acceptor cells. Data are presented as mean values ± SD (n=3). Co-expression of ACE2 with various doses of TNPRSS2 in acceptor cells gradually promoted fusion of mS1/S2 expressing cells to similar level as WT S-induced fusion. However sACE2 had no effect on mS1/S2. So at high levels of TMPRSS in ACE2 acceptor cells fusion between cells is possible with or without cleavage at S1/S2 site.

[0092] *Figure 18* shows SARS-CoV-2 viral entry in HEK293 cells is primarily mediated via a pH-dependent pathway. Co-expression of ACE2 with various doses of TMPRSS2 in acceptor cells gradually promoted fusion of mS1/S2 expressing cells to similar level as WT S-induced fusion. However sACE2 had no effect on mS1/S2. So at high levels of TMPRSS in ACE2 acceptor cells fusion between cells is possible with or without cleavage at S1/S2 site. 293T-ACE2 were pretreated with chloroquine (CLQ; 100 μM) for 2 h and subsequently inoculated with luciferase-expressing HIV particles pseudotyped with SARS-CoV-2 wild-type (WT) or mutated (μS1/S2) spike (S). HIV particles made in the absence of S (no S) served as a negative control. Efficiency of viral entry was determined by luciferase activity. Each dot represents an independent experiment (median luciferase of biological triplicates). Error bars show SD.

[0093] *Figure 19* shows novel furin-like inhibitors block viral entry in human epithelial cells but not in model HEK293 cells stably expressing ACE2. Pseudoviruses were produced in 293T17 in the presence or absence of Compound 219 and Compound 192. 293T-ACE2 cells and Calu-3 cells were inoculated with these viruses, and viral entry was determined based upon luciferase activity (Figure 19A, 19B). Each dot represents a different experiment (median luciferase of biological triplicates). Error bars show the SD from the mean.

[0094] *Figure 20* shows Furin-like inhibitors strongly reduce SARS-CoV-2 infection in Calu-3 cells. (Figure 20A and 20B) The virus titers (PFU per milliliter) released in the supernatant (24 hr post infection) of infected Calu-3 cells treated with indicated

concentrations of (A) Compound 219, and (B) Compound 192 were determined by plaque assay (mean ± SD of triplicates, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$). The selectivity index (SI) of (A) Compound 219, and (B) Compound 192 in Calu-3 cells as shown in the top right panel was determined by CC_{50}/IC_{50}. The left y axis indicates the inhibition of virus titer (percent) relative to that of the untreated control group (red). The right y axis indicates the cell viability (percent) relative to that of the untreated control group (green). Representative plaque images of infected Calu-3 cells treated with indicated doses of the compounds are shown in the bottom right panel.

[0095] *Figure 21* shows furin-like inhibitors modestly reduce virus production in SARS-CoV-2-infected Vero E6 cells in a concentration-dependent manner. Replication kinetics were studied at 12, 24 and 48 hr post infection by plaque assay to determine the plaque-forming units (PFUs) of SARS-CoV-2 virus in the supernatant of infected Vero E6 cells treated or not with 1 μM Compound 93, 219, and 192 (Figure 21A). A line graph represents results of the triplicate plaque assay (mean ± SD). Virus released in the supernatant (48 hr post infection) of infected Vero E6 cells treated with indicated concentrations of Compound 93 (Figure 21B), Compound 219 (Figure 21C), and Compound 192 (Figure 21D) were determined by plaque assay (mean ± SD of triplicates, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$).

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

[0096] The present disclosure provides methods, pharmaceutical compositions, and kits for the treatment and/or prevention of a viral infection caused by a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus), comprising administering to the subject a therapeutically effective amount of a compound of Formula (**I**), a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**) as described herein. Further provided herein are methods, pharmaceutical compositions, and kits for the treatment and/or prevention of a viral infection caused by a variant of a SARS-CoV-2 virus (e.g. B.1.351 (i.e., the South African COVID-19 variant), B.1.1.7 (i.e., the UK COVID-19 variant), P.1 (i.e., the Brazilian COVID-19 variant)).

[0097] Further provided herein are methods for inhibiting viral entry into a cell of a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) in a subject in need thereof, comprising

administering to the subject a therapeutically effective amount of a compound of Formula (**I**) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**) as described herein.

[0098] Further provided herein are methods for decreasing the pathogenicity of a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (**I**) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**) as described herein.

[0099] Also provided herein are methods for inhibiting viral exit from a cell of a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (**I**) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**) as described herein.

[00100] In certain embodiments, the present disclosure provides methods for the treatment and/or prevention of a viral infection caused by a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus), comprising administering to the subject a therapeutically effective amount of a compound of Formula (**I**) or pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**) as described herein. In certain embodiments, the provided methods are for the treatment and/or prevention of viral infections caused by a coronaviridae family virus. In certain embodiments, the provided methods are for the treatment and/or prevention of viral infections caused by an alphacoronavirus. In certain embodiments, the provided methods are for the treatment and/or prevention of viral infections caused by HCoV-NL63 or HCoV-229E. In certain embodiments, the provided methods are for the treatment and/or prevention of viral infections caused by a betacoronavirus. In certain embodiments, the provided methods are for the treatment and/or prevention of viral infections caused by SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, or HCoV-HKU1. In certain embodiments, the provided methods are for the treatment and/or prevention of viral infections caused by SARS-CoV. In certain

embodiments, the provided methods are for the treatment and/or prevention of viral infections caused by SARS-CoV-2. In certain embodiments, the provided methods are for the treatment and/or prevention of viral infections caused by MERS-CoV.

[00101] In another aspect, the present disclosure provides methods of treating a viral infection resulting from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) in a subject in need thereof, the method comprising administering to the subject in need thereof an effective amount (e.g., therapeutically effective amount) of a compound of Formula (**I**) or a pharmaceutical acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**) as described herein. In certain embodiments, provided herein are methods of treating viral infections resulting from an alphacoronavirus. In certain embodiments, provided herein are methods of treating viral infections resulting from HCoV-NL63 or HCoV-229E. In certain embodiments, provided herein are methods of treating viral infections resulting from a betacoronavirus. In certain embodiments, provided herein are methods of treating viral infections resulting from SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, or HCoV-HKU1. In certain embodiments, provided herein are methods of treating viral infections resulting from SARS-CoV. In certain embodiments, provided herein are methods of treating viral infections resulting from SARS-CoV-2. In certain embodiments, provided herein are methods of treating viral infections resulting from MERS-CoV. In certain embodiments, provided herein are methods of treating viral infections resulting from HCoV-OC43. In certain embodiments, provided herein are methods of treating viral infections resulting from HCoV-HKU1.

[00102] In another aspect, the present disclosure provides methods of preventing a viral infection resulting from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) in a subject in need thereof, the method comprising administering to the subject in need thereof an effective amount (e.g., a prophylactically effective amount) of a compound of Formula (**I**) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising Formula (**I**) as described herein. In certain embodiments, the present disclosure provides methods of preventing a viral infection resulting from a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) in a subject in need thereof, the method comprising administering to the

subject in need thereof an effective amount (e.g., a prophylactically effective amount) of a compound of Formula (**I**) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising Formula (**I**) as described herein. In certain embodiments, the present disclosure provides methods of preventing a viral infection resulting from SARS-CoV in a subject in need thereof, the method comprising administering to the subject in need thereof an effective amount (e.g., a prophylactically effective amount) of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising Formula (**I**) as described herein.

[00103] In another aspect, the present disclosure provides methods of inhibiting the entry of a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) into a cell, in a subject in need thereof, the method comprising administering to the subject in need thereof an effective amount of a compound of Formula (**I**) or pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**) as described herein.

[00104] In certain embodiments, provided herein are methods of inhibiting the entry of a coronaviridae family virus into a cell, in a subject by at least 1%, at least 3%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. In certain embodiments, the entry of a coronaviridae family virus into a cell, in a subject is inhibited by at least 1%, at least 3%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. In certain embodiments, provided herein are methods of inhibiting the entry of a coronaviridae family virus into a cell, in a subject by at least 30%. In certain embodiments, provided herein are methods of inhibiting the entry of a coronaviridae family virus into a cell, in a subject by at least 50%. In certain embodiments, provided herein are methods of inhibiting the entry of a coronaviridae family virus into a cell, in a subject by at least 75%.

[00105] In another aspect, the present disclosure provides methods of inhibiting the replication of a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) in a subject in need thereof, the method comprising administering to the subject in need thereof an effective amount of a compound of Formula (**I**) or pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**) as described herein.

[00106] In certain embodiments, provided herein are methods of inhibiting the replication of a coronaviridae family virus in a subject by at least 1%, at least 3%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. In certain embodiments, the replication of a coronaviridae family virus in a subject is inhibited by at least 1%, at least 3%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. In certain embodiments, provided herein are methods of inhibiting the replication of a coronaviridae family virus in a subject by at least 30%. In certain embodiments, provided herein are methods of inhibiting the replication of a coronaviridae family virus in a subject by at least 50%. In certain embodiments, provided herein are methods of inhibiting the replication of a coronaviridae family virus in a subject by at least 75%.

[00107] In another aspect, the present disclosure provides methods of decreasing viral infectivity of a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) in a subject, the method comprising administering to the subject an effective amount of a compound of Formula (**I**) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising Formula (**I**) as described herein.

[00108] In another aspect, the present disclosure provides methods of inhibiting viral infectivity in a biological sample (e.g., an *in vitro* biological sample), the method comprising contacting the biological sample with an effective amount of a compound of Formula (**I**) or a pharmaceutical composition described herein. In another aspect, the present disclosure provides methods of inhibiting viral infectivity in a cell (e.g., an *in vitro* cell), the method comprising contacting the cell with an effective amount of a compound of Formula (**I**) or a pharmaceutical composition described herein.

[00109] In certain embodiments, the methods, uses, pharmaceutical compositions, kits, and compounds described herein further comprise administering one or more additional pharmaceutical agents (e.g., therapeutically and/or prophylactically active agents). The compounds or compositions can be administered in combination with additional pharmaceutical agents that improve their activity (e.g., activity (e.g., potency and/or efficacy) in treating a disease in a subject in need thereof, in preventing a disease in a subject in need thereof, in reducing the risk to develop a disease in a subject in need thereof, and/or in inhibiting the activity of a transcription factor in a subject or cell), improve bioavailability, improve safety, reduce drug resistance, reduce and/or modify metabolism, inhibit excretion,

and/or modify distribution in a subject or cell. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects. In certain embodiments, a pharmaceutical composition described herein including a compound described herein and an additional pharmaceutical agent shows a synergistic effect that is absent in a pharmaceutical composition including one of the compounds and the additional pharmaceutical agent, but not both. For example, the methods, uses, pharmaceutical compositions, kits, and compounds comprising a compound of Formula (**I**) and camostat may show a synergistic effect over compositions comprising Compound (**I**) or camostat in treating viral infections. The methods, uses, pharmaceutical compositions, kits, and compounds comprising a compound of Formula (**I**) and camostat may also show additive effects over compositions comprising Compound (**I**) or camostat in treating viral infections.

[00110] The compound or composition can be administered concurrently with, prior to, or subsequent to one or more additional pharmaceutical agents, which may be useful as, e.g., combination therapies. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. Pharmaceutical agents include small organic molecules such as drug compounds (e.g., compounds approved for human or veterinary use by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells. In certain embodiments, the additional pharmaceutical agent is a pharmaceutical agent useful for treating and/or preventing a viral infection (e.g., a viral infection resulting from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus). Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the compound or composition described herein in a single dose or administered separately in different doses. The particular combination to employ in a regimen will take into account compatibility of the compound described herein with the additional pharmaceutical agent(s) and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agent(s) in combination be utilized at levels that do not exceed the levels at

which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[00111] The additional pharmaceutical agents include, but are not limited to, anti-inflammatory agents, immunosuppressants, antibacterial agents, antiviral agents, cardiovascular agents, anti-allergic agents, and pain-relieving agents. In certain embodiments, the additional pharmaceutical agent is an antiviral agent (e.g., Abacavir, Acyclovir, Amantadine, Atazanavir, Chloroquine, Darunavir, Elvitegravir, Fosamprenavir, Ganciclovir, Indinavir, Ledipasvir, Lopinavir, Nitazoxanide, Oseltamivir, Penciclovir, Peramivir, Raltegravir, Ribavirin, Rimantadine, Ritonavir, Saquinavir, Sofosbuvir, Tipranavir, Velpatasvir, Zanamivirfavipiravir, remdesivir, Oya1, galidesivir, umifenovir, hydroxychloroquine). In certain embodiments, the antiviral agent is chloroquine. In certain embodiments, the antiviral agent is hydroxychloroquine. In certain embodiments, the additional pharmaceutical agent is an antibacterial agent (e.g., azithromycin). In certain embodiments, the additional pharmaceutical agent is an anti-inflammatory (e.g., Gimsilumab, IL-6 antibodies, actemra, paracetamol, Nonsteroidal anti-inflammatory drugs (NSAIDs)). In certain embodiments, the anti-inflammatory may be a tumor necrosis factor (TNF) inhibitor (e.g., adalimumab, etanercept, infliximab, golimumab, certolizumab).

[00112] In certain embodiments, the additional pharmaceutical agent is an antifibrotic agent (e.g., Pirfenidone, Nintedanib). In certain embodiments, the additional pharmaceutical agent is Pirfenidone. In certain embodiments, the additional pharmaceutical agent is Nintedanib.

[00113] In certain embodiments, the additional pharmaceutical agent is in the form of an additional therapy (e.g., receiving antibodies from survivor patients' blood, DNA vaccines, RNA vaccines). In certain embodiments, the additional therapy is treatment with an antibody. In certain embodiments, the additional therapy is treatment with a human antibody. In certain embodiments, the additional therapy is treatment with a human body from a survivor patients' blood. In certain embodiments, the additional therapy is treatment with a monoclonal antibody. In certain embodiments, the additional therapy is treatment with antibodies that bind the S-spike protein. In certain embodiments, the additional therapy is treatment with a monoclonal antibody that binds the S-spike protein.

[00114] In certain embodiments, the additional pharmaceutical agent is an N-methyl-D-aspartate (NDMA) receptor glutamate receptor antagonist (e.g., ifenprodil). In certain embodiments, the additional pharmaceutical agent is an ACE2 blocker (e.g., APNO1). In certain embodiments, the additional pharmaceutical agent is a CCR5 antagonist. In certain embodiments, the additional pharmaceutical agent is an antibody that bind S-spike protein

(e.g., REGN3048-3051). In certain embodiments, the additional pharmaceutical agent is idebenone. In certain embodiments, the additional pharmaceutical agent is interferon beta. In certain embodiments, the additional pharmaceutical agent is an ADAM-17 inhibitor. In certain embodiments, the additional pharmaceutical agent is 4-methylumbelliferone.

[00115] Additional pharmaceutical agents may also include serine protease inhibitors (e.g., TMPRSS2 inhibitors (e.g., camostat, nafamostat)), ACE2 inhibitors (e.g., benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, or trandolapril). In certain embodiments, the additional pharmaceutical agent is a TMPRSS2 inhibitor (e.g., camostat, nafamostat)). In certain embodiments, the additional pharmaceutical agent is camostat. In certain embodiments, the additional pharmaceutical agent is nafamostat. In certain embodiments, the additional pharmaceutical agent is benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, or trandolapril. In certain embodiments, the additional pharmaceutical agent is benazepril. In certain embodiments, the additional pharmaceutical agent is captopril. In certain embodiments, the additional pharmaceutical agent is enalapril. In certain embodiments, the additional pharmaceutical agent is fosinopril. In certain embodiments, the additional pharmaceutical agent is lisinopril. In certain embodiments, the additional pharmaceutical agent is moexipril. In certain embodiments, the additional pharmaceutical agent is perindopril. In certain embodiments, the additional pharmaceutical agent is quinapril. In certain embodiments, the additional pharmaceutical agent is ramipril. In certain embodiments, the additional pharmaceutical agent is trandolapril.

[00116] In another aspect, the present disclosure provides compounds of Formula (**I**) or a pharmaceutically acceptable salt thereof, and pharmaceutical compositions described herein for use in treating and/or preventing a viral infection caused by a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus), comprising administering to the subject a therapeutically effective amount of a compound of Formula (**I**) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**) as described herein.

[00117] In another aspect, the present disclosure provides uses of compounds of Formula (**I**) or a pharmaceutically acceptable salt thereof, and pharmaceutical compositions as described herein in the manufacture of a medicament for treating a viral infection resulting from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-

229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) in a subject in need thereof.

[00118] In another aspect, the present disclosure provides uses of compounds of Formula (**I**) and pharmaceutical compositions described herein in the manufacture of a medicament for preventing a viral infection resulting from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) in a subject in need thereof.

[00119] In certain embodiments, the virus is a coronaviridae family virus. In certain embodiments, the coronaviridae family virus is an alphacoronavirus. In certain embodiments, the alphacoronavirus is HCoV-NL63. In certain embodiments, the alphacoronavirus is HCoV-229E. In certain embodiments, the coronaviridae family virus is a betacoronavirus. In certain embodiments, the betacoronavirus is SARS-CoV. In certain embodiments, the betacoronavirus is SARS-CoV-2. In certain embodiments, the betacoronavirus is MERS-CoV. In certain embodiments, the betacoronavirus is HCoV-OC43. In certain embodiments, the betacoronavirus is HCoV-HKU1. In certain embodiments, the coronaviridae family virus is a deltacoronavirus. In certain embodiments, the coronaviridae family virus is a gammacoronavirus.

[00120] In certain embodiments, the virus is a variant of a SARS-Cov-2 virus (e.g., B.1.351, B.1.1.7, P.1). In certain embodiments, the SARS-Cov-2 variant is the B.1.351 variant (i.e., the South African COVID-19 variant). In certain embodiments, the SARS-Cov-2 variant is the B.1.1.7 variant (i.e., the UK COVID-19 variant). In certain embodiments, the SARS-CoV-2 variant is the P.1 variant (i.e., the Brazilian COVID-19 variant).

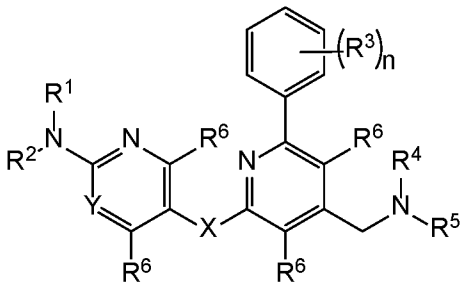
[00121] Without wishing to be bound by any particular theory, in certain embodiments, the compounds of Formula (**I**) useful in the methods, compositions, and uses of this disclosure prevents or inhibits the furin-mediated processing Spike (S)-protein, which may be cleaved during virus egress.

[00122] Without wishing to be bound by any particular theory, in certain embodiments, the compounds of Formula (**I**) useful in the methods, compositions, and uses of this disclosure prevents or inhibits the furin-mediated processing Spike (S)-protein, which may be cleaved during virus entry into a cell.

[00123] Without wishing to be bound by any particular theory, in certain embodiments, the compounds of Formula (**I**) useful in the present disclosure inhibit viral fusion by cleaving the glycoproteins of a virus.

[00124] Without wishing to be bound by any particular theory, in certain embodiments, the compounds of Formula (**I**) useful in the present disclosure inhibit viral fusion (during viral entry or exit of the cell) by inhibiting the furin-mediated processing of the Spike (S)-protein. Cleavage of the (S)-protein may be required to expose the fusion protein, which allows for viral entry and exit into the cell.

[00125] In certain embodiments, the compounds useful in the present disclosure are of Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt thereof, wherein:

X is –O– or –N(R^8)–;

Y is –N= or –C(R^6)=;

R^1 and R^2 are each independently H or optionally substituted (C_1-C_4)alkyl; optionally, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, –OCONR^{8}R^9, –CO_2R^8, –C(O)CO_2R^8, –R^7, –OR^7, –NHR^8, –NR^{7}R^8, –C(O)R^7, –CONHR^8, –CONR^{7}R^8, or –SO_2R^7;

each R^3 is independently halogen, –CN, –O(C_1-C_4)alkyl, or optionally substituted (C_1-C_4)alkyl;

R^4 and R^5 are each independently H or optionally substituted (C_1-C_4)alkyl; optionally, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, –OCONR^{8}R^9, –CO_2R^8, –C(O)CO_2R^8, –SO_2(C_1 C_4)alkyl, –R^7, –OR^7, –NHR^8, –NR^{7}R^8, –N(R^8)C(O)R^9, –N(R^8)SO_2R^9, –N(R^8)CONR^{8}R^9, –N(R^8)CON(R^8)SO_2R^9, –C(O)R^7, –CONHR^8, –CONR^{7}R^8, or –P(O)R^{8}R^9;

each R^6 is independently H, halogen, optionally substituted (C_1-C_4)alkyl, –OH, or optionally substituted (C_1-C_4)alkoxy;

each R^7 is independently (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, or (C_1-C_4)alkyl(C_3-C_6)cycloalkyl, each of which is optionally substituted with one or two of triazolyl, tetrazolyl, $–CO_2R^8$, $–CONR^8R^9$, $–CON(R^8)CO_2(C_1$-$C_4)$alkyl, hydroxyl, oxo, –(C_1-C_4)alkoxy, $–OCONR^8R^9$, $–OCON(R^8)C(O)R^9$, (C_1-C_4)alkyl, (C_1-C_4)alkylOH, $–NR^8R^9$, $–N(O)R^8R^9$, $–N(R^8)C(O)R^9$, $–N(R^8)CO_2(C_1$-$C_4)$alkyl, $–N(R^8)CH_2CO_2R^9$, $–N(R^8)CONR^8R^9$, $–N(R^8)CON(R^8)C(O)R^9$, $–N(R^8)CON(R^8)CO_2(C_1$-$C_4)$alkyl, $–N(R^8)SO_2R^9$, $–N(R^8)CON(R^8)SO_2R^9$, $–SO(C_1$-$C_4)$alkyl, $–SO_2(C_1$-$C_4)$alkyl, $–SO_3R^8$, $–SO_2NR^8R^9$, $–B(OH)_2$, $–P(O)R^8R^9$, or $–P(O)(OR^8)(OR^9)$;

each of R^8 and R^9 is independently H, optionally substituted (C_1-C_4)alkyl, or optionally substituted (C_3-C_6)cycloalkyl;

n is 1, 2, 3, or 4.

[00126] In certain embodiments, X is –O– or $–NR^8$, wherein R^8 is (C_1-C_4)alkyl. In another embodiment, X is $–NR^8$, wherein R^8 is (C_1-C_4)alkyl. In certain embodiments, X is –O–.

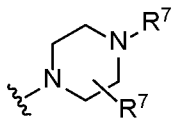
[00127] In certain embodiments, Y is –N= or $–C(R^6)=$, wherein R^6 is independently H, halogen, optionally substituted (C_1-C_4)alkyl, –OH, or optionally substituted (C_1-C_4)alkoxy. In certain embodiments, Y is –N=. In certain embodiments, Y is $–C(R^6)=$.

[00128] In certain embodiments, R^3 is optionally substituted $–O(C_1$-$C_4)$alkyl. In certain embodiments, R^3 is optionally substituted $–OCF_3$. In certain embodiments, R^3 is optionally substituted (C_1-C_4)alkyl. In certain embodiments, R^3 is –Me. In certain embodiments, R^3 is $–CF_3$. In certain embodiments, R^3 is $–CHF_2$. In certain embodiments, R^3 is $–CH_2F$. In certain embodiments, R^3 is halogen. In certain embodiments, R^3 is –F. In certain embodiments, R^3 is –Cl. In certain embodiments, R^3 is –Br. In certain embodiments, R^3 is –I. In certain embodiments, R^3 is –Me. In certain embodiments, each R^3 is independently halogen, methyl, or difluoromethyl. In another embodiment, each R^3 is independently fluoro, chloro, bromo, methyl, or difluoromethyl. In one embodiment, each R^3 is independently halogen. In another embodiment, each R^3 is independently fluoro, chloro, or bromo. In another embodiment, each R^3 is independently fluoro or chloro. In certain embodiments, each R^3 is chloro. In certain embodiments, R^3 is –CN.

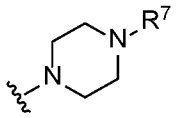
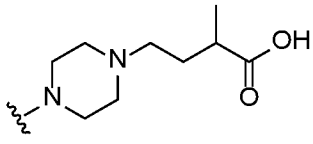
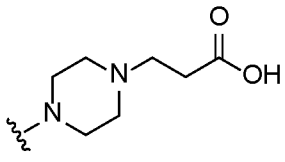
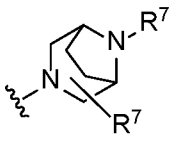
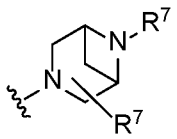
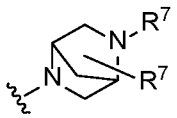
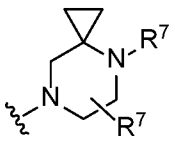
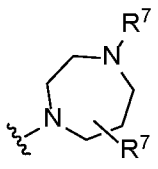
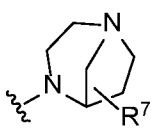
[00129] In certain embodiments, R^1 and R^2 are each independently H, (C_1-C_4)alkyl, or (C_1-C_4)alkylNH_2. In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms

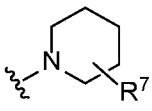
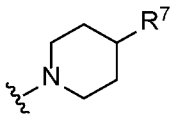
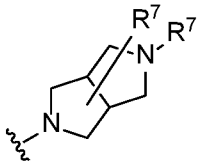
independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, $-OCONR^8R^9$, $-CO_2R^8$, $-C(O)CO_2R^8$, $-R^7$, $-OR^7$, $-NHR^8$, $-NR^7R^8$, $-C(O)R^7$, $-CONHR^8$, $-CONR^7R^8$, or $-SO_2R^7$. In one embodiment, R^1 and R^2 are each independently H, $(C_1\text{-}C_4)$alkyl, or $-(C_1\text{-}C_4)$alkylNH_2. In another embodiment, R^1 and R^2 are each independently H or $-(C_1\text{-}C_4)$alkylNH_2. R^1 and R^2 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, $-OCONR^8R^9$, $-CO_2R^8$, $-C(O)CO_2R^8$, $-R^7$, $-OR^7$, $-NHR^8$, $-NR^7R^8$, $-C(O)R^7$, $-CONHR^8$, $-CONR^7R^8$, or $-SO_2R^7$. In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form an optionally substituted pyrrolidine, pyrazolidine, imidazolidine, piperidine, piperazine, or morpholine ring.

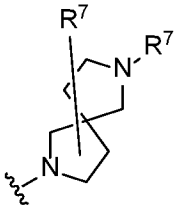
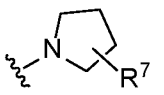
[00130] In another embodiment, R^1 and R^2 taken together with the nitrogen atom to which they are attached represent a 6- or 7-membered monocyclic ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted by one, two, or three substituents independently halogen, hydroxyl, oxo, $-OCONR^8R^9$, $-CO_2R^8$, $-C(O)CO_2R^8$, $-R^7$, $-OR^7$, $-NHR^8$, $-NR^7R^8$, $-C(O)R^7$, $-CONHR^8$, $-CONR^7R^8$, or $-SO_2R^7$. In another embodiment, R^1 and R^2 taken together with the nitrogen atom to which they are attached represent a 6- or 7-membered monocyclic ring, optionally containing one or two additional nitrogen heteroatoms, wherein said ring is optionally substituted by one, two, or three substituents independently selected from halogen, hydroxyl, oxo, R^7, $-OR^7$, $-NHR^8$, $-NR^7R^8$, and $-C(O)R^7$. In another embodiment, R^1 and R^2 taken together with the nitrogen atom to which they are attached represent a 6- or 7-membered monocyclic ring, optionally containing one additional nitrogen heteroatom, wherein said ring is optionally substituted by one substituent which is R^7. In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached represent an optionally substituted piperazine ring.

[00131] In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form an optionally substituted piperazine ring. In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a piperazine ring of the formula: 

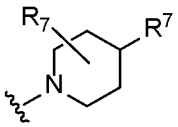
. In certain embodiments, R^1 and R^2 taken together with the

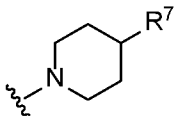
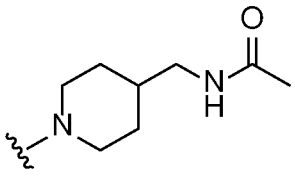
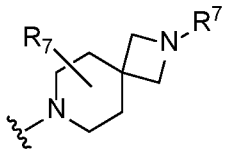
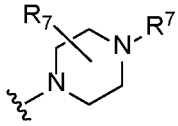
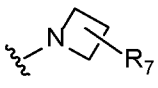
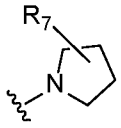
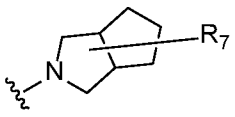
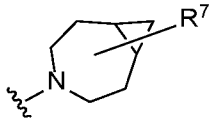
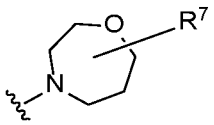
nitrogen atom to which they are attached form a piperazine ring of the formula: . In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a piperazine ring of the formula: . In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a piperazine ring of the formula: . In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a piperazine ring of the formula: . In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a piperazine ring of the formula: . In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a piperazine ring of the formula: . In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a piperazine ring of the formula: . In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a ring of the formula: . In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a ring of the formula: . In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a piperidine ring of the formula:

. In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a piperidine ring of the formula: . In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a ring of the formula: . In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a ring of the formula:

. In certain embodiments, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a pyrrolidine ring of the formula: .

[00132] In certain embodiments, R^4 and R^5 are each independently H, or optionally substituted (C_1-C_4)alkyl. In certain embodiment, R^4 and R^5 are the same. In certain embodiments, R^4 and R^5 are different. In certain embodiments, R^4 is H. In certain embodiments, R^5 is H. In one embodiment, R^4 and R^5 are each independently H, (C_1-C_4)alkyl, or (C_2-C_4)alkyl(C_1-C_4)alkoxy. In certain embodiments, R^4 is –Me. In certain embodiments, R4 is $-C(O)R^7$. In certain embodiments, R^4 is –C(O)Me. In another embodiment, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, $-OCONR^8R^9$, $-CO_2R^8$, $-C(O)CO_2R^8$, $-SO_2(C_1\ C_4)$alkyl, $-R^7$, $-OR^7$, $-NHR^8$, $-NR^7R^8$, $-N(R^8)C(O)R^9$, $-N(R^8)SO_2R^9$, $-N(R^8)CONR^8R^9$, $-N(R^8)CON(R^8)SO_2R^9$, $-C(O)R^7$, $-CONHR^8$, $-CONR^7R^8$, or $-P(O)R^8R^9$. In another embodiment, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a piperidine ring of the formula:

. In another embodiment, R^4 and R^5 taken together with the nitrogen atom to

which they are attached form a piperidine ring of the formula: . In another embodiment, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a piperidine ring of the formula: . In another embodiment, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a ring of the formula: . In another embodiment, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a piperazine ring of the formula: . In another embodiment, R^4 and R^5 taken together with the nitrogen atom to which they are attached form ring of the formula: . In another embodiment, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a pyrrolidine ring of the formula: . In another embodiment, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a pyrrolidine ring of the formula: . In another embodiment, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a pyrrolidine ring of the formula: . In another embodiment, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a ring of the formula: . In another embodiment, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a ring of the formula: .

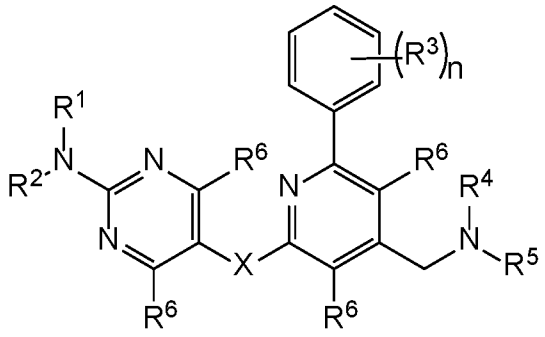
[00133] In one embodiment, each R^6 is independently halogen or $(C_1$-$C_4)$alkyl. In another embodiment, each R^6 is independently halogen. In another embodiment, each R^6 is independently selected from the group consisting of fluoro, chloro, bromo, and methyl. In another embodiment, each R^6 is independently selected from the group consisting of fluoro, chloro, and bromo. In another embodiment, each R^6 is independently fluoro or chloro. In certain embodiments, each R^6 is fluoro. In another embodiment, each R^6 is chloro. In another embodiment, each R^6 is independently $(C_1$-$C_4)$alkyl. In another embodiment, each R^6 is methyl.

[00134] In one embodiment, each R^7 is independently $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, or –$(C_1$-$C_4)$alkyl$(C_3$-$C_6)$cycloalkyl, each of which is optionally substituted by one or two of triazolyl, tetrazolyl, $–CO_2R^8$, $–CONR^8R^9$, $–CON(R^8)CO_2(C_1$-$C_4)$alkyl, –OH, $(C_1$-$C_4)$alkoxy, $–OCONR^8R^9$, $–OCON(R^8)C(O)R^9$, $(C_1$-$C_4)$alkyl, –$(C_1$-$C_4)$alkylOH, $–NR^8R^9$, $–N(O)R^8R^9$, $–N(R^8)C(O)R^9$, $-N(R^8)CO_2(C_1$-$C_4)$alkyl, $–N(R^8)CONR^8R^9$, $–N(R^8)CON(R^8)C(O)R^9$, $–N(R^8)CON(R^8)CO_2(C_1$-$C_4)$alkyl, $–N(R^8)SO_2R^9$, $–N(R^8)CON(R^8)SO_2R^9$, $–SO(C_1$-$C_4)$alkyl, $–SO_2(C_1$-$C_4)$alkyl, $–SO_3R^8$, $–SO_2NR^8R^9$, $–B(OH)_2$, $–P(O)R^8R^9$, or $–P(O)(OR^8)(OR^9)$. In another embodiment, each R^7 is independently $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, halo$(C_1$-$C_4)$alkyl, $(C_3$-$C_6)$cycloalkyl, or –$(C_1$-$C_2)$alkyl$(C_3$-$C_6)$cycloalkyl, each of which is optionally substituted with $–CO_2R^8$, $–CONR^8R^9$, –OH, oxo, –$(C_1$-$C_4)$alkoxy, $–OCONR^8R^9$, –$(C_1$-$C_4)$alkylOH, $–NR^8R^9$, $–N(R^8)C(O)R^9$, $–N(R^8)CO_2(C_1$-$C_4)$alkyl, $–N(R^8)CH_2CO_2R^9$, $–N(R^8)CONR^8R^9$, $–N(R^8)SO_2R^9$, $–SO(C_1$-$C_4)$alkyl, $–SO_2(C_1$-$C_4)$alkyl, $–SO_3R^8$, $–SO_2NR^8R^9$, or $–P(O)(OR^8)(OR^9)$. In another embodiment, each R^7 is independently $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, halo$(C_1$-$C_4)$alkyl, $(C_3$-$C_6)$cycloalkyl, or –$(C_1$-$C_2)$alkyl$(C_3$-$C_6)$cycloalkyl, each of which is optionally substituted by one or two substituents $–CO_2R^8$, $–CONR^8R^9$, –OH, $(C_1$-$C_4)$alkoxy, $–OCONR^8R^9$, –$(C_1$-$C_4)$alkylOH, $–NR^8R^9$, $–N(R^8)C(O)R^9$, $–N(R^8)CO_2(C_1$-$C_4)$alkyl, $–N(R^8)CONR^8R^9$, $–N(R^8)SO_2R^9$, $–SO(C_1$-$C_4)$alkyl, $–SO_2(C_1$-$C_4)$alkyl, $–SO_3R^8$, $–SO_2NR^8R^9$, or $–P(O)(OR^8)(OR^9)$. In another embodiment, each R^7 is $(C_1$-$C_6)$alkyl which is optionally substituted by one substituent which is $–CO_2H$, –OH, $–N(R^8)C(O)R^9$, or $–SO(C_1$-$C_4)$alkyl. In another embodiment, each R^7 is $(C_1$-$C_4)$alkyl which is optionally substituted by one substituent which is $–CO_2H$, –OH, $–N(R^8)C(O)R^9$, or $–SO(C_1$-$C_4)$alkyl.

[00135] In certain embodiments, each of R^8 and R^9 is independently H, optionally substituted $(C_1\text{-}C_4)$alkyl, or optionally substituted $(C_3\text{-}C_6)$cycloalkyl. In one embodiment, each R^8 and R^9 is independently H or $(C_1\text{-}C_4)$alkyl. In another embodiment, each R^8 and R^9 is independently $(C_1\text{-}C_4)$alkyl. In another embodiment, R^8 and R^9 are each methyl. In another embodiment, each R^8 and R^9 is H. In another embodiment, R^8 is H; and R^9 is $(C_1\text{-}C_4)$alkyl. In another embodiment, R^8 is H; and R^9 is –Me. In another embodiment, R^8 is $(C_1\text{-}C_4)$alkyl. In another embodiment, R^8 is –Me. In another embodiment, R^8 is –H. In another embodiment, R^9 is $(C_1\text{-}C_4)$alkyl. In another embodiment, R^9 is –Me. In another embodiment, R^9 is –H.

[00136] In one embodiment, n is 1, 2, or 3. In another embodiment, n is 2 or 3. In another embodiment, n is 2.

[00137] In certain embodiments, the compound of Formula (**I**) useful in the present disclosure is of the Formula (**II**):



(**II**),

or a pharmaceutically acceptable salt thereof, wherein:

X is –O– or $–N(R^8)–$;

R^1 and R^2 are each independently H or optionally substituted $(C_1\text{-}C_4)$alkyl;

optionally, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, $–OCONR^8R^9$, $–CO_2R^8$, $–C(O)CO_2R^8$, $–R^7$, $–OR^7$, $–NHR^8$, $–NR^7R^8$, $–C(O)R^7$, $–CONHR^8$, $–CONR^7R^8$, or $–SO_2R^7$;

each R^3 is independently halogen, –CN, $–O(C_1\text{-}C_4)$alkyl, or optionally substituted $(C_1\text{-}C_4)$alkyl;

R^4 and R^5 are each independently H or optionally substituted $(C_1\text{-}C_4)$alkyl;

optionally, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen,

nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, $-OCONR^8R^9$, $-CO_2R^8$, $-C(O)CO_2R^8$, $-SO_2(C_1\ C_4)$alkyl, $-R^7$, $-OR^7$, $-NHR^8$, $-NR^7R^8$, $-N(R^8)C(O)R^9$, $-N(R^8)SO_2R^9$, $-N(R^8)CONR^8R^9$, $-N(R^8)CON(R^8)SO_2R^9$, $-C(O)R^7$, $-CONHR^8$, $-CONR^7R^8$, or $-P(O)R^8R^9$;

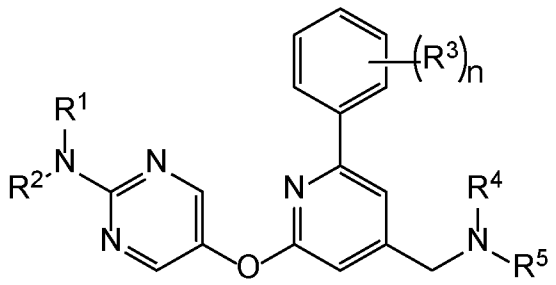
each R^6 is independently H, halogen, optionally substituted $(C_1\text{-}C_4)$alkyl, –OH, or optionally substituted $(C_1\text{-}C_4)$alkoxy;

each R^7 is independently $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, or $(C_1\text{-}C_4)$alkyl$(C_3\text{-}C_6)$cycloalkyl, each of which is optionally substituted with one or two of triazolyl, tetrazolyl, $-CO_2R^8$, $-CONR^8R^9$, $-CON(R^8)CO_2(C_1\text{-}C_4)$alkyl, hydroxyl, oxo, $-(C_1\text{-}C_4)$alkoxy, $-OCONR^8R^9$, $-OCON(R^8)C(O)R^9$, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkylOH, $-NR^8R^9$, $-N(O)R^8R^9$, $-N(R^8)C(O)R^9$, $-N(R^8)CO_2(C_1\text{-}C_4)$alkyl, $-N(R^8)CH_2CO_2R^9$, $-N(R^8)CONR^8R^9$, $-N(R^8)CON(R^8)C(O)R^9$, $-N(R^8)CON(R^8)CO_2(C_1\text{-}C_4)$alkyl, $-N(R^8)SO_2R^9$, $-N(R^8)CON(R^8)SO_2R^9$, $-SO(C_1\text{-}C_4)$alkyl, $-SO_2(C_1\text{-}C_4)$alkyl, $-SO_3R^8$, $-SO_2NR^8R^9$, $-B(OH)_2$, $-P(O)R^8R^9$, or $-P(O)(OR^8)(OR^9)$;

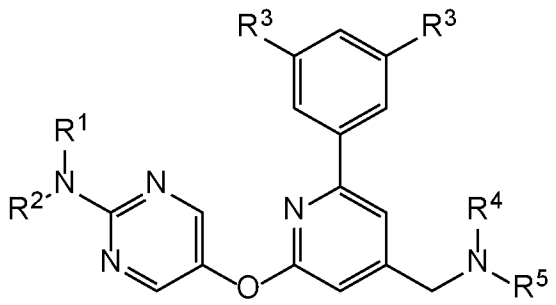
each of R^8 and R^9 is independently H, optionally substituted $(C_1\text{-}C_4)$alkyl, or optionally substituted $(C_3\text{-}C_6)$cycloalkyl;

n is 1, 2, 3, or 4.

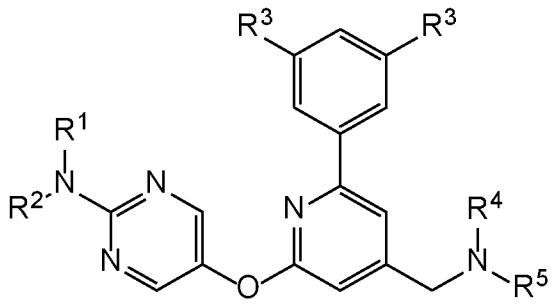
[00138] In certain embodiments, the compound of Formula (**II**) useful in the present disclosure is of the formula:



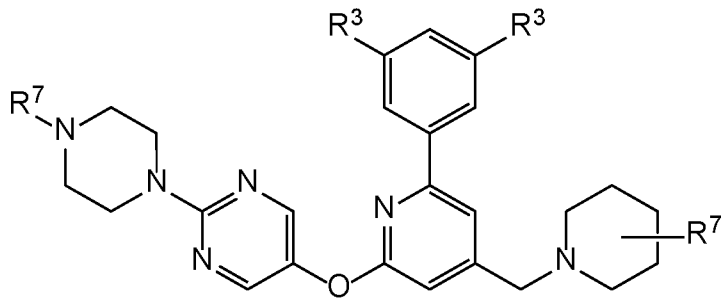
[00139] In certain embodiments, the compound of Formula (**II**) useful in the present disclosure is of the formula:



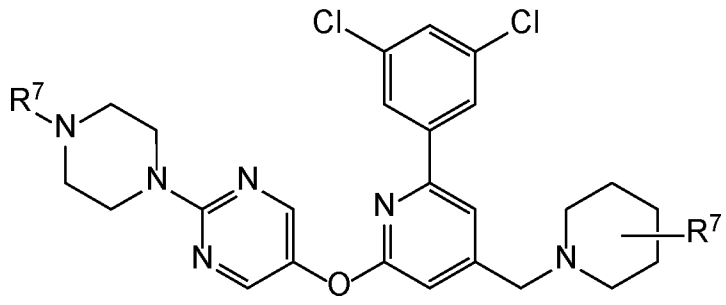
[00140] In certain embodiments, the compound of Formula (**II**) useful in the present disclosure is of the formula:



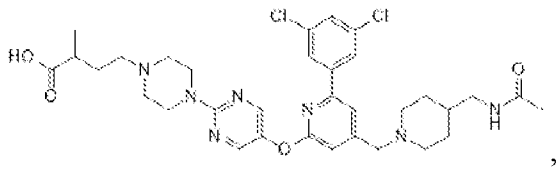
[00141] In certain embodiments, the compound of Formula (**II**) useful in the present disclosure is of the formula:



[00142] In certain embodiments, the compound of Formula (**II**) useful in the present disclosure is of the formula:



[00143] In certain embodiments, the compound of Formula (**II**) useful in the present disclosure is of the formula (Table 1, #192):

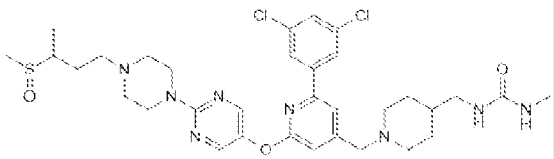
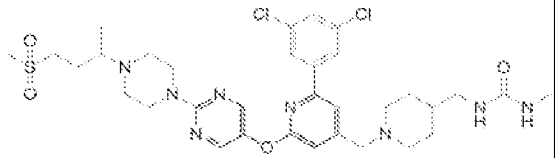
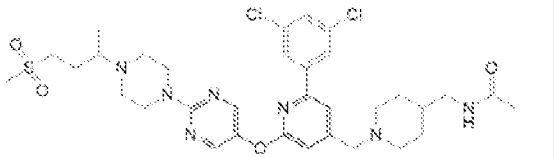
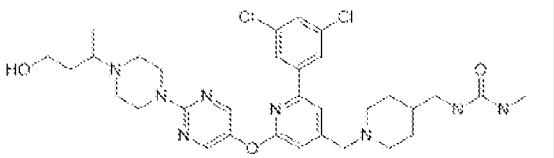
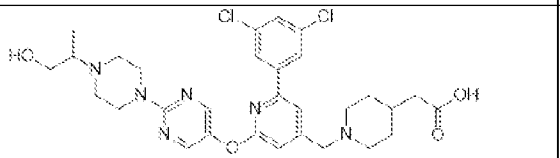
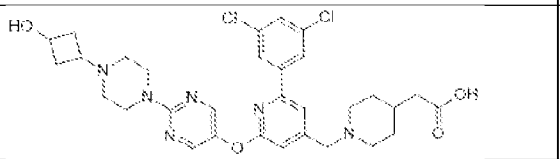
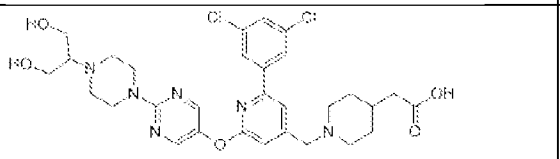
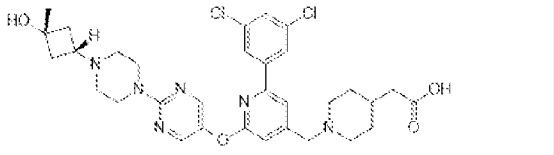
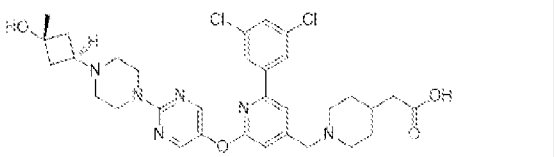


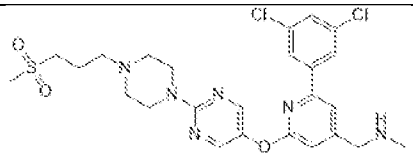
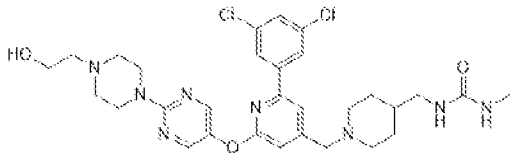
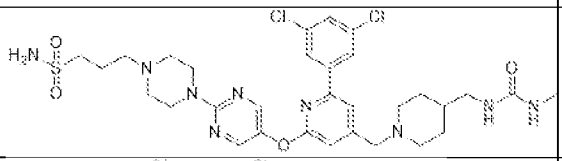
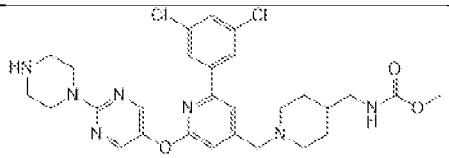
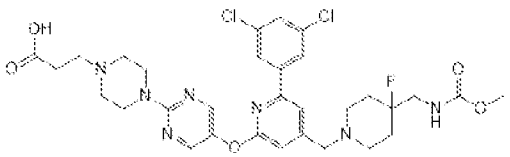
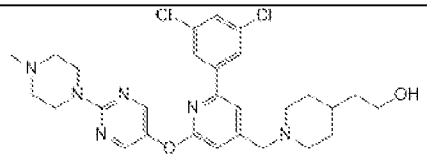
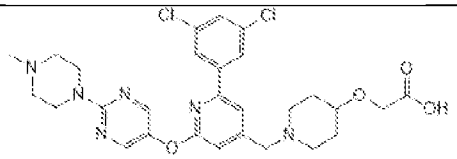
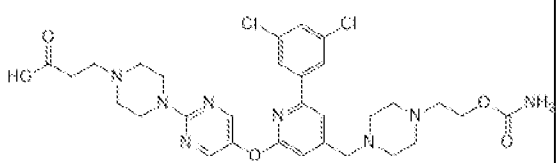
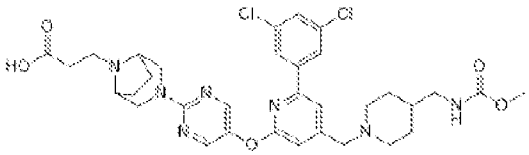
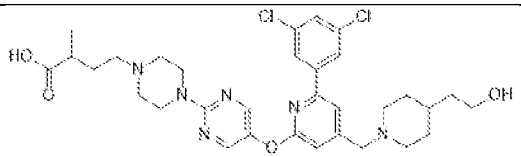
or a pharmaceutically acceptable salt thereof.

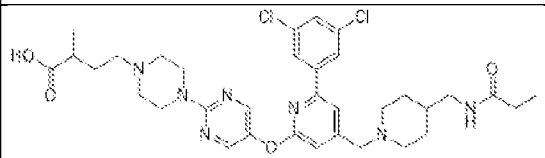
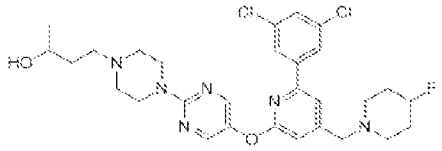
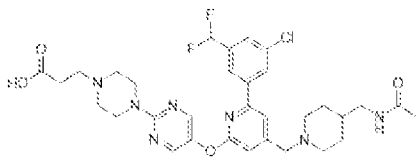
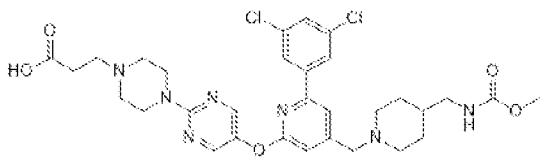
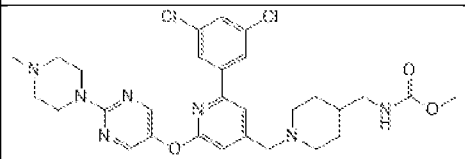
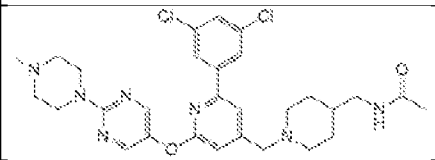
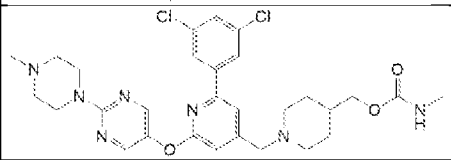
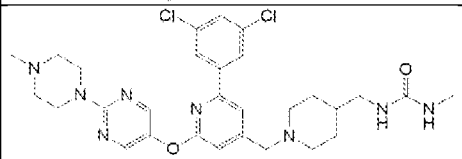
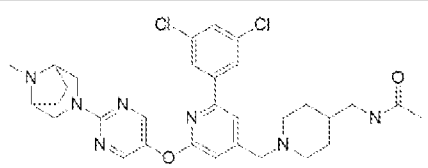
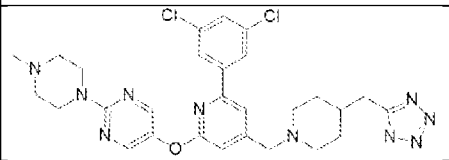
[00144] In certain embodiments, a compound of Formula (**I**) or Formula (**II**) may be any one of the compounds found in **Table 1** below. In certain embodiments, the disclosed

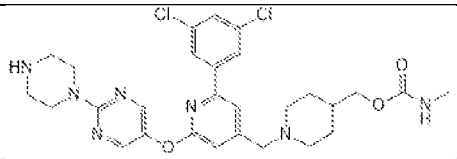
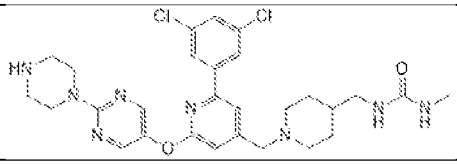
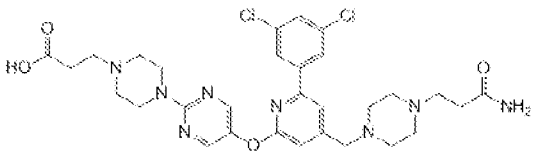
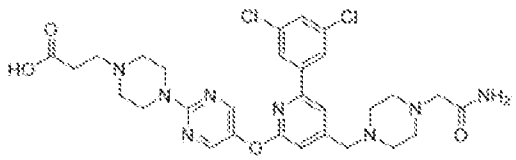
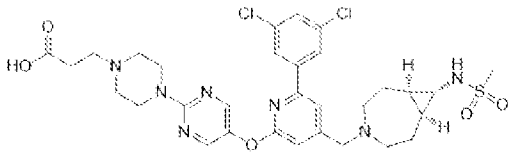
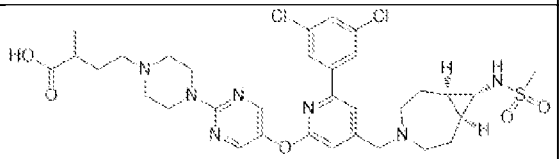
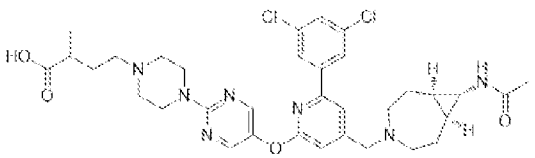
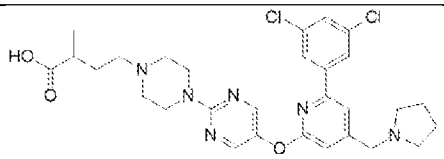
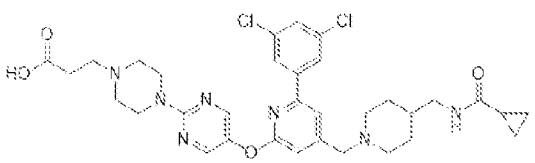
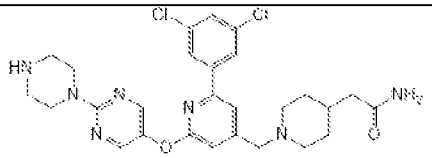
compositions, methods, and uses comprise administering to the subject in need thereof a therapeutically effective amount of any one of the compounds found in **Table 1** below.

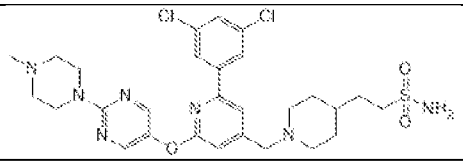
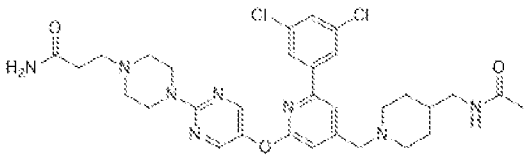
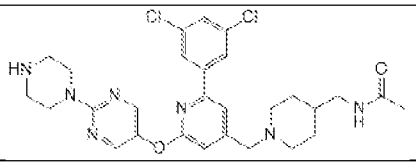
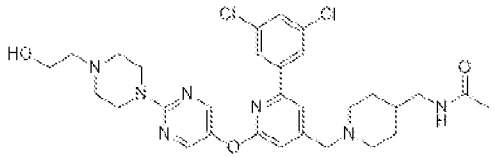
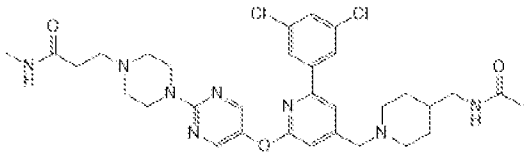
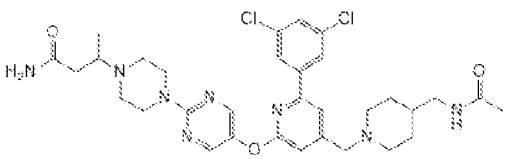
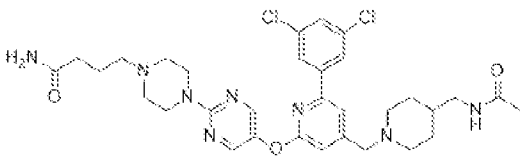
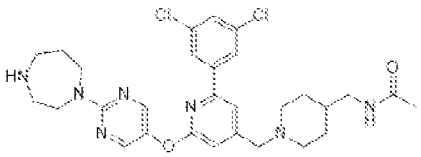
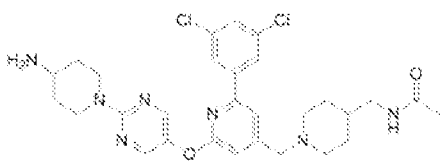
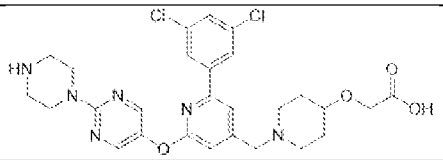
Table 1. Compounds useful in the present disclosure

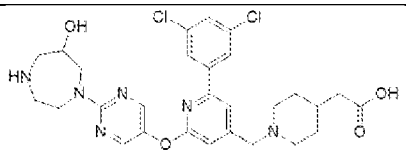
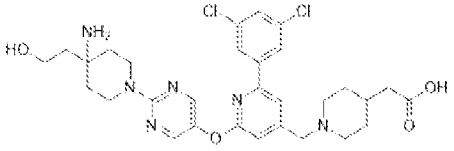
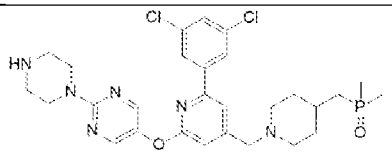
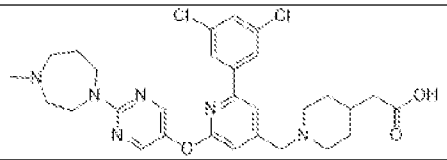
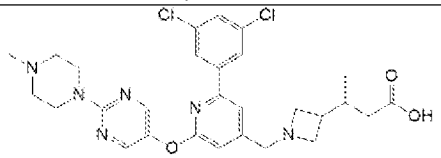
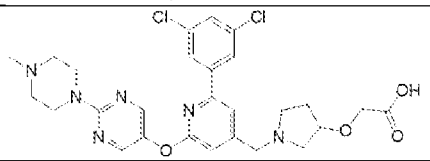
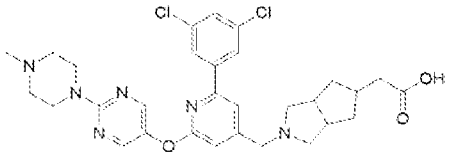
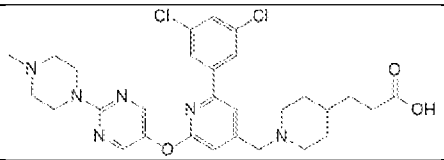
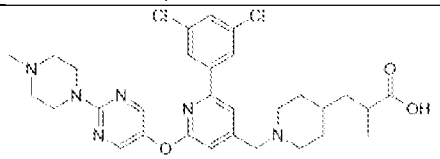
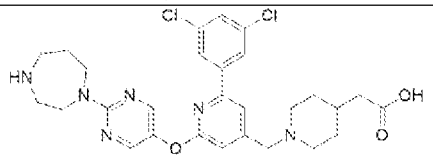
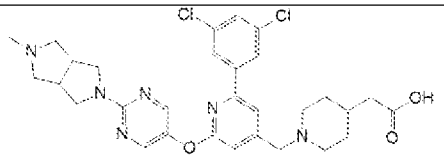
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2		1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(4-(methylsulfonyl)butan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
3		N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(4-(methylsulfonyl)butan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
4		1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(4-hydroxybutan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
5		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(1-hydroxypropan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
6		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-hydroxycyclobutyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
7		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(1,3-dihydroxypropan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
8		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-((1s,3s)-3-hydroxy-3-methylcyclobutyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
9		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-((1r,3r)-3-hydroxy-3-methylcyclobutyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid

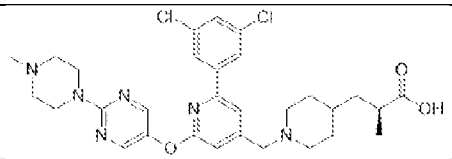
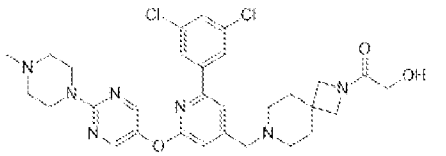
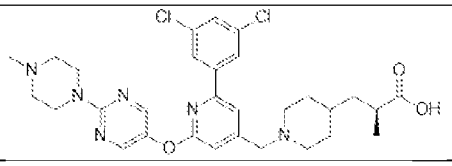
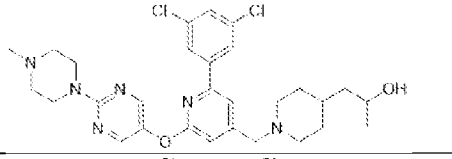
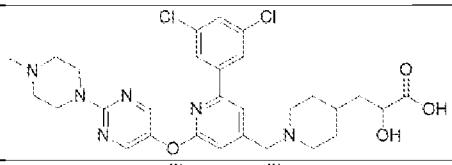
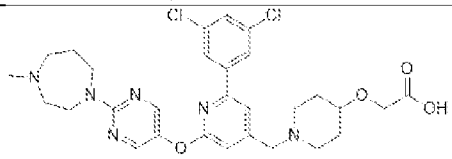
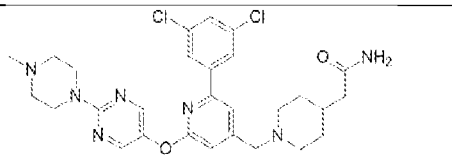
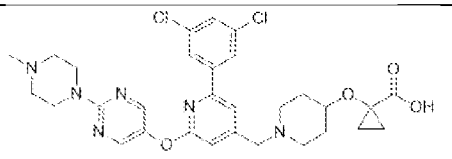
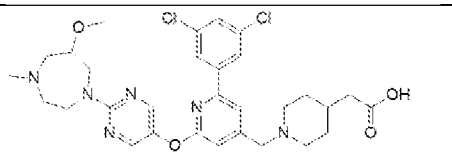
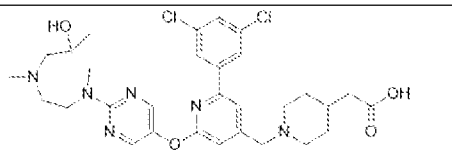
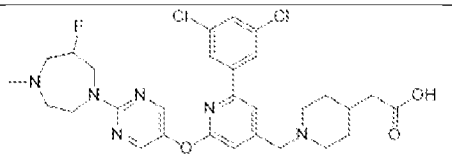
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11		1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
12		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propane-1-sulfonamide
13		methyl((1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate
14		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-fluoro-4-(((methoxycarbonyl)amino)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid
15		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)ethanol
16		2-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)oxy)acetic acid
17		3-(4-(5-((4-((4-(2-(carbamoyloxy)ethyl)piperazin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid
18		3-(3-(5-((6-(3,5-dichlorophenyl)-4-((4-(((methoxycarbonyl)amino)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)propanoic acid
19		4-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(2-hydroxyethyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylbutanoic acid

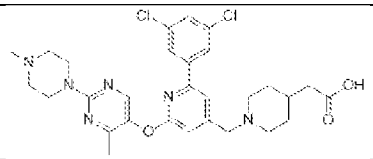
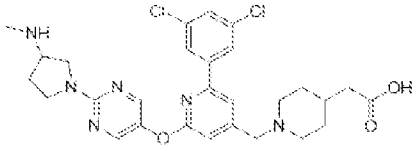
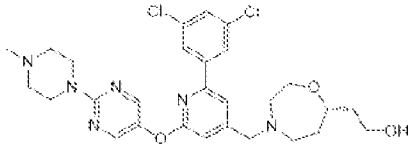
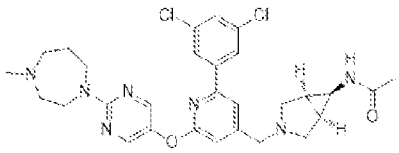
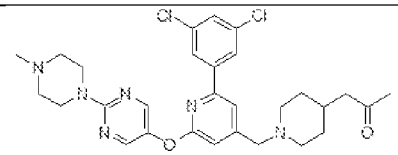
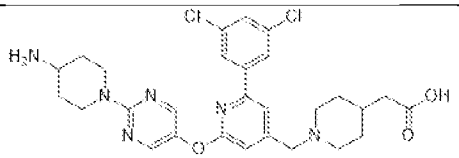
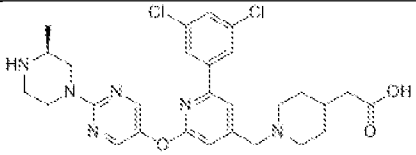
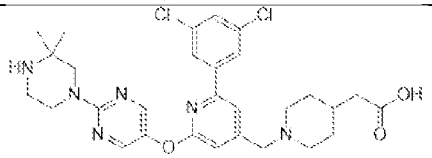
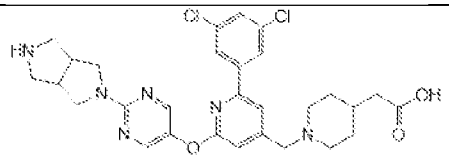
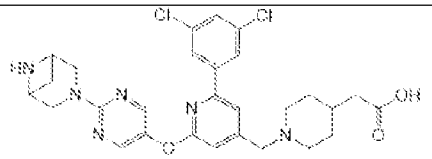
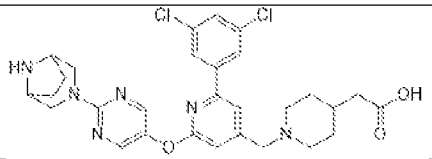
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21		4-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-fluoropiperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)butan-2-ol
22		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3-chloro-5-(difluoromethyl)phenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid
23		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(((methoxycarbonyl)amino)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid
24		methyl((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate
25		N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
26		(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate
27		1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
28		N-((1-((2-(3,5-dichlorophenyl)-6-((2-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
29		5-((4-((4-((1H-tetrazol-5-yl)methyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)-2-(4-methylpiperazin-1-yl)pyrimidine

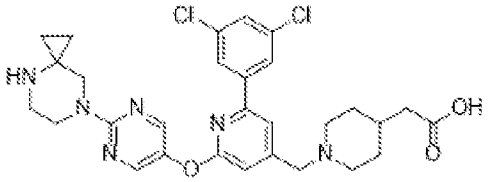
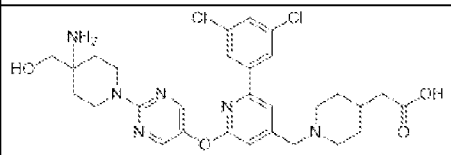
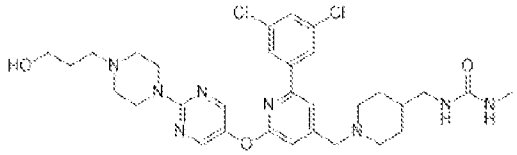
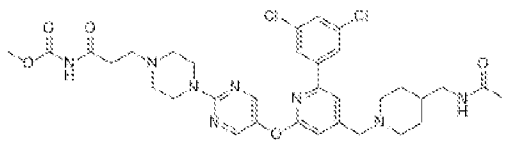
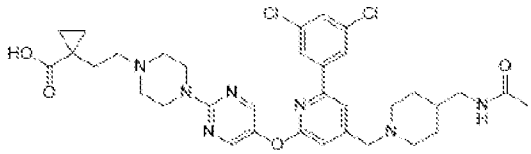
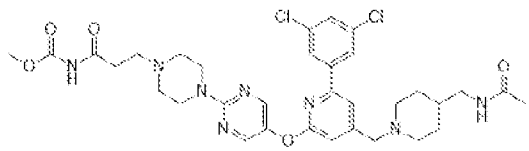
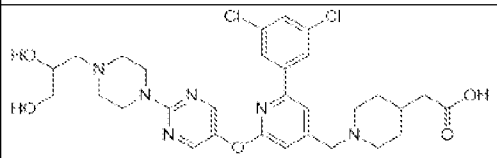
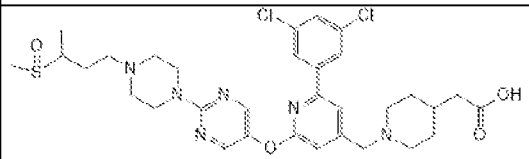
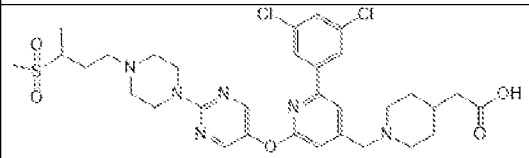
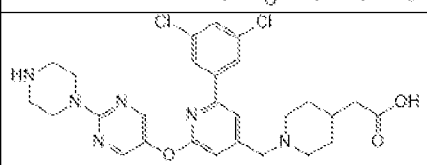
#	Structure	Name
30		(1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate
31		1-((1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
32		3-(4-(5-((4-((4-(3-amino-3-oxopropyl)piperazin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid
33		3-(4-(5-((4-((4-(2-amino-2-oxoethyl)piperazin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid
34		3-(4-(5-((6-(3,5-dichlorophenyl)-4-(((1R,7S,8r)-8-(methylsulfonamido)-4-azabicyclo[5.1.0]octan-4-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid
35		4-(4-(5-((6-(3,5-dichlorophenyl)-4-(((1R,7S,8r)-8-(methylsulfonamido)-4-azabicyclo[5.1.0]octan-4-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylbutanoic acid
36		4-(4-(5-((4-(((1R,7S,8r)-8-acetamido-4-azabicyclo[5.1.0]octan-4-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylbutanoic acid
37		4-(4-(5-((6-(3,5-dichlorophenyl)-4-(pyrrolidin-1-ylmethyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylbutanoic acid
38		3-(4-(5-((4-((4-(cyclopropanecarboxamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid
39		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetamide

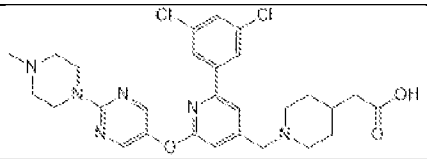
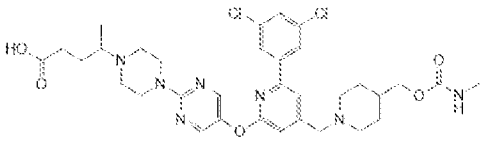
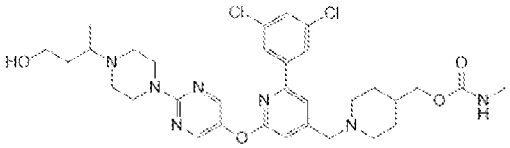
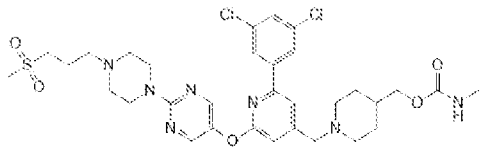
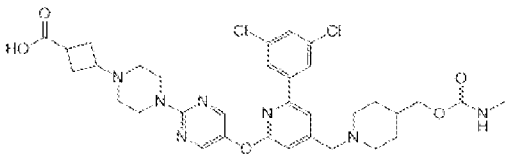
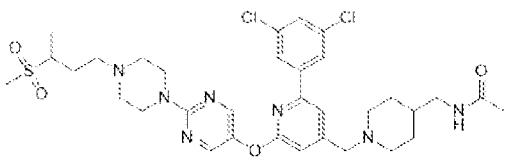
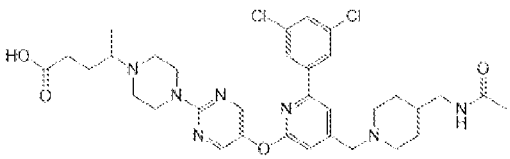
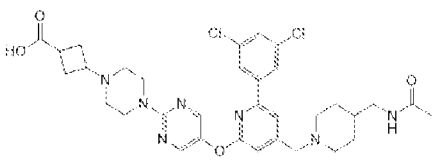
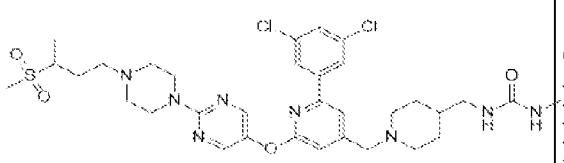
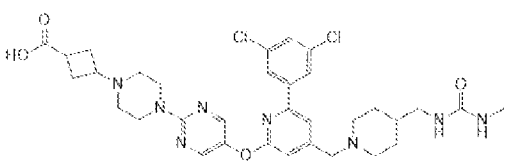
#	Structure	Name
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41		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanamide
42		N-((1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
43		N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
44		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-N-methylpropanamide
45		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)butanamide
46		4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)butanamide
47		N-((1-((2-((2-(1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
48		N-((1-((2-((2-(4-aminopiperidin-1-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
49		2-((1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)oxy)acetic acid

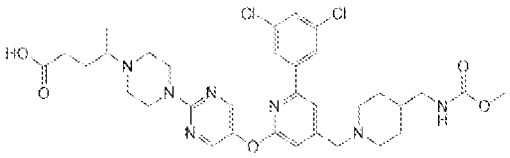
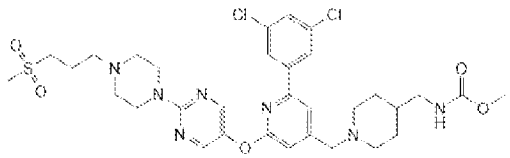
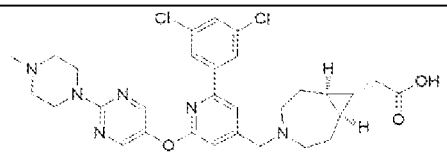
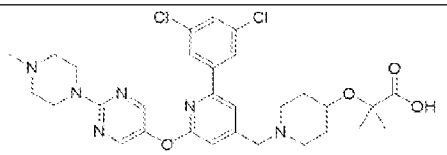
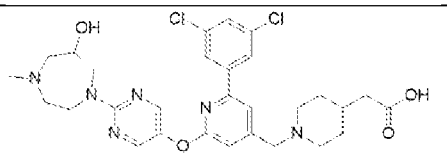
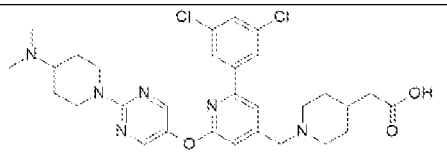
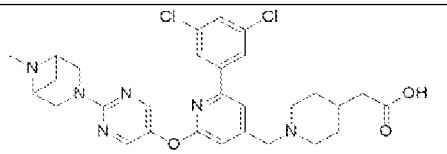
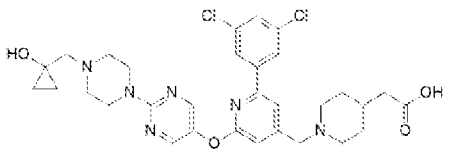
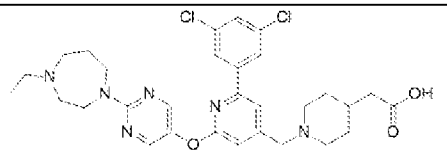
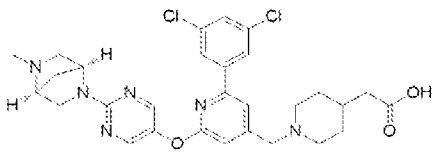
#	Structure	Name
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51		2-(1-((2-((2-(4-amino-4-(2-hydroxyethyl)piperidin-1-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
52		((1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)dimethylphosphineoxide
53		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
54		3-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)azetidin-3-yl)butanoic acid
55		2-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)pyrrolidin-3-yl)oxy)acetic acid
56		2-(2-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)octahydrocyclopenta[c]pyrrol-5-yl)acetic acid
57		3-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)propanoic acid
58		3-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)-2-methylpropanoic acid
59		2-(1-((2-((2-(1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
60		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid

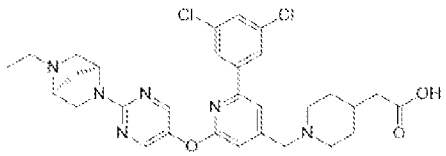
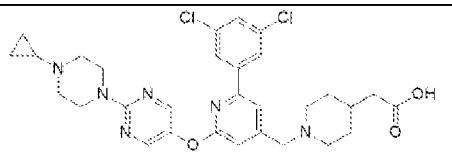
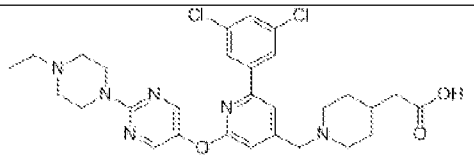
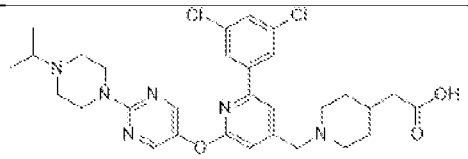
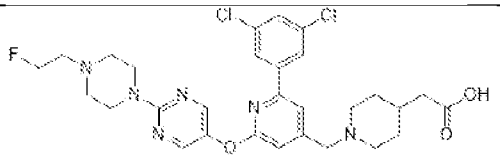
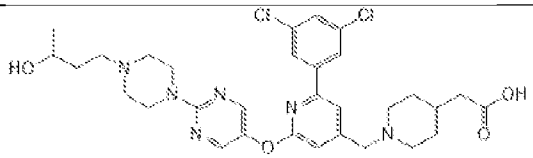
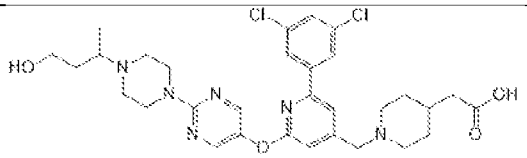
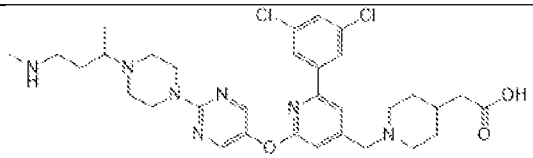
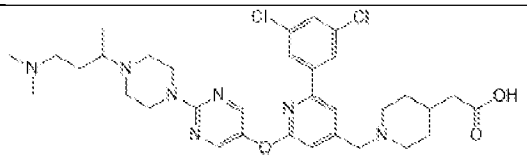
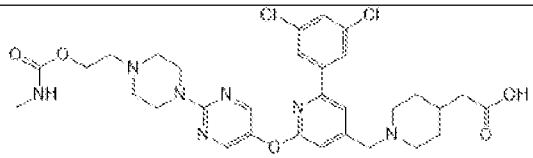
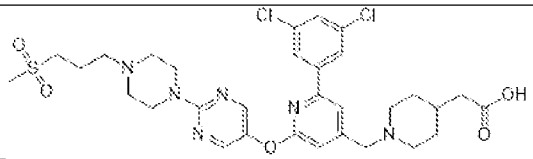
#	Structure	Name
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62		1-(7-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-hydroxyethanone
63		(R)-3-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)-2-methylpropanoic acid
64		1-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)propan-2-ol
65		3-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)-2-hydroxypropanoic acid
66		2-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)oxy)acetic acid
67		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetamide
68		1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)oxy)cyclopropanecarboxylic acid
69		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(6-methoxy-4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
70		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(6-hydroxy-4,6-dimethyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
71		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(6-fluoro-4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid

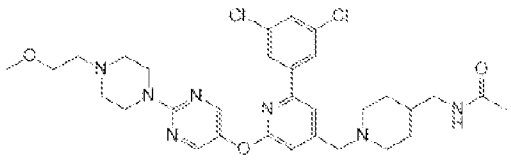
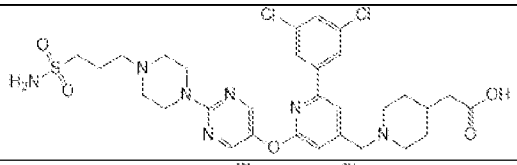
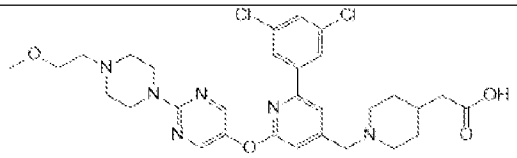
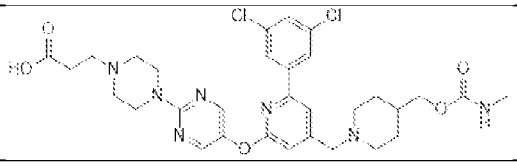
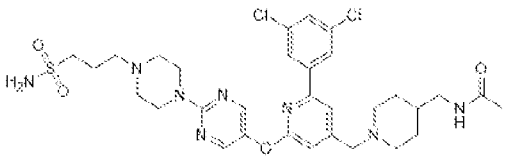
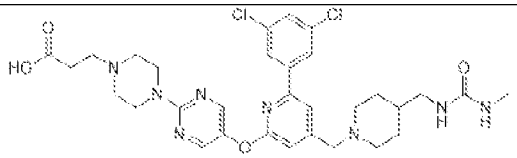
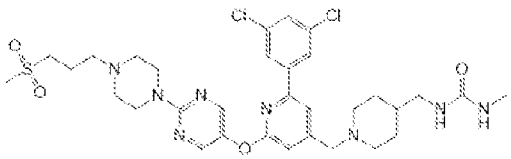
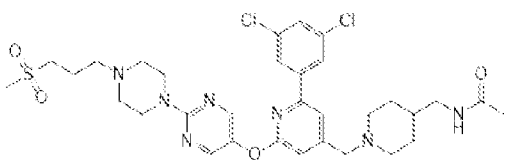
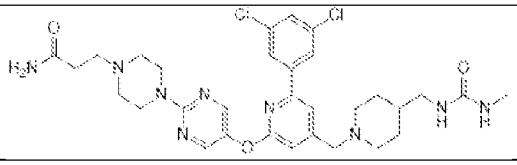
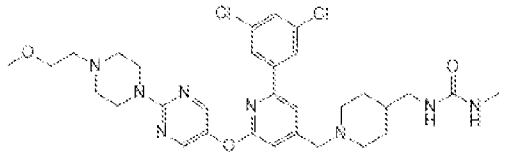
#	Structure	Name
72		2-(1-((2-(3,5-dichlorophenyl)-6-((4-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
73		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(3-(methylamino)pyrrolidin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
74		(S)-2-(4-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)-1,4-oxazepan-7-yl)ethanol
75		N-((1R,5S,6r)-3-((2-(3,5-dichlorophenyl)-6-((2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)-3-azabicyclo[3.1.0]hexan-6-yl)acetamide
76		1-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)propan-2-one
77		2-(1-((2-((2-(4-aminopiperidin-1-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
78		(S)-2-(1-((2-(3,5-dichlorophenyl)-6-((2-(3-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
79		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(3,3-dimethylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
80		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
81		2-(1-((2-((2-(3,6-diazabicyclo[3.1.1]heptan-3-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
82		2-(1-((2-((2-(3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid

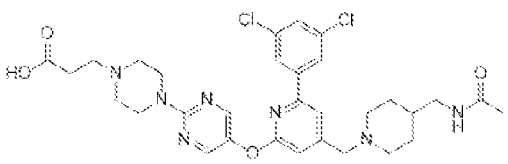
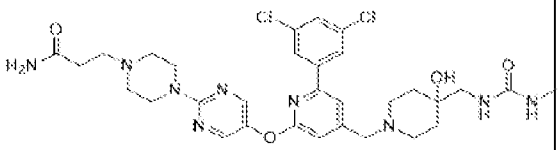
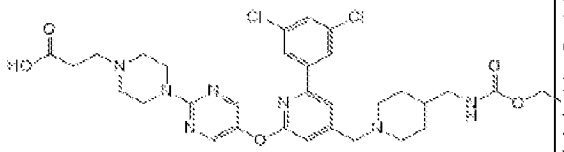
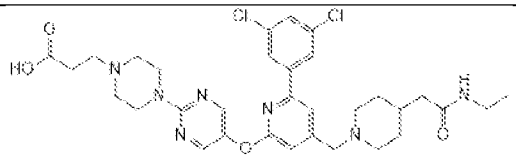
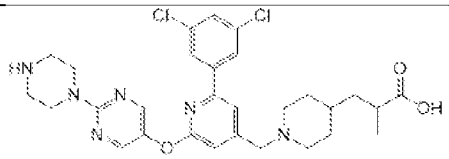
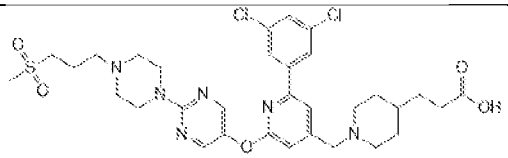
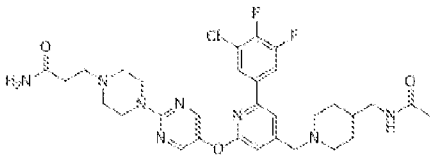
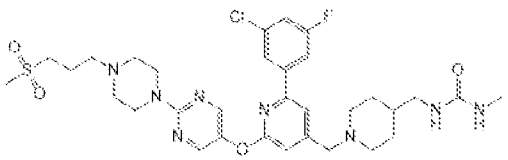
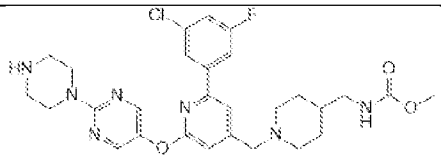
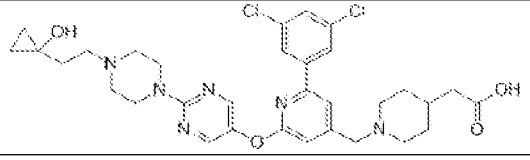
#	Structure	Name
83		2-(1-((2-((2-(4,7-diazaspiro[2.5]octan-7-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
84		2-(1-((2-((2-(4-amino-4-(hydroxymethyl)piperidin-1-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
85		1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
86		methyl (3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoyl)carbamate
87		1-(2-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)ethyl)cyclopropanecarboxylic acid
88		methyl (3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoyl)carbamate
89		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2,3-dihydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
90		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfinyl)butyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
91		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)butyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
92		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid

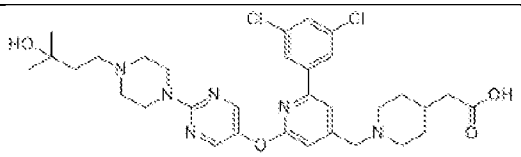
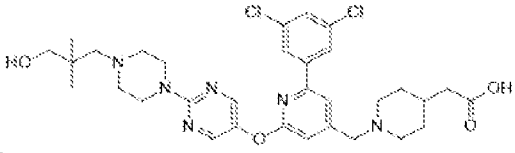
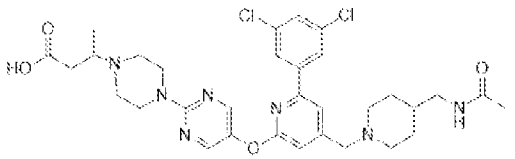
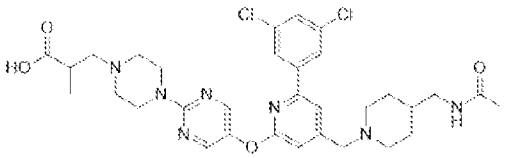
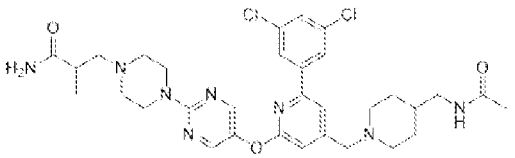
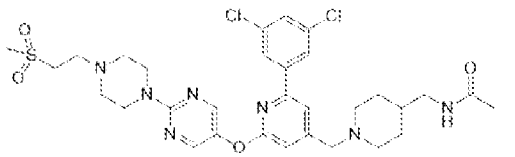
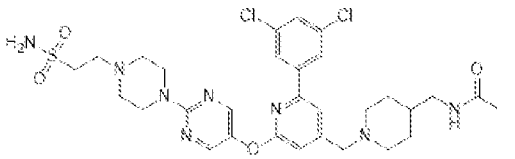
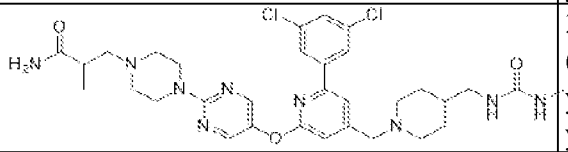
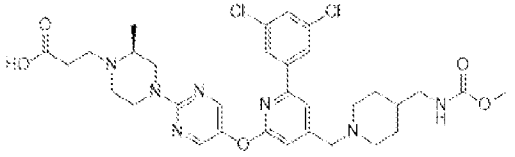
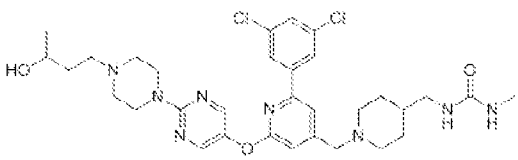
#	Structure	Name
93		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
94		4-(4-(5-((6-(3,5-dichlorophenyl)-4-(((((methylcarbamoyl)oxy)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)pentanoic acid
95		(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(4-hydroxybutan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate
96		(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate
97		3-(4-(5-((6-(3,5-dichlorophenyl)-4-(((((methylcarbamoyl)oxy)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)cyclobutanecarboxylic acid
98		N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)butyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
99		4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)pentanoic acid
100		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)cyclobutanecarboxylic acid
101		1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)butyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
102		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)cyclobutanecarboxylic acid

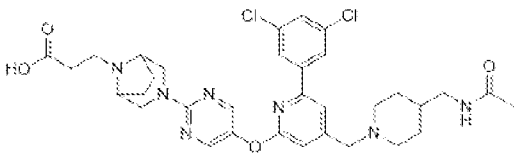
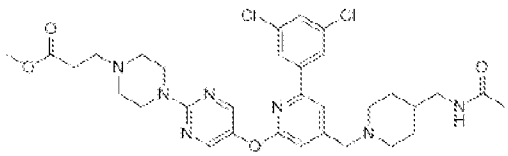
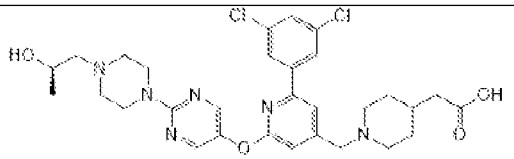
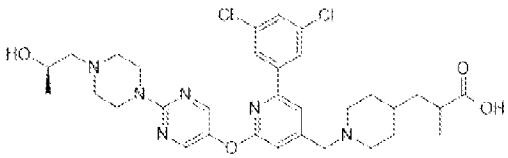
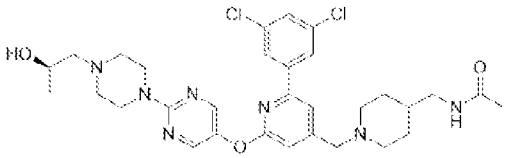
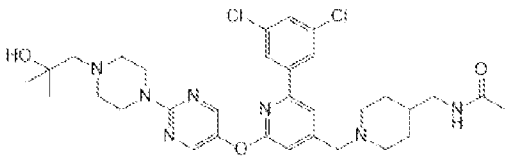
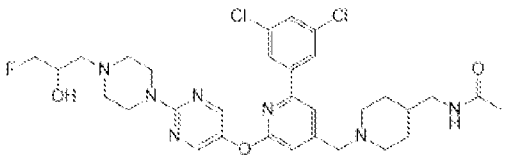
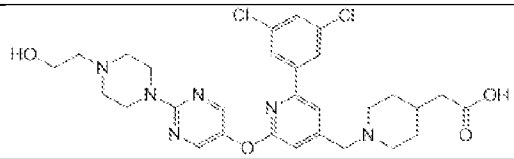
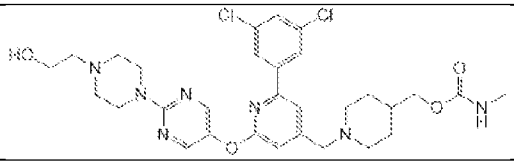
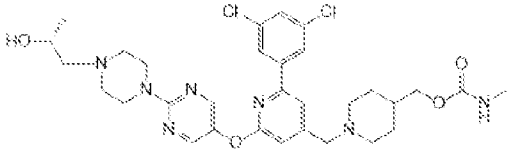
#	Structure	Name
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104		methyl ((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate
105		2-((1R,7S,8r)-4-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)-4-azabicyclo[5.1.0]octan-8-yl)acetic acid
106		2-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)oxy)-2-methylpropanoic acid
107		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(6-hydroxy-4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
108		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(dimethylamino)piperidin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
109		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(6-methyl-3,6-diazabicyclo[3.1.1heptan-3-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
110		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-((1-hydroxycyclopropyl)methyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
111		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-ethyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
112		2-(1-((2-(3,5-dichlorophenyl)-6-((2-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid

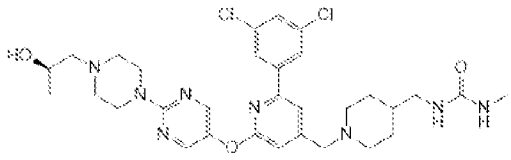
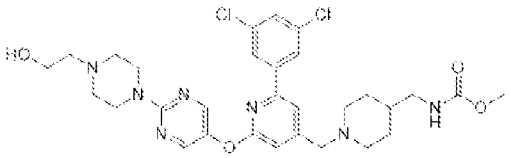
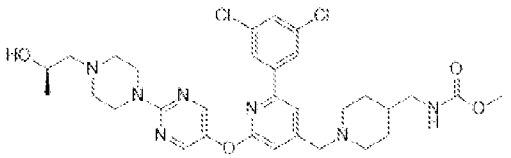
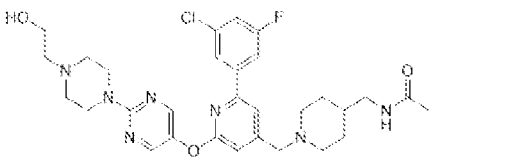
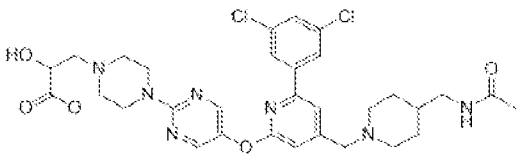
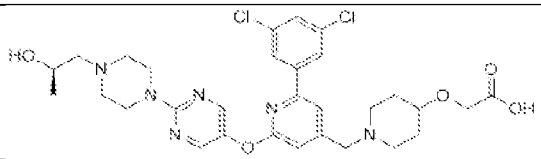
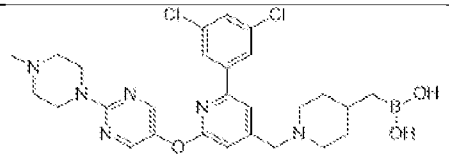
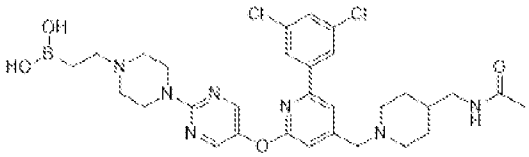
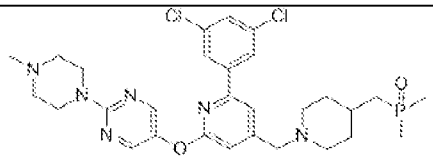
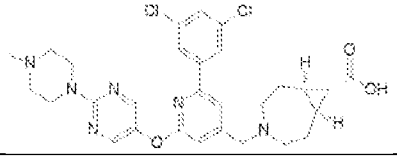
#	Structure	Name
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114		2-(1-((2-((2-(4-cyclopropylpiperazin-1-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
115		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-ethylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
116		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-isopropylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
117		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-fluoroethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
118		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-hydroxybutyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
119		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(4-hydroxybutan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
120		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(4-(methylamino)butan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
121		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(4-(dimethylamino)butan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
122		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-((methylcarbamoyl)oxy)ethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
123		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid

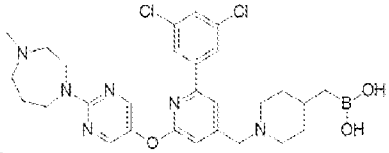
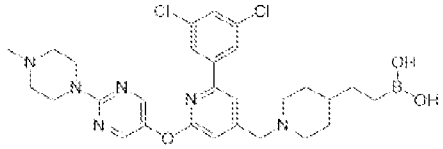
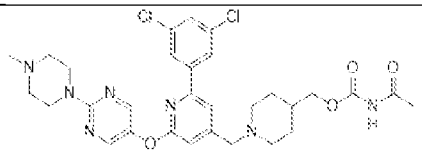
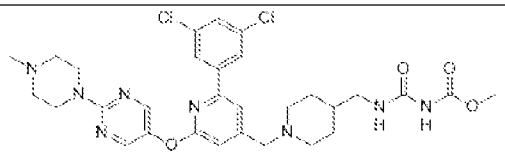
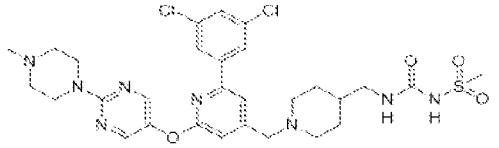
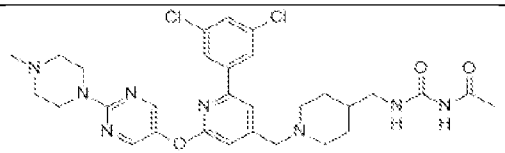
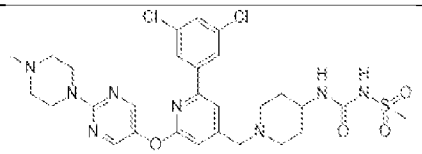
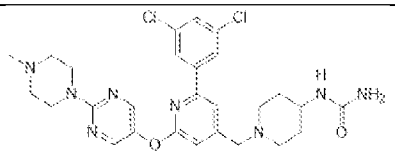
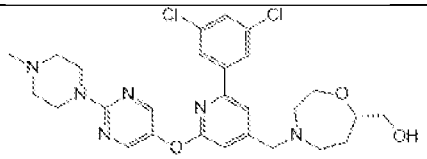
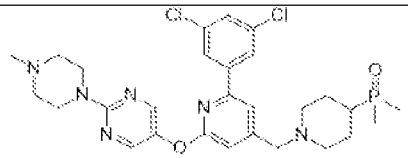
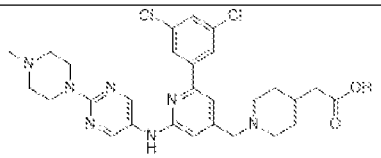
#	Structure	Name
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125		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-sulfamoylpropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
126		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-methoxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
127		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(((methylcarbamoyl)oxy)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid
128		N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-sulfamoylpropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
129		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid
130		1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
131		N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
132		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanamide
133		1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-methoxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea

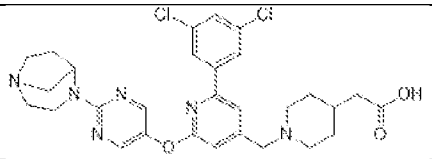
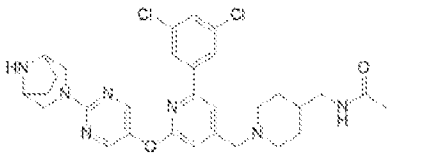
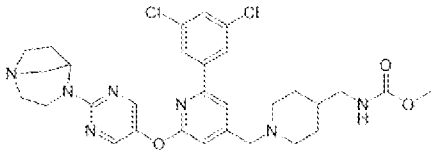
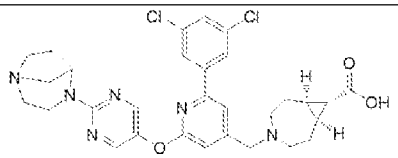
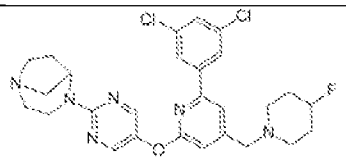
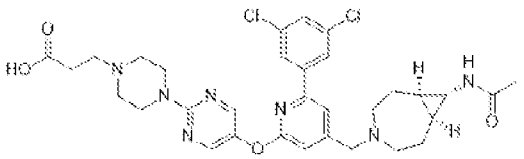
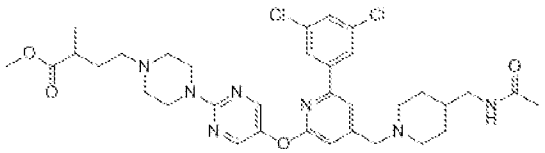
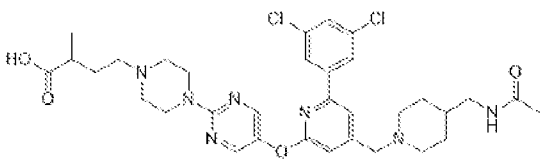
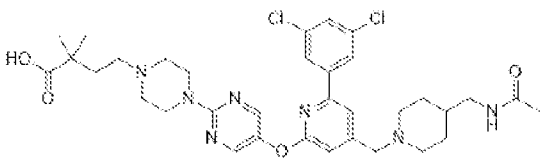
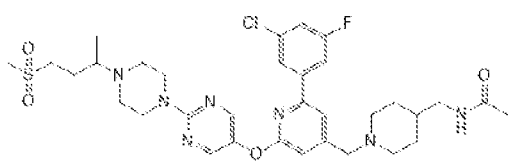
#	Structure	Name
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135		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-hydroxy-4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanamide
136		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(((ethoxycarbonyl)amino)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid
137		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(2-(ethylamino)-2-oxoethyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid
138		3-(1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)-2-methylpropanoic acid
139		3-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)propanoic acid
140		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3-chloro-4,5-difluorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanamide
141		1-((1-((2-(3-chloro-5-fluorophenyl)-6-((2-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
142		methyl ((1-((2-(3-chloro-5-fluorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate
143		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-(1-hydroxycyclopropyl)ethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid

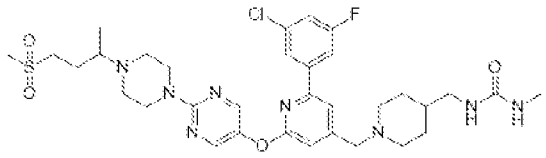
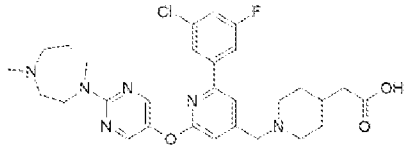
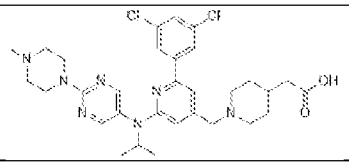
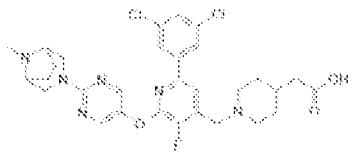
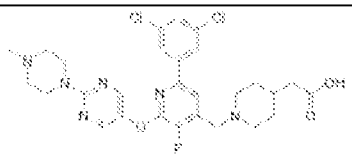
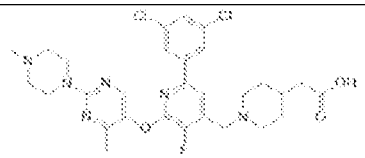
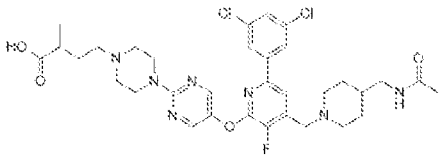
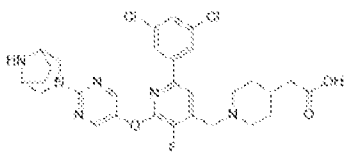
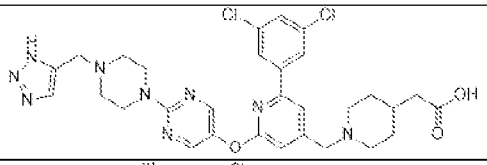
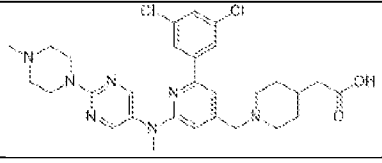
#	Structure	Name
144		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-hydroxy-3-methylbutyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
145		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-hydroxy-2,2-dimethylpropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
146		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)butanoic acid
147		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylpropanoic acid
148		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylpropanamide
149		N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
150		N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-sulfamoylethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
151		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylpropanamide
152		(S)-3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(((methoxycarbonyl)amino)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)-2-methylpiperazin-1-yl)propanoic acid
153		1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-hydroxybutyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea

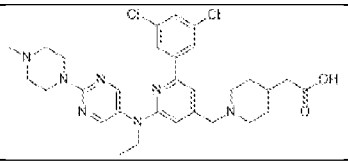
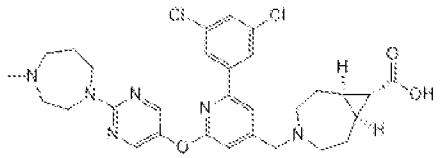
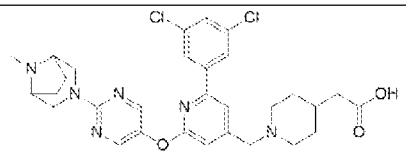
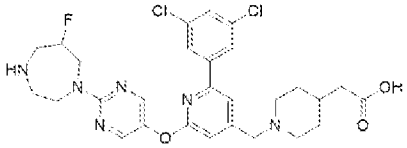
#	Structure	Name
154		3-(3-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)propanoic acid
155		methyl3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoate
156		(R)-2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
157		3-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-((R)-2-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)-2-methylpropanoic acid
158		(R)-N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
159		N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxy-2-methylpropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
160		N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-fluoro-2-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
161		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
162		(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate
163		(R)-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate

#	Structure	Name
164		(R)-1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
165		methyl((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate
166		(R)-methyl((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate
167		N-((1-((2-(3-chloro-5-fluorophenyl)-6-((2-(4-(2-hydroxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
168		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-hydroxypropanoic acid
169		(R)-2-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)oxy)acetic acid
170		((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)boronic acid
171		(2-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)ethyl)boronic acid
172		((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)dimethylphosphineoxide
173		(1R,7S,8r)-4-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)-4-azabicyclo[5.1.0]octane-8-carboxylic acid

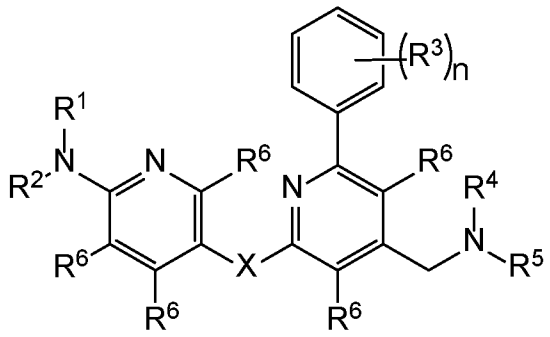
#	Structure	Name
174		((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)boronic acid
175		(2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)ethyl)boronic acid
176		(1-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylacetylcarbamate
177		N-1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-N'-methoxylcarbonylurea
178		N-(((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamoyl)methanesulfonamide
179		N-(((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamoyl)acetamide
180		N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)carbamoyl)methanesulfonamide
181		1-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)urea
182		(S)-(4-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)-1,4-oxazepan-7-yl)methanol
183		(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)dimethylphosphineoxide
184		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)amino)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid

#	Structure	Name
185		2-(1-((2-((2-(1,4-diazabicyclo[3.2.1]octan-4-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
186		N-((1-((2-((2-(3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
187		methyl((1-((2-((2-(1,4-diazabicyclo[3.2.1]octan-4-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate
188		4-((2-((2-(1,4-diazabicyclo[3.2.1]octan-4-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)-4-azabicyclo[5.1.0]octane-8-carboxylic acid
189		4-(5-((6-(3,5-dichlorophenyl)-4-((4-fluoropiperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)-1,4-diazabicyclo[3.2.1]octane
190		3-(4-(5-((4-(((1R,7S,8r)-8-acetamido-4-azabicyclo[5.1.0]octan-4-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid
191		methyl4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylbutanoate
192		4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylbutanoic acid
193		4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2,2-dimethylbutanoic acid
194		N-((1-((2-(3-chloro-5-fluorophenyl)-6-((2-(4-(4-(methylsulfonyl)butan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide

#	Structure	Name
195		1-((1-((2-(3-chloro-5-fluorophenyl)-6-((2-(4-(4-(methylsulfonyl)butan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
196		2-(1-((2-(3-chloro-5-fluorophenyl)-6-((2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
197		2-(1-((2-(3,5-dichlorophenyl)-6-(isopropyl(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)amino)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
198		2-(1-((6-(3,5-dichlorophenyl)-3-fluoro-2-((2-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
199		2-(1-((6-(3,5-dichlorophenyl)-3-fluoro-2-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
200		2-(1-((6-(3,5-dichlorophenyl)-3-fluoro-2-((4-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
201		4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)-3-fluoropyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylbutanoic acid
202		2-(1-((2-((2-(3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)-3-fluoropyridin-4-yl)methyl)piperidin-4-yl)acetic acid
203		2-(1-((2-((2-(4-((1H-1,2,3-triazol-5-yl)methyl)piperazin-1-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
204		2-(1-((2-(3,5-dichlorophenyl)-6-(methyl(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)amino)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid

#	Structure	Name
205		2-(1-((2-(3,5-dichlorophenyl)-6-(ethyl(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)amino)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
206		(1R,7S,8r)-4-((2-(3,5-dichlorophenyl)-6-((2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)-4-azabicyclo[5.1.0]octane-8-carboxylic acid
207		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid
208		2-(1-((2-(3,5-dichlorophenyl)-6-((2-(6-fluoro-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid

[00145] In certain embodiments, the compound of Formula (**I**) useful in the present disclosure is of the Formula (**III**):



(**III**),

or a pharmaceutically acceptable salt thereof, wherein:

X is –O– or –N(R^8)–;

R^1 and R^2 are each independently H or optionally substituted (C_1-C_4)alkyl; optionally, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, –OCONR^{8}R^9, –CO_2R^8, –C(O)CO_2R^8, –R^7, –OR^7, –NHR^8, –NR^7R^8, –C(O)R^7, –$CONHR^8$, –$CONR^7R^8$, or –SO_2R^7;

each R^3 is independently halogen, –CN, –O(C_1-C_4)alkyl, or optionally substituted (C_1-C_4)alkyl;

R^4 and R^5 are each independently H or optionally substituted (C_1-C_4)alkyl; optionally, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, $-OCONR^8R^9$, $-CO_2R^8$, $-C(O)CO_2R^8$, $-SO_2(C_1\ C_4)$alkyl, $-R^7$, $-OR^7$, $-NHR^8$, $-NR^7R^8$, $-N(R^8)C(O)R^9$, $-N(R^8)SO_2R^9$, $-N(R^8)CONR^8R^9$, $-N(R^8)CON(R^8)SO_2R^9$, $-C(O)R^7$, $-CONHR^8$, $-CONR^7R^8$, or $-P(O)R^8R^9$;

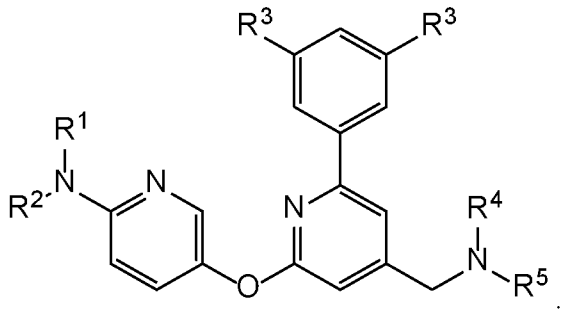
each R^6 is independently H, halogen, optionally substituted (C_1-C_4)alkyl, –OH, or optionally substituted (C_1-C_4)alkoxy;

each R^7 is independently (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, or (C_1-C_4)alkyl(C_3-C_6)cycloalkyl, each of which is optionally substituted with one or two of triazolyl, tetrazolyl, $-CO_2R^8$, $-CONR^8R^9$, $-CON(R^8)CO_2(C_1$-$C_4)$alkyl, hydroxyl, oxo, $-(C_1$-$C_4)$alkoxy, $-OCONR^8R^9$, $-OCON(R^8)C(O)R^9$, (C_1-C_4)alkyl, (C_1-C_4)alkylOH, $-NR^8R^9$, $-N(O)R^8R^9$, $-N(R^8)C(O)R^9$, $-N(R^8)CO_2(C_1$-$C_4)$alkyl, $-N(R^8)CH_2CO_2R^9$, $-N(R^8)CONR^8R^9$, $-N(R^8)CON(R^8)C(O)R^9$, $-N(R^8)CON(R^8)CO_2(C_1$-$C_4)$alkyl, $-N(R^8)SO_2R^9$, $-N(R^8)CON(R^8)SO_2R^9$, $-SO(C_1$-$C_4)$alkyl, $-SO_2(C_1$-$C_4)$alkyl, $-SO_3R^8$, $-SO_2NR^8R^9$, $-B(OH)_2$, $-P(O)R^8R^9$, or $-P(O)(OR^8)(OR^9)$;

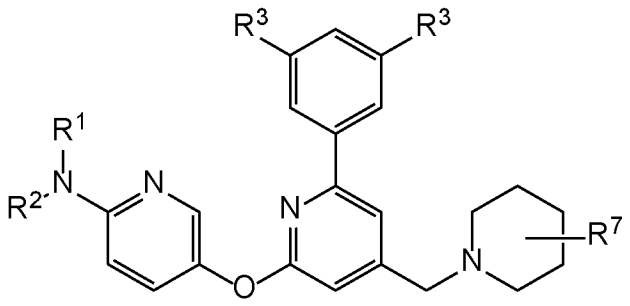
each of R^8 and R^9 is independently H, optionally substituted (C_1-C_4)alkyl, or optionally substituted (C_3-C_6)cycloalkyl; and

n is 1, 2, 3, or 4.

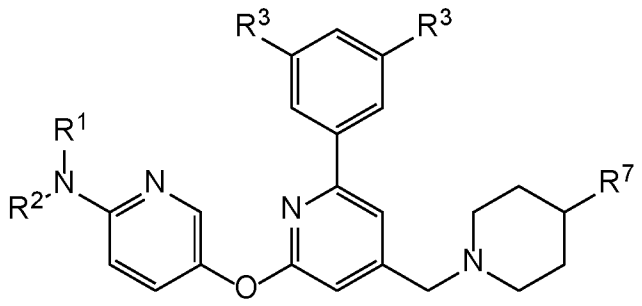
[00146] In certain embodiments, the compound of Formula (**III**), or a pharmaceutically acceptable salt thereof, useful in the present disclosure is of the formula:



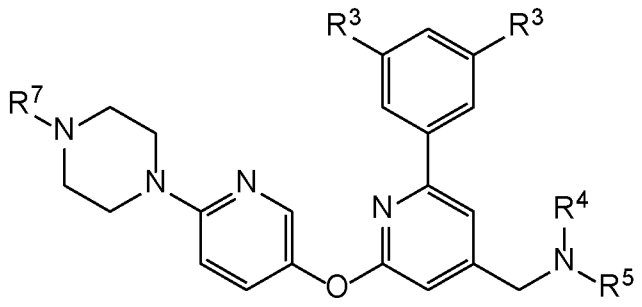
[00147] In certain embodiments, the compound of Formula (**III**), or a pharmaceutically acceptable salt thereof, useful in the present disclosure is of the formula:



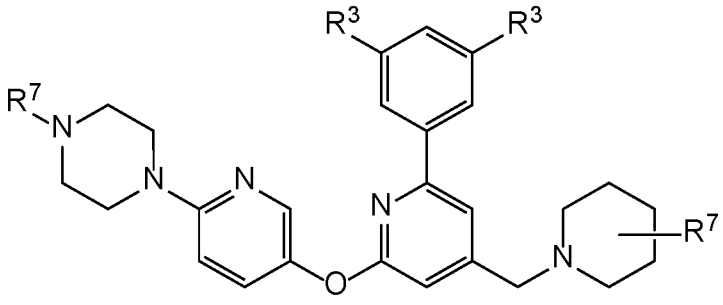
[00148] In certain embodiments, the compound of Formula (**III**), or a pharmaceutically acceptable salt thereof, useful in the present disclosure is of the formula:



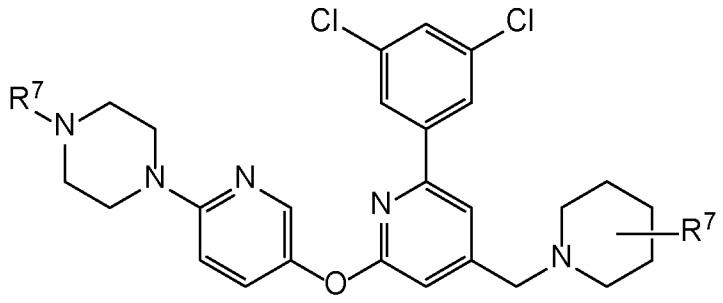
[00149] In certain embodiments, the compound of Formula (**III**), or a pharmaceutically acceptable salt thereof, useful in the present disclosure is of the formula:



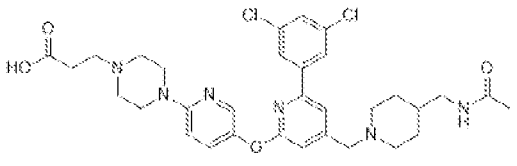
[00150] In certain embodiments, the compound of Formula (**III**), or a pharmaceutically acceptable salt thereof, useful in the present disclosure is of the formula:



[00151] In certain embodiments, the compound of Formula (**III**) useful in the present disclosure is of the formula thereof, useful in the present disclosure is of the formula:



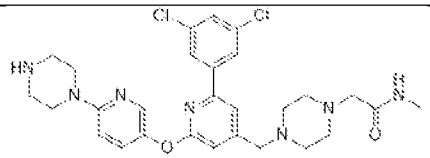
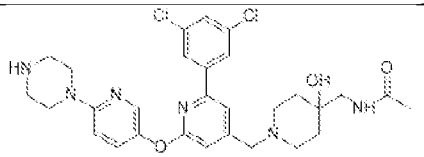
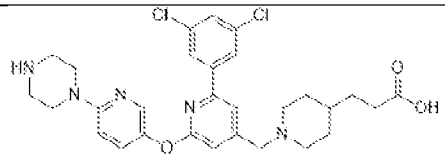
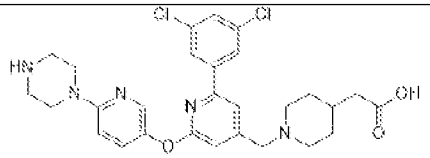
[00152] In certain embodiments, the compound of Formula (**III**) useful in the present disclosure is of the formula (Table 2, #219):

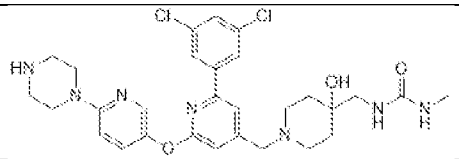
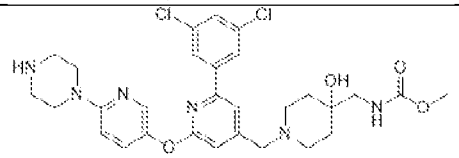
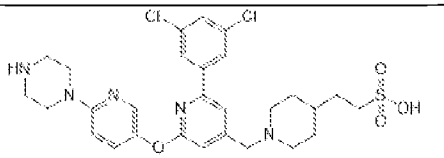
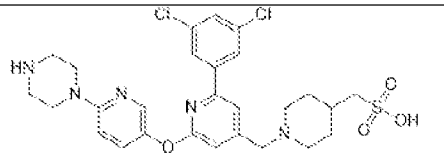
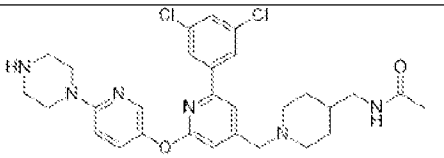
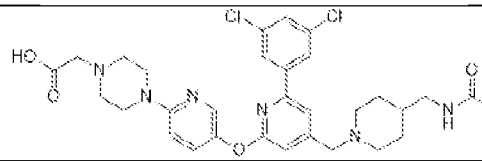
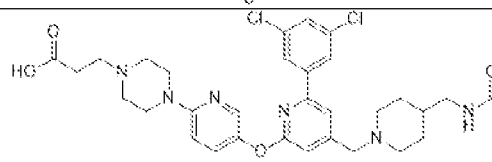
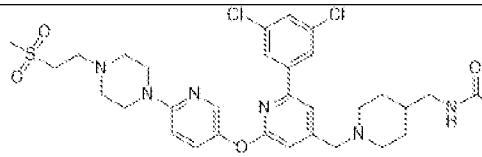
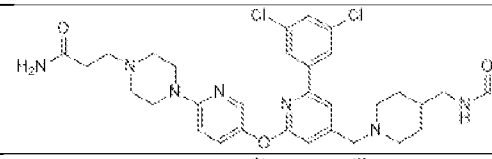
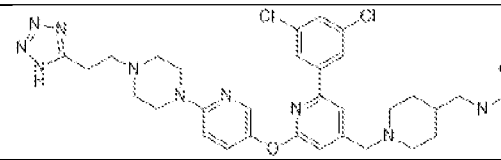
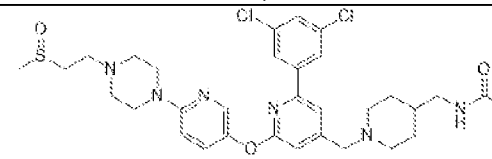


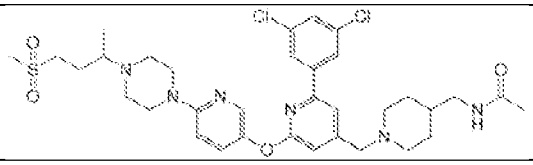
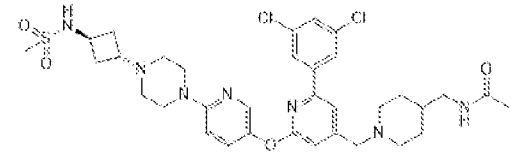
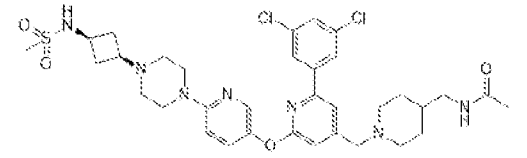
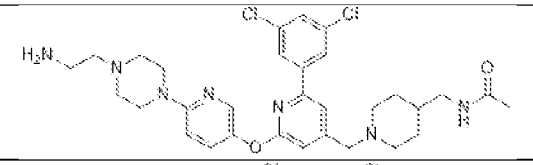
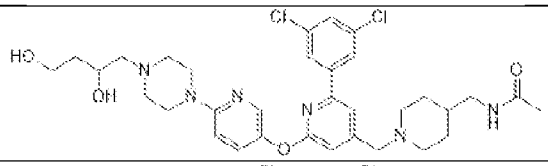
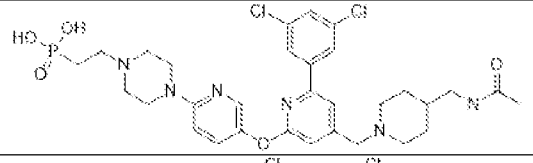
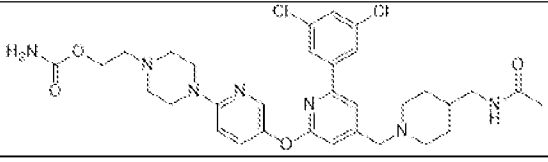
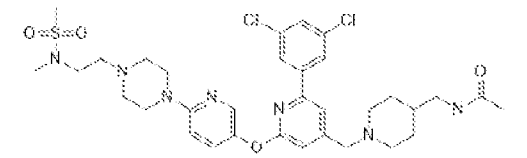
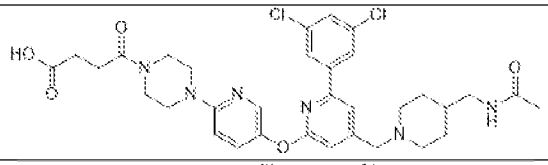
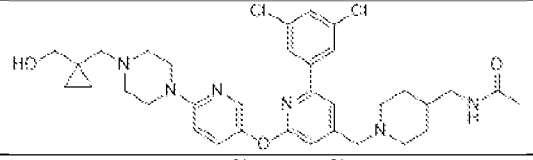
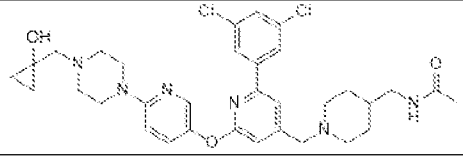
or a pharmaceutically acceptable salt thereof.

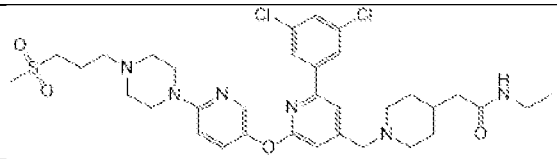
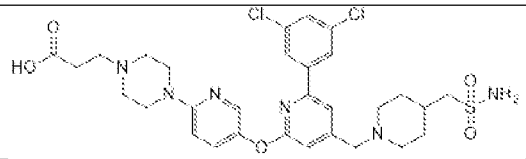
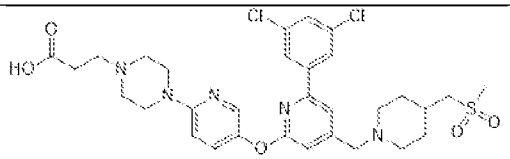
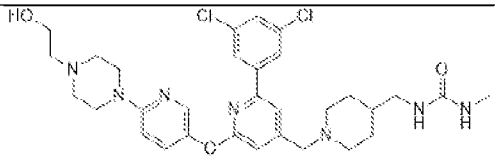
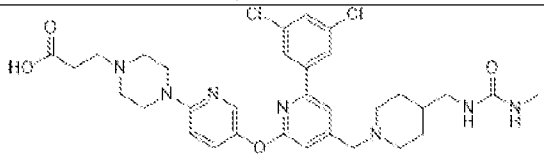
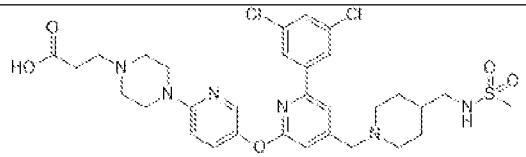
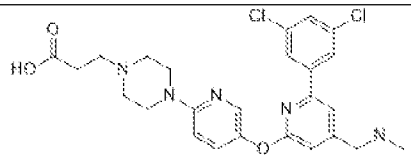
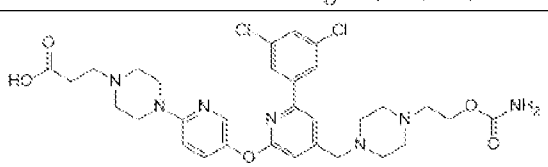
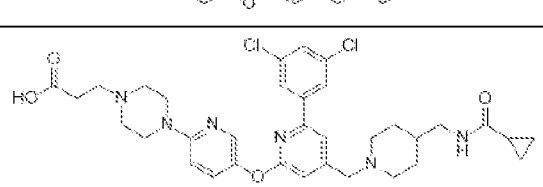
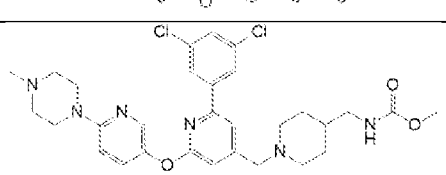
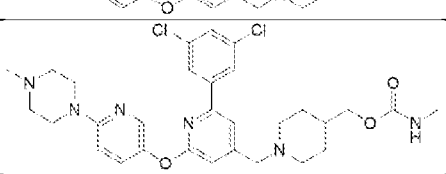
[00153] In certain embodiments, a compound of Formula (**I**) or Formula (**III**) may be any one of the compounds found in **Table 2** below. In certain embodiments, the disclosed compositions, methods, and uses comprise administering to the subject in need thereof a therapeutically effective amount of any one of the compounds found in **Table 2** below.

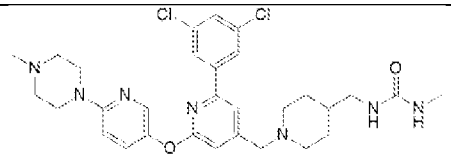
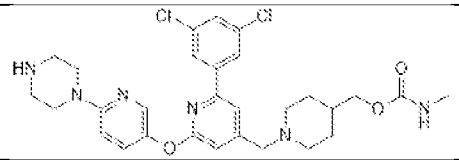
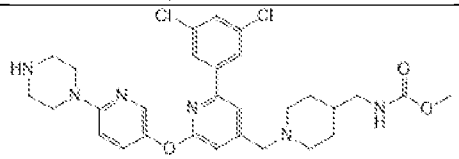
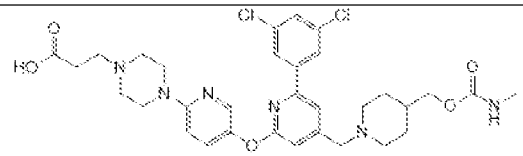
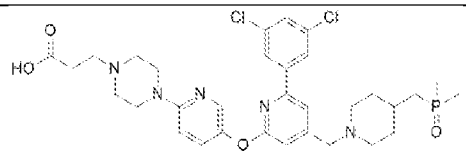
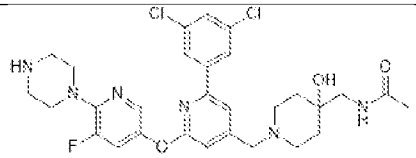
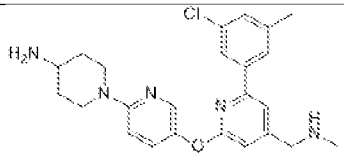
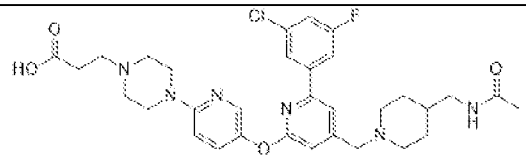
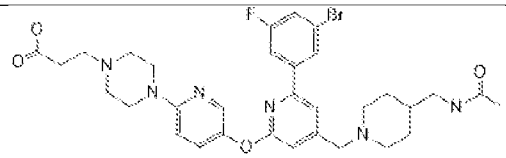
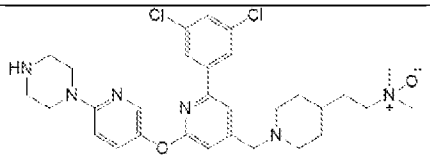
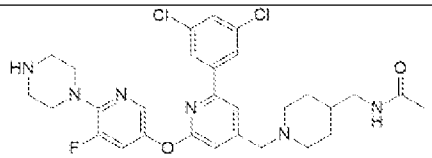
Table 2. Compounds useful in the present disclosure

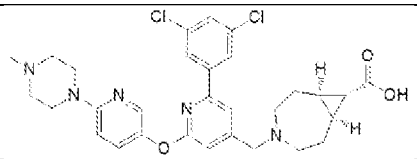
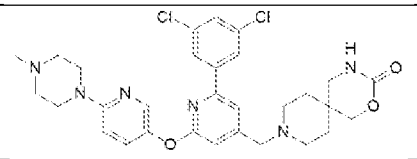
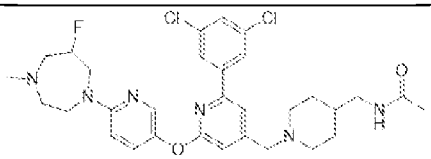
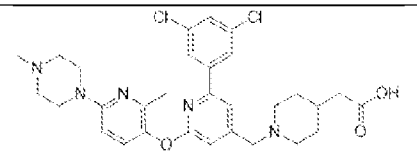
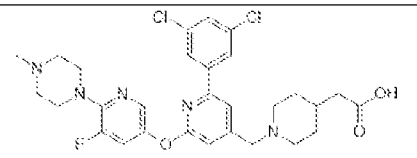
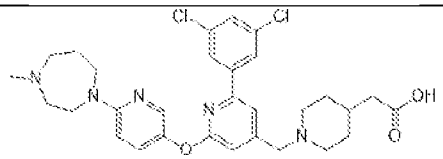
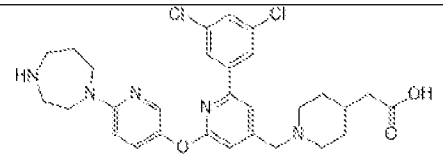
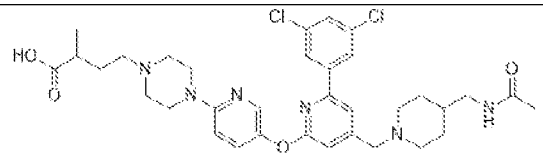
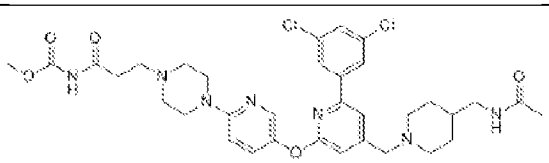
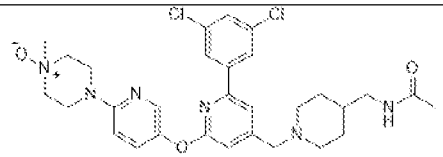
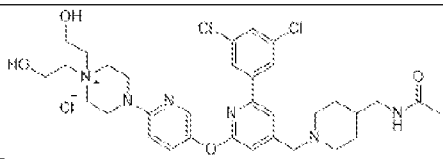
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210		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)-4-hydroxypiperidin-4-yl)methyl)acetamide
211		3-(1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)propanoicacid
212		2-(1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid

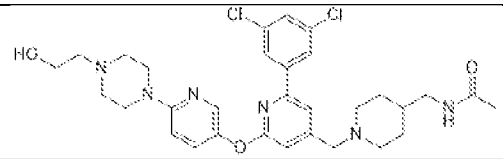
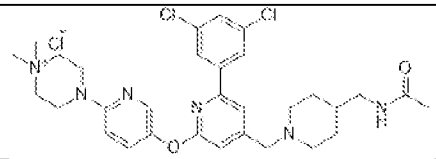
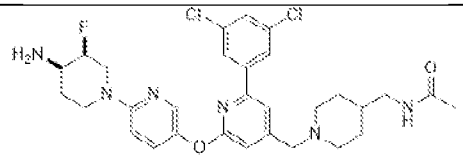
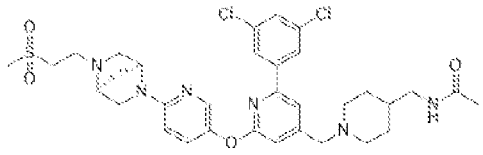
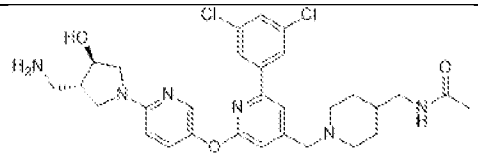
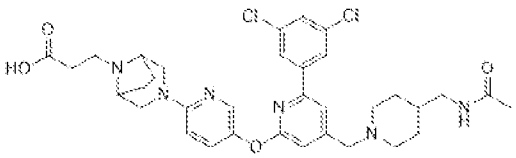
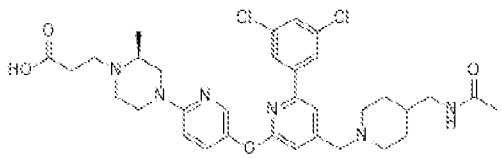
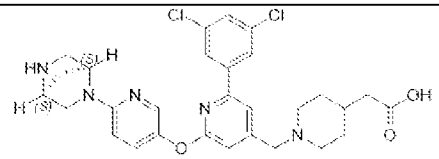
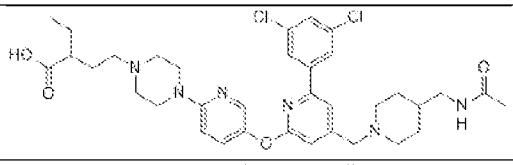
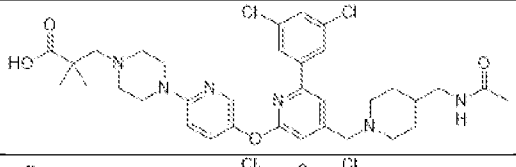
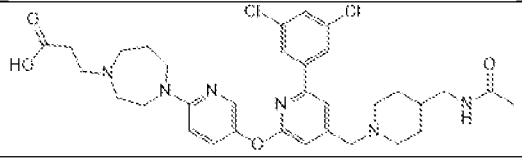
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214		methyl((1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)-4-hydroxypiperidin-4-yl)methyl)carbamate
215		2-(1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)ethanesulfonicacid
216		(1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methanesulfonicacid
217		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
218		2-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)aceticacid
219		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid
220		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
221		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanamide
222		N-((1-((2-((6-(4-(2-(1H-tetrazol-5-yl)ethyl)piperazin-1-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
223		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-(methylsulfinyl)ethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide

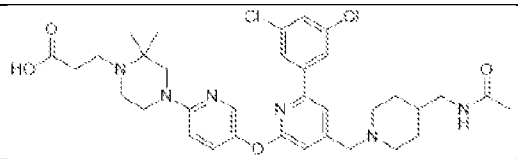
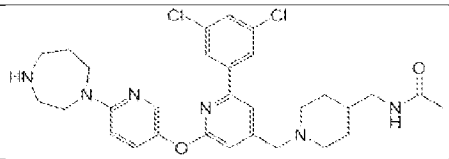
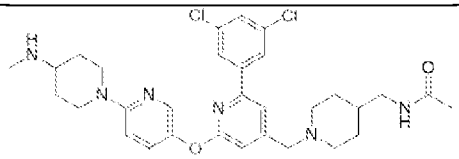
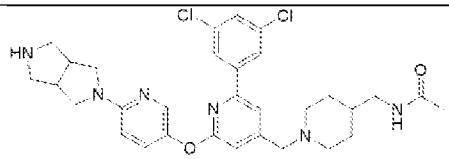
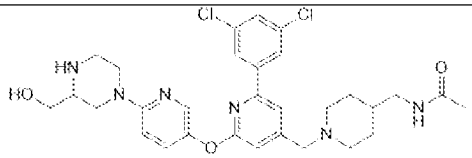
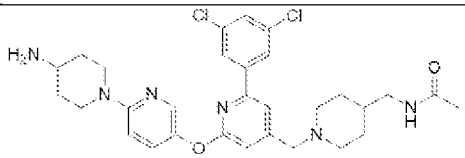
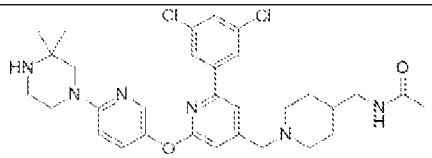
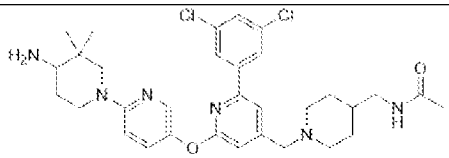
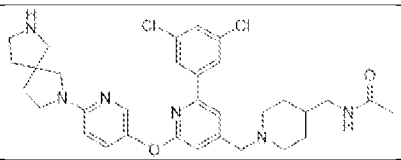
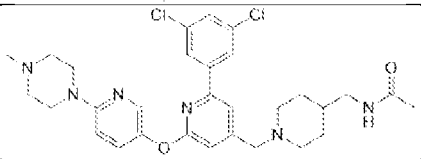
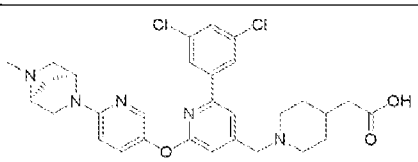
#	Structure	Name
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225		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-((trans)-3-(methylsulfonamido)cyclobutyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
226		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-((cis)-3-(methylsulfonamido)cyclobutyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
227		N-((1-((2-((6-(4-(2-aminoethyl)piperazin-1-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
228		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2,4-dihydroxybutyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
229		(2-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)ethyl)phosphonicacid
230		2-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)ethylcarbamate
231		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-(N-methylmethylsulfonamido)ethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
232		4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)-4-oxobutanoicacid
233		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-((1-(hydroxymethyl)cyclopropyl)methyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
234		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-((1-hydroxycyclopropyl)methyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide

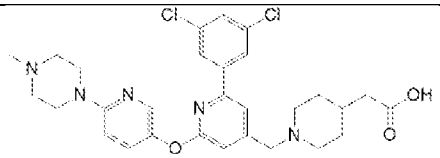
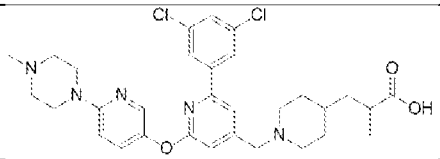
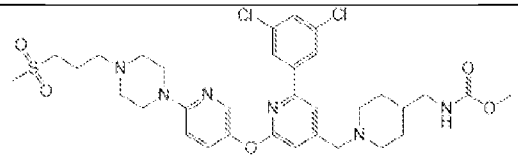
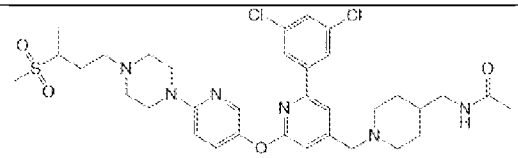
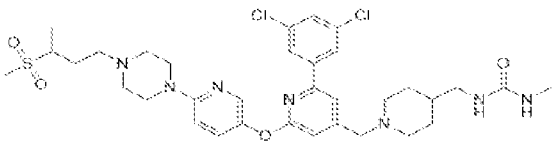
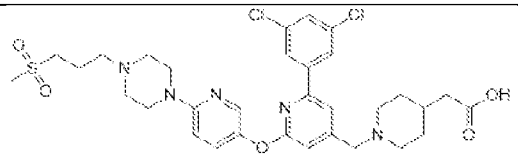
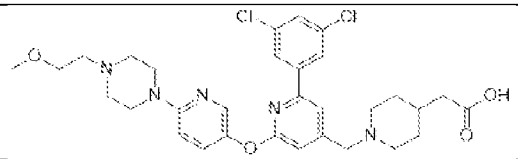
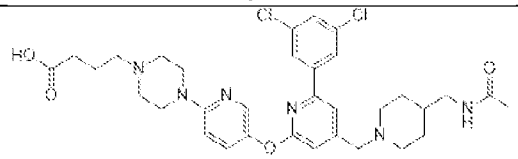
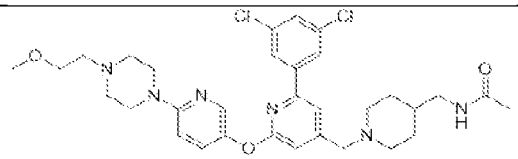
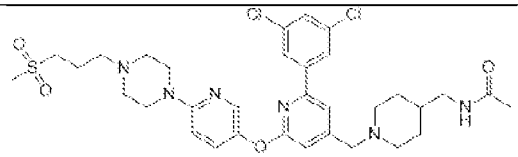
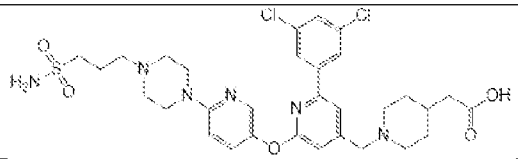
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236		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(sulfamoylmethyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid
237		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((methylsulfonyl)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid
238		1-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-hydroxyethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
239		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid
240		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(methylsulfonamidomethyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid
241		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((methylamino)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid
242		3-(4-(5-((4-((4-(2-(carbamoyloxy)ethyl)piperazin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid
243		3-(4-(5-((4-((4-(cyclopropanecarboxamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid
244		methyl((1-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate
245		(1-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate

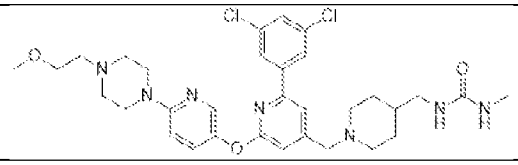
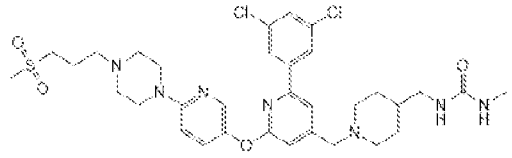
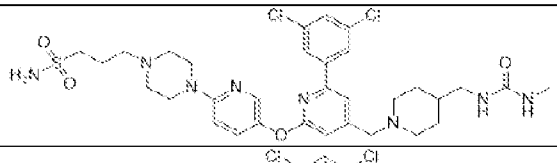
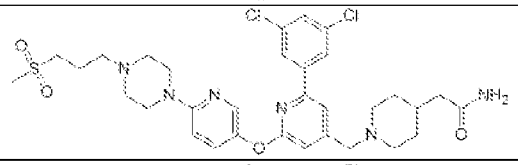
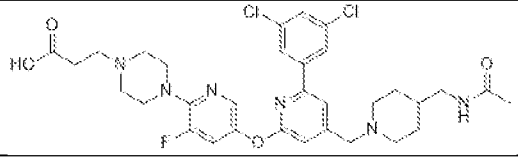
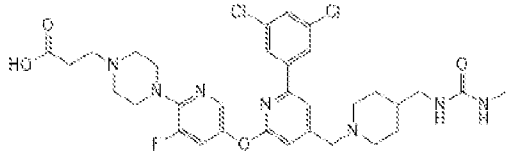
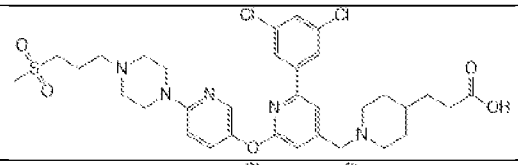
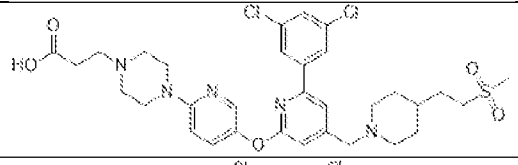
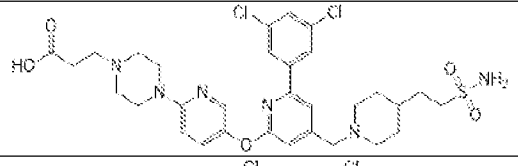
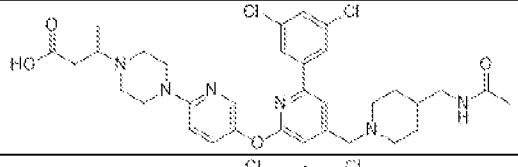
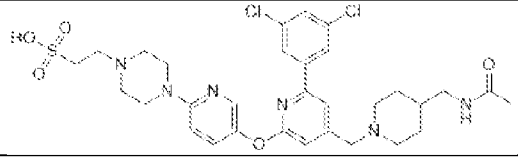
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247		(1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate
248		methyl((1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate
249		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(((methylcarbamoyl)oxy)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid
250		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((dimethylphosphoryl)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid
251		N-((1-((2-(3,5-dichlorophenyl)-6-((5-fluoro-6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)-4-hydroxypiperidin-4-yl)methyl)acetamide
252		1-(5-((6-(3-chloro-5-methylphenyl)-4-((methylamino)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperidin-4-amine
253		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3-chloro-5-fluorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid
254		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3-bromo-5-fluorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid
255		2-(1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)-N,N-dimethylethanamineoxide
256		N-((1-((2-(3,5-dichlorophenyl)-6-((5-fluoro-6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide

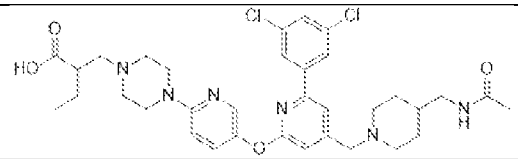
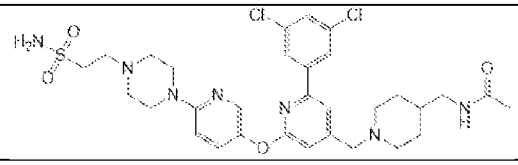
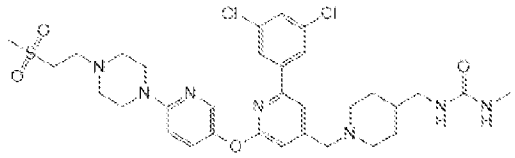
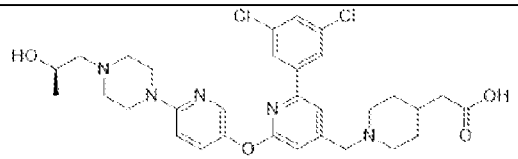
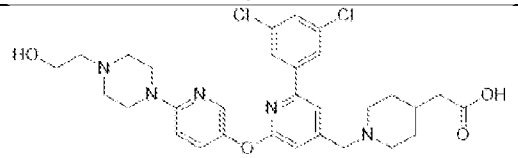
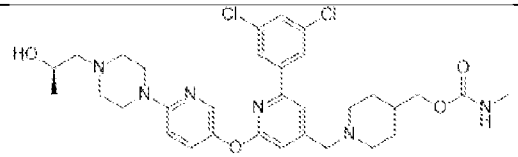
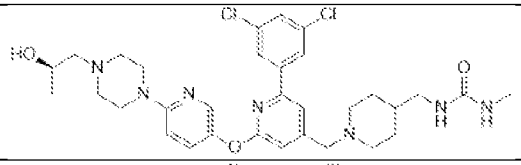
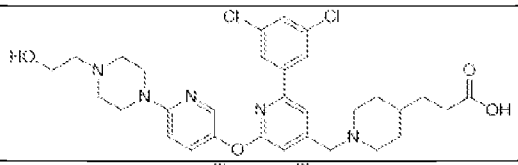
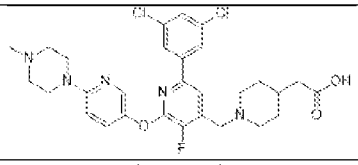
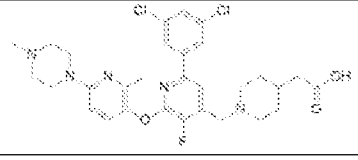
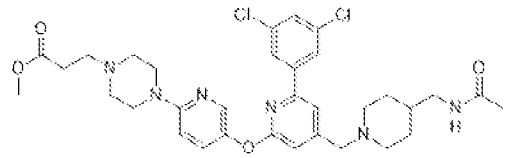
#	Structure	Name
257		(1R,7S,8r)-4-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)-4-azabicyclo[5.1.0]octane-8-carboxylicacid
258		9-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)-2-oxa-4,9-diazaspiro[5.5]undecan-3-one
259		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(6-fluoro-4-methyl-1,4-diazepan-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
260		2-(1-((2-(3,5-dichlorophenyl)-6-((2-methyl-6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid
261		2-(1-((2-(3,5-dichlorophenyl)-6-((5-fluoro-6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid
262		2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-methyl-1,4-diazepan-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid
263		2-(1-((2-((6-(1,4-diazepan-1-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid
264		4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)-2-methylbutanoicacid
265		methyl(3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoyl)carbamate
266		4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)-1-methylpiperazine1-oxide
267		4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)-1,1-bis(2-hydroxyethyl)piperazin-1-ium

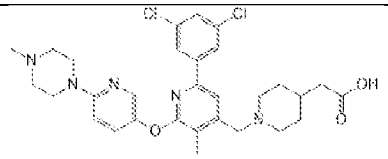
#	Structure	Name
268		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-hydroxyethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
269		4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)-1,1-dimethylpiperazin-1-ium
270		N-((1-((2-((6-(4-amino-3-fluoropiperidin-1-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
271		N-((1-((2-(3,5-dichlorophenyl)-6-((6-((1S,4S)-5-(2-(methylsulfonyl)ethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
272		N-((1-((2-((6-((3S,4R)-3-(aminomethyl)-4-hydroxypyrrolidin-1-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
273		3-((1R,5S)-3-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)propanoicacid
274		(S)-3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)-2-methylpiperazin-1-yl)propanoicacid
275		2-(1-((2-((6-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid
276		4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)-2-ethylbutanoicacid
277		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)-2,2-dimethylpropanoicacid
278		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)-1,4-diazepan-1-yl)propanoicacid

#	Structure	Name
279		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)-2,2-dimethylpiperazin-1-yl)propanoicacid
280		N-((1-((2-((6-(1,4-diazepan-1-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
281		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(methylamino)piperidin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
282		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
283		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(3-(hydroxymethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
284		N-((1-((2-((6-(4-aminopiperidin-1-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
285		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(3,3-dimethylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
286		N-((1-((2-((6-(4-amino-3,3-dimethylpiperidin-1-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
287		N-((1-((2-((6-(2,7-diazaspiro[4.4]nonan-2-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
288		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
289		2-(1-((2-(3,5-dichlorophenyl)-6-((6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid

#	Structure	Name
290		2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid
291		3-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)-2-methylpropanoicacid
292		methyl((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate
293		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)butyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
294		1-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)butyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
295		2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid
296		2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-methoxyethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid
297		4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)butanoicacid
298		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-methoxyethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
299		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
300		2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-sulfamoylpropyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid

#	Structure	Name
301		1-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-methoxyethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
302		1-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
303		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propane-1-sulfonamide
304		2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetamide
305		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)-3-fluoropyridin-2-yl)piperazin-1-yl)propanoicacid
306		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)-3-fluoropyridin-2-yl)piperazin-1-yl)propanoicacid
307		3-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)propanoicacid
308		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(2-(methylsulfonyl)ethyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid
309		3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(2-sulfamoylethyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid
310		3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)butanoicacid
311		2-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)ethanesulfonicacid

#	Structure	Name
312		2-((4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)methyl)butanoicacid
313		N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-sulfamoylethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide
314		1-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
315		(R)-2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-hydroxypropyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid
316		2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-hydroxyethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid
317		(R)-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-hydroxypropyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate
318		(R)-1-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-hydroxypropyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea
319		3-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-hydroxyethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)propanoicacid
320		2-(1-((6-(3,5-dichlorophenyl)-3-fluoro-2-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid
321		2-(1-((6-(3,5-dichlorophenyl)-3-fluoro-2-((2-methyl-6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid
322		methyl3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoate

#	Structure	Name
323		2-(1-((6-(3,5-dichlorophenyl)-3-methyl-2-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid

[00154] The synthesis and characterization of the compounds in **Table 1** and **Table 2** can be found in international PCT application no.: PCT/EP2019/062098, filed May 10, 2019, published on November 14, 2019 with publication No. WO 2019/215341, which is incorporated herein by reference.

[00155] Typically, but not absolutely, the salts of the present disclosure are pharmaceutically acceptable salts. Salts of the disclosed compounds containing a basic amine or other basic functional group may be prepared by any suitable method known in the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, trifluoroacetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, pyranosidyl acid, such as glucuronic acid or galacturonic acid, alpha-hydroxy acid, such as citric acid or tartaric acid, amino acid, such as aspartic acid or glutamic acid, aromatic acid, such as benzoic acid or cinnamic acid, sulfonic acid, such as *p*-toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid or the like. Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, phenylacetates, phenylpropionates, phenylbutrates, citrates, lactates, γ-hydroxybutyrates, glycolates, tartrates mandelates, and sulfonates, such as xylenesulfonates, methanesulfonates, propanesulfonates, naphthalene-1-sulfonates, and naphthalene-2-sulfonates.

[00156] Salts of the disclosed compounds containing a carboxylic acid or other acidic functional group can be prepared by reacting with a suitable base. Such a pharmaceutically acceptable salt may be made with a base which affords a pharmaceutically acceptable cation, which includes alkali metal salts (especially sodium and potassium), alkaline earth metal salts (especially calcium and magnesium), aluminum salts, and ammonium salts, as well as salts made from physiologically acceptable organic bases, such as trimethylamine, triethylamine,

morpholine, pyridine, piperidine, picoline, dicyclohexylamine, *N*,*N*'-dibenzylethylenediamine, 2-hydroxyethylamine, *bis*-(2-hydroxyethyl)amine, tri-(2-hydroxyethyl)amine, procaine, dibenzylpiperidine, dehydroabietylamine, *N*,*N*'-*bis*dehydroabietylamine, glucamine, *N*-methylglucamine, collidine, quinine, quinoline, and basic amino acid such as lysine and arginine.

[00157] Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of this disclosure and these should be considered to form a further aspect of this disclosure. These salts, such as oxalic or trifluoroacetate, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of this disclosure and their pharmaceutically acceptable salts.

[00158] This disclosure further provides a pharmaceutical composition useful in the present disclosure (also referred to as pharmaceutical formulation) comprising a compound of Formula (**I**), or pharmaceutically acceptable salt thereof, and one or more excipients (also referred to as carriers and/or diluents in the pharmaceutical arts). The excipients are acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof (i.e., the patient).

[00159] Suitable pharmaceutically acceptable excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the carrying or transporting of the compound or compounds of this disclosure once administered to the patient from one organ, or portion of the body, to another organ, or portion of the body. Certain pharmaceutically acceptable excipients may be chosen for their ability to enhance patient compliance.

[00160] Suitable pharmaceutically acceptable excipients include the following types of excipients: diluents, fillers, binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavoring agents, flavor masking agents, coloring agents, anticaking agents, hemectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants, preservatives, stabilizers, surfactants, and buffering agents. The skilled artisan will appreciate

that certain pharmaceutically acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the formulation and what other ingredients are present in the formulation.

[00161] Pharmaceutical compositions may be adapted for administration by any appropriate route, for example, by oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intramuscular, intravenous, or intradermal) routes. Such compositions may be prepared by any method known in the art of pharmacy, for example, by bringing into association the active ingredient with the excipient(s).The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound, mode of administration, and the like. An effective amount may be included in a single dose (e.g., single oral dose) or multiple doses (e.g., multiple oral doses). In certain embodiments, the duration between the first dose and last dose of the multiple doses is three months, six months, or one year. In certain embodiments, the duration between the first dose and last dose of the multiple doses is the lifetime of the subject. In certain embodiments, a dose (e.g., a single dose, or any dose of multiple doses) described herein includes independently between 0.1 μg and 1 μg, between 0.001 mg and 0.01 mg, between 0.01 mg and 0.1 mg, between 0.1 mg and 1 mg, between 1 mg and 3 mg, between 3 mg and 10 mg, between 10 mg and 30 mg, between 30 mg and 100 mg, between 100 mg and 300 mg, between 300 mg and 1,000 mg, or between 1 g and 10 g, inclusive, of a compound described herein. In certain embodiments, a dose described herein includes independently between 1 mg and 3 mg, inclusive, of a compound described herein. In certain embodiments, a dose described herein includes independently between 3 mg and 10 mg, inclusive, of a compound described herein. In certain embodiments, a dose described herein includes independently between 10 mg and 30 mg, inclusive, of a compound described herein. In certain embodiments, a dose described herein includes independently between 30 mg and 100 mg, inclusive, of a compound described herein.

[00162] Dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[00163] A therapeutically effective amount of a compound of the present disclosure will depend upon a number of factors including, for example, the age and weight of the intended

recipient, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant prescribing the medication. However, an effective amount of a compound of Formula (**I**) for the treatment of a viral infection resulting from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus) will generally be in the range of 0.001 to 100 mg/kg body weight of recipient per day, suitably in the range of 0.01 to 10 mg/kg body weight per day. In certain embodiments, the effective amount of a compound of Formula (**I**) for the treatment of a viral infection resulting from SARS-CoV-2 is in the range of 0.001 to 100 mg/kg body weight of recipient per day. For example, a 70 kg adult mammal, the actual amount per day would suitably be from 7 to 700 mg and this amount may be given in a single dose per day or in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. Inhaled daily dosages range from 10 μg - 10 mg/day, with preferred 10 μg - 2 mg/day, and more preferred 50 μg - 500 μg/day. An effective amount of a salt or solvate, etc., may be determined as a proportion of the effective amount of the compound of Formula (**I**) *per se*. It is envisaged that similar dosages would be appropriate for treatment of the other conditions referred to above.

[00164] Also encompassed by the present disclosure are kits (e.g., pharmaceutical packs). In certain embodiments, the kit comprises a compound or pharmaceutical composition described herein, and instructions for using the compound or pharmaceutical composition. In certain embodiments, the kit comprises a first container, wherein the first container includes the compound or pharmaceutical composition. In some embodiments, the kit further comprises a second container. In certain embodiments, the second container includes an excipient (e.g., an excipient for dilution or suspension of the compound or pharmaceutical composition). In certain embodiments, each of the first or second containers are independently a vial, ampule, bottle, syringe, dispenser package, tube, or inhaler.

[00165] In certain embodiments, a kit described herein includes a first container comprising a compound of Formula (**I**), or a pharmaceutical composition, as described herein. In certain embodiments, a kit described herein is useful in treating and/or preventing a viral infection resulting from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus).

[00166] In certain embodiments, the kit comprises a compound of Formula (**I**), or a

pharmaceutical composition thereof; and instructions for using the compound or pharmaceutical composition.

[00167] In certain embodiments, a kit described herein further includes instructions for using the compound or pharmaceutical composition included in the kit. A kit described herein may also include information as required by a regulatory agency such as the U.S. Food and Drug Administration (FDA). In certain embodiments, the information included in the kits is prescribing information. In certain embodiments, the kits and instructions provide for treating a viral infection resulting from a coronaviridae family virus (e.g., an alphacoronavirus (e.g., HCoV-NL63, HCoV-229E), a betacoronavirus (e.g., SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1), a deltacoronavirus, a gammacoronavirus).

[00168] In certain embodiments, the instructions are for administering the compound or pharmaceutical composition to a subject (e.g., a subject in need of treatment or prevention of a disease described herein). In certain embodiments, the instructions comprise information required by a regulatory agency, such as the U.S. Food and Drug Administration (FDA) or the European Agency for the Evaluation of Medicinal Products (EMA). In certain embodiments, the instructions comprise prescribing information.

EXAMPLES

[00169] In order that the disclosure described herein may be more fully understood, the following examples are set forth. The examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, methods, and uses provided herein and are not meant to be limiting in any way .

Example 1. In-vitro inhibition of Furin-like enzymes in different cell lines

[00170] To test the effect of the compounds on the processing of the pro-(S) protein to active (S)-protein by endogenous furin-like enzymes, three cell lines (VeroE6 (African green monkey kidney), BHK21 (Chinese hamster kidney), and A549 (human pulmonary epithelial)) were transfected to transiently express the proS Sars-Cov-2 protein. Each cell line was incubated for 5 h with either Compound 192, Compound 219, or a cell/permeable pan-PCSK inhibitor, decanoyl-RVKR-chloromethylketone (RVKR). The cells were washed and transfected (Lipofectamine™) with 1 microgram of a cDNA coding for codon optimized (S)-protein (obtained from Sino Biologicals) inserted in a pIRES expression vector with a V5 tagged at the C-terminus of the S-protein. All three cell lines were then incubated for 24 h with Compound 192 or Compound 219 at 0.3 μM, 1 μM, or 10 μM, or decanoyl-RVKR-

CMK (RVKR) at 50 μM (Figure 2). Next, cell lysates were obtained. Separation by SDS-PAGE (8%) and Western blot analyses were done with a V5 mAb. Inhibition was observed in BHK21 cells and somewhat in VeroE6 cells. However, there was less inhibition in the A549 cells. One explanation could be that A549 cells do not process the pro-(S) protein by endogenous furin-like enzymes.

Example 2. ProS processing by furin-like convertases and TMPRSS2.

[00171] The susceptibility to furin-cleavages of SARS-CoV-2' S-glycoprotein was first assessed *in vitro*. Incubation of quenched fluorogenic peptides encompassing S1/S2 and S2' sites (Table 3), demonstrated that the S1/S2 cleavage of SARS-CoV-2 is efficiently hydrolysed by furin at pH 7.5 and less at pH 6, whereas the SARS-CoV-1 S1/S2 and MERS-CoV are poorly cleaved (Figure 3B).

[00172] **Table 3.** Sequence of different peptides mimicking the Covid spike cleavage sites that has been tested in the enzymatic assay (The arrow indicates the expected cleavage site).

	S1/S2 Site	S2' Site
Sars-CoV 1	YHTVSLLR↓STSQ	
Mers CoV	TLTPRSVR↓SVPG	GSRSAR↓SAIE
Sars-CoV 2	TNSPRRAR↓SVAS	SKPSKR↓SFIE
Sars-CoV 2 Mutant 1	TNSPRRAA SVAS	
Sars-CoV 2 Mutant 2	TNSPARAA SVAS	
Sars-CoV 2 Mutant 3	TNSPARAR SVAS	

[00173] Furin less efficiently cleaved the SARS-CoV-2 and MERS-CoV at S2', requiring 50-fold higher enzyme concentrations to detect cleavage (inset Figure 3B). The high specificity of the SARS-CoV-2 to cleavage at furin-like motifs was next confirmed by demonstrating that the substitution of basic residues at the S1/S2 cleavage site (PRRA**A**$_{685}$↓S, P**A**RAR$_{685}$↓S, P**A**RA**A**$_{685}$↓S) dramatically impaired the S1/S2 cleavage (Figure 3C). Altogether these data show that furin best cleaves at S1/S2 and less efficiently at S2'. Based on camostat inhibition, TMPRSS2 was also proposed to participate in SARS-CoV-2 entry in some cells. Accordingly, it was then determined whether TMPRSS2 can cleave at S1/S2 or S2' *in vitro*. However, TMPRSS2 that cleaves a peptide mimicking SARS-CoV-1 at S1/S2, was unable to process SARS-CoV-2 at S1/S2 or S2' (Figure 3D).

[00174] To further decipher the cellular role of furin-like enzymes, HeLa cells were co-transfected with a plasmid containing a codon optimized cDNA coding for V5-tagged proS

(Figure 3A) with cDNAs encoding furin, PC5A, PACE4 and PC7. Cell lysates were analyzed by Western blot (WB) after SDS-PAGE separation and probed with a V5-mAb. Endogenous proteases expressed in HeLa cells were found to process proS, likely at S1/S2, into a ~100 kDa S2-like product (Figure 3E). Furthermore, only overexpression of furin and PC5A enhanced the production of the less abundant ~75 kDa S2'-like fragment (Figure 3E). The remaining ~200 kDa $proS_{im}$ corresponds to an immature precursor form that has not exited the ER, as attested by its sensitivity to endoglycosidase-F and endoglycosidase-H (Figure 9A), and insensitivity to furin-like convertases that are only active in the *trans* Golgi network (TGN) and/or cell surface/endosomes.

[00175] The double Ala-mutant [R685A + R682A] (denoted μS1/S2) of the S1/S2 site **R**RA**R**$_{685}$↓S eliminated the P1 and P4 Arg critical for recognition by furin-like enzymes, and completely abrogated processing of proS at S1/S2 and putative S2' by endogenous enzymes or by overexpressed furin (Figure 3F). These data support a role of furin in the S1/S2 cleavage and revealed that the latter may be a prerequisite for the subsequent S2' processing. The loss of furin-like cleavage at S1/S2 resulted in the accumulation of a higher molecular sized $proS_m$ (~230 kDa), which likely represents a mature form of this precursor that exited the ER and became endoglycosidase-H-resistant but remained endoglycosidase-F-sensitive (Figure 9A). The cell-permeable PC-inhibitor decanoyl-RVKR-cmk (RVKR) effectively prevented the endogenous formation of S2, but not the cell-impermeable D6R inhibitor, suggesting that proS cleavage by furin into S1 and S2 occurs intracellularly and not at the cell surface (Figure 9B).

[00176] In order to better define the Arg-residues critical for processing at S1/S2, HeLa cells were expressed with the proS carrying single residue mutations: R682A, R685A and S686A in the absence or presence of furin (Figure 4A). The latter was based on a prediction that Ser_{686} could be O-glycosylated, which may hamper processing at S1/S2. However, as for the WT, the S686A mutant was similarly processed by furin into S2 and S2' (Figure 4A). The data confirmed the critical importance of P4-Arg_{682} or P1-Arg_{685} for the generation of S2 by endogenous furin. However, in contrast to the μS1/S2 double Ala mutant (Figure 3F), under conditions of excess furin these single mutants were partially cleaved (Figure 4A). This reflects the multi-basic nature of the S1/S2 recognition sequence **R**RA**R**$_{685}$↓S, whereby **RR**AA$_{685}$ and A**R**A**R**$_{685}$ may still be cleavable, but not ARAA$_{685}$, suggesting that the P3 site may also be important.

[00177] The processing of proS by TMPRSS2 in HeLa cells was also examined (Figure 3F). In accordance with our *in vitro* data (Figure 3D), overexpressed TMPRSS2 did not cleave proS at S1/S2 or S2', but rather generated two minor distinct C-terminal products, herein called S2a (~85 kDa) and S2b (~70 kDa). These fragments were seen with both wild-type (WT)-S and its μS1/S2 mutant (Figure 3F), revealing that they are S1/S2-independent. The S2 product generated by endogenous furin-like enzymes is absent when TMPRSS2 is co-expressed with WT proS (Figure 3F), suggesting that TMPRSS2 generates S2a and S2b before proS encounters endogenous active furin, i.e., before it reaches the trans-golgi network. Indeed, like $proS_{im}$, both S2a and S2b are endoglycosidase-H-sensitive (Figure 9C), indicating that they are generated in the ER and can no longer exit this compartment. Thus, high levels of TMPRSS2 would effectively inactivate S2 by preventing its ER-exit to reach the cell surface. As expected, single-Arg mutations in the S1/S2 site did not affect the ability of TMPRSS2 to generate S2a and S2b (Figure 4A).

[00178] The implication of ACE2 in the processing of proS in HeLa cells, was next assessed by co-expression of proS with furin or TMPRSS2 in the absence or presence of ACE2. While not significantly affecting S1/S2 cleavage, the expression of ACE2 strongly enhanced the generation of smaller-sized S2' by furin, and S2b by TMPRSS2 (Figure 4B), likely reflecting a change in the proS conformation upon ACE2-binding.

[00179] Proteomic analysis of the V5 labeled S2 product confirmed the assignment of the primary $PRRAR_{685}$↓ and secondary KR_{815}↓ furin cleavage sites (Figure 10).

Example 3. Furin-inhibitors block S1/S2 cleavage, without affecting TMPRSS2 processing.

[00180] The efficacy and selectivity of representative Compounds 93, 192, and 219 was tested *in vitro* on purified soluble forms of furin, PC5A, PACE4, and PC7. The enzymatic activity was determined using a quenched fluorogenic substrate FAM-Q**R**V**RR**AVGIDK-TAMRA, and compared to those obtained with the known PC-inhibitor RVKR-cmk. The data showed that all three inhibitors effectively blocked the processing of the above dibasic substrate by all convertases with an IC_{50} of ~7 nM compared to ~9 nM for RVKR-cmk (Figure 5C). The furin S1/S2 cleavage was also validated *in vitro* using a 12-residue quenched fluorogenic substrate DABSYL/Glu-TNSP**RR**A**R**↓SVAS-EDANS. The inhibition deduced after hill-plot curve fitting (Figure 5D) gave an estimated IC_{50} of 4 ± 0.7 nM (Compound 192), 32 ± 4 nM (Compound 219), and 35 ± 5 nM (Compound 93).

[00181] The inhibition of PC-activities by the compounds of this disclosure was next assessed intracellularly using a cell-based Golgi imaging assay of U2OS cells. The data

demonstrated that the compounds inhibited endogenous furin processing of a BMP10-mimic with an IC_{50} of ~8 nM *versus* 5 nM for RVKR-cmk (Figure 5C). The above enzymatic assays showed that all 3 inhibitors can inhibit furin, but may also inhibit other members of the PC-family such as PC5A, PACE4, and PC7.

[00182] The effects of Compound 93, 192, and 219 on the processing of proS in HeLa cells stably expressing ACE2 was evaluated (HeLa-ACE2; Figure 5E). In agreement with the *in vitro* data (Figure 5D), all three compounds blocked the S1/S2 and S2' processing by endogenous furin-like enzymes with Compound 192 showing almost complete inhibition at 300 nM (Figure 5E), comparable to that obtained with a control 50 μM decanoyl-RVKR-cmk. In contrast, in HeLa cells none of the compounds affected the generation of S2a and S2b by TMPRSS2 (Figure 11), in agreement with the distinct cleavage specificities of furin and TMPRSS2.

Example 4. TMPRSS2 sheds ACE2 and cleaves S1.

[00183] The data does not support the direct implication of TMPRSS2 in the generation of S2 or S2', since it was found that overexpression of TMPRSS2 cleaves proS to generate ER-retained S2a and less so S2b (Figure 3F, Figures 9B, 9C) and does not cleave proS at S2'. To confirm that S2a, and S2b are generated by TMPRSS2 activity in the ER, HeLa-ACE2 cells were incubated with 120 μM Camostat, known to inhibit TMPRSS2. The data showed that this inhibitor can reach the ER as it blocked the autocatalytic activation of TMPRSS2 at RQS**R**$_{255}$↓ (loss of ~25 kDa form in the media), prevented the formation of both S2a and S2b with increasing concentrations of TMPRSS2, and gradually allowed the resumption of the furin-like cleavage at S1/S2 (Figure 12A).

[00184] Accordingly, other functions that TMPRSS2 may exert were explored to explain its reported enhancement of viral entry. Hence, increasing amounts of TRMPSS2 were expressed in HeLa-ACE2 cells and followed the S1 and TRMPSS2 processing by WB-analysis using anti-S1 and anti-TRMPSS2 antibodies. First, it was found that TMPRSS2 cleaved the furin-generated S1-subunit (~135 kDa) into a shorter S1' fragment (~115 kDa) secreted into the medium (Figure 12A). This cleavage may enhance the efficacy of separation of the S1 and S2 domains when S1 is bound to ACE-2, but before membrane fusion by the S2-subunit. It was previously reported that TMPRSS2 sheds ACE2 into a soluble form (sACE2), and the latter activity may be associated with enhanced kinetics of cell-to-cell fusion (syncytia) and ACE2-receptor viral uptake. In agreement, overexpression of

TMPRSS2 in HeLa-ACE2 cells enhanced the shedding of ACE2 into ~120 and ~110 kDa sACE2 forms. The generation of both sACE2 and in large part S1' are inhibited by 120 μM Camostat (Figure 12A). Note that the small background shedding of ACE2 is not sensitive to Camostat, suggesting that another endogenous protease, possibly ADAM17, is also implicated. Co-immunoprecipitation experiments showed that sACE2 and S1' are found as a complex bound to each other in the media (Figure 12B). Incubation of HeLa cells expressing S with media containing sACE2 and active mature ~25 kDa TMPRSS2m generated by co-expression of full length ACE2 with TMPRSS2 in HEK293 cells revealed that sACE2 enhanced the levels of S2' in cells and S1 in media (Figure 13A). Finally, co-expression of TMPRSS2 with WT proS or its μS1/S2 mutant in HeLa cells in the absence or presence of ACE2 resulted in the similar generation of: (**i**) secreted S1' only in the presence of ACE2 and (**ii**) secreted sACE2 (Figure 13B). Furthermore, these data revealed that furin-processing at S1/S2 is not a prerequisite for these TMPRSS2-mediated cleavages.

Example 5. Immunocytochemistry.

[00185] Immunocytochemical analyses of HeLa cells co-expressing the S-protein or μS1/S2 with ACE2 in the absence or presence of 1 μM Compound 192 was also investigated under cell-permeabilization (P; V5 and ACE2 antibodies) and non-permeabilization (NP; S2 and ACE2 antibodies) conditions (Figures 14, 15). In the absence of Compound 192, the S-protein and ACE2 co-localized abundantly at the cell surface (Figure 14-a). HeLa cells expressing both S-protein and ACE2 formed many syncytia, associated with reduced cell surface expression of the S-protein, and an even greater reduction of ACE2 (Figure 14-b). Cells expressing both μS1/S2 and ACE2 showed an accumulation of both proS and ACE2 inside the cells and at the cell surface (Figure 14-c). However, they barely induced the formation of syncytia, and when they did, the cell surface expression of S-protein and to a lesser extent ACE2 were decreased (Figure 14-d). In the presence of 1 μM Compound 192, S-expressing HeLa cells (Figures 15-a,b) phenocopy those expressing μS1/S2 (Figures 6B-c,d).

Example 6. Cell-to-cell fusion.

[00186] Having established that S-protein and ACE2 co-localize at the cell surface, the impact of furin-cleavage at S1/S2 on the ability of S-protein to induce cell-to-cell fusion was analyzed. Accordingly, a luminescence-based assay was developed using HeLa TZM-bl reporter cells stably transfected with an HIV-1-based vector expressing luciferase under the

control of the HIV-1 long terminal repeat (LTR), which can be activated by HIV Tat protein. These cells endogenously express the HIV receptor CD4 and its co-receptors CCR5 and CXCR4. Without wishing to be bound by any particular theory, it is possible that fusion of donor WT HeLa cells (expressing Tat and the fusogenic S-protein) with acceptor TZM-bl cells expressing ACE2 would result in accrued luciferase activity (Figure 6A). When donor cells expressing HIV gp160 and Tat fuse with TZM-bl acceptor cells, luciferase activity increases compared to that observed in TZM-bl control cells co-cultured with donor Hela cells expressing only Tat. (Figure 16C). The expression of S-protein in HeLa cells did not induce fusion with TZM-bl control cells (Figures 16A, 16C). However, ACE2 expression in TZM-bl allowed fusion with HeLa-expressing S-protein in a dose-dependent manner (Figure 16B). The linearity of our assay (correlation coefficient of 0.87) validated the use of luminescence as an indicator of cell-to-cell fusion. Conversely, expression of μS1/S2 in donor cells did not enhance fusion with TZM-bl expressing ACE2 and >60% fusion-inhibition was observed upon incubation of cells with 300 nM of Compound 93, 192, or 219 or 10 μM of the PC-inhibitor RVKR-cmk (Figure 6B), indicating that S1/S2 cleavage promotes ACE2-dependent cell-to-cell fusion.

[00187] TMPRSS2 was co-expressed with S-protein or with μS1/S2 in donor cells to assess the role of TMPRSS2 in cell-to-cell fusion. In agreement with our cell-biology data (Figures 3F, 4), TMPRSS2 abolished the fusogenic activity of S, providing evidence that TMPRSS2-mediated retention of S-protein in the ER by the generation of S2a and S2b impaired the cell-to-cell fusion activity of S-protein at the plasma membrane (Figure 6C). However, co-expression of TMPRSS2 and ACE2 in acceptor cells tended to enhance the fusion with donor S-containing cells, an effect much more evident with μS1/S2-containing donor cells, resulting in similar cell-to-cell fusion between donor cells expressing either WT-S or μS1/S2 and acceptor ACE2-TMPRSS2 cells (Figure 6D). This phenotype suggests that in the absence of furin-cleavage (μS1/S2) the TMPRSS2-generated S1' releases the N-terminal part of the S1 cap, thereby favoring furin-cleavage at S2' and cell-cell-fusion. Indeed, co-expression of ACE2 with various doses of TMPRSS2 in acceptor cells gradually promoted the fusion of the μS1/S2 to similar levels as the WT-S-induced fusion (Figure 17). However, sACE2 alone had no effect on μS1/S2 (panels A versus B), as the S2' site would still be capped by the un-cleaved S1-subunit (Figure 17). Thus, only high levels of TMPRSS2 in ACE2-acceptor cells allow similar fusion with donor cells expressing WT-S and μS1/S2 (Figure 17A). Interestingly, overexpression of a soluble form of ACE2 (sACE2) in acceptor cells significantly enhanced fusion with donor cells containing WT-S. Here the sACE2-S1

complex may bind a receptor on acceptor cells, e.g., to integrins via their RGD motifs or S1-binding to neuropilin 1, 2, to promote cell-to-cell fusion.

Example 7. Effects of furin inhibitors on entry of pseudoviruses.

[00188] To asses the importance of spike processing at the S1/S2 site in SARS-CoV-2 entry, gp160-defective HIV with WT or μS1/S2 S-protein was pseudotyped and tested viral entry in different target cells. Using lung Calu-3 and kidney HEK293T-ACE2 as model cell targets, cell-entry of viruses expressing μS1/S2 were completely defective in Calu-3, but not in 293T-ACE2 that exhibited enhanced viral-entry (Figure 7A), similar to Vero E6 cells. Since SARS-CoV-2 can enter target cells *via* "pH-independent" or "pH-dependent" pathways and the virus reportedly uses the latter to infect Vero E6 cells. The pH-raising chloroquine efficiently blocked entry of pseudotyped SARS-CoV-2 and its μS1/S2 mutant (Figure 18), suggesting that in the 293T-ACE2 system the S-protein, which mediates viral entry, is activated by endosomal pH-dependent proteases. This aligns with previous findings that HEK293 cells allow endocytosis of pseudovirions carrying SARS-CoV-2 spike protein *via* clathrin-coated vesicles.

[00189] When 293T17 producing cells were treated with representative compounds of this disclosure during viral packaging, HIV particles expressing the WT proS-protein remained highly infectious in 293T-ACE2 but were completely defective in Calu-3 (Figure 7B; Figure 19). Thus, treatment of the cells with the compounds of this disclosure phenocopied the effect of the μS1/S2 in both target cells. Importantly, these phenotypes were not due to increased pseudoviral production/release since levels of HIV p24 were comparable in all cases (Figure 7C). Similarly, in the presence of 1 μM Compound 93, processing of WT-S was clearly impaired, while the overall μS1/S2 expression profile was not affected (Figure 7C). The data indicate that processing of S-protein by furin-like convertases is essential for the pH-independent viral entry in Calu-3 cells but not in HEK293 cells stably expressing ACE2 where the virus enters by the endocytic pathway.

Example 8. Furin-like inhibitors reduce virus production in SARS-CoV-2-infected cells.

[00190] The possible antiviral effects of these furin-like inhibitors on SARS-CoV-2 replication was evaluated in Calu-3 cells pretreated with 1 μM Compound 93, 192, or 219 24h before infection with laboratory isolated SARS-CoV-2 virus (MOI: 0.01) and harvested at 12, 24 and 48h post infection for plaque assay analysis. Compound 93, 192, or 219 significantly decreased viral titers at 12, 24 and 48h post-infection (Figure 8A). The

inhibitory effect of various doses of these inhibitors on the yield of infectious virus produced 24h post-infection was investigated, and it was found that the titer of progeny viruses was reduced by more than 30-fold with 1 μM Compound 93 although the inhibitory effect could be observed starting at 0.25 μM (Figure 8B; left panel). As well, the IC_{50} and selectivity index (SI) of Compound 93 were found to be 0.2 μM and 624.1, respectively, underlining the inhibitor's *bona fide* efficacy (Figure 8B; right panel). A similar analysis with Compound 219 and Compound 192 revealed comparable antiviral effects and selectivity index (Figures. 20A, 20B). Importantly, the levels of viral spike (full length and cleaved S) and nucleocapsid proteins in Calu-3 cells treated with different doses of Compound 93 and the corresponding progeny virus levels were similarly decreased (Figure 8C), underscoring the crucial role played by furin-like convertases in the production of infectious SARS-CoV-2 during infection of lung epithelial cells. In addition, the antiviral effect of these inhibitors for SARS-CoV-2 infection was also evaluated in Vero E6, a cell target that is reported to be primarily infected *via* the endocytic pathway. In this system, the best inhibitory effect with 1 μM Compound 93 demonstrated a ~5.7-fold decrease in virus production sustained over a 12-48h -infection period (Figure 21), reflecting some furin-activity in endosomes.

[00191] Based on the SI of the representative compounds in Vero E6 and Calu-3 cells, Compound 192 was further used in combination with Camostat to explore a potential synergistic effect of these inhibitors on viral replication in Calu-3 cells. To this end, it was observed that the two inhibitors could individually and meaningfully reduce viral replication, but co-treatment with both (1 μM Compound 192 + 100 μM Camostat) inhibited >99% of progeny viruses (Figure 8D). This highlights a synergistic effect of these drugs and the importance of endogenous furin-like proteases, and presumably TMPRSS2, in the efficient infection of Calu-3 cells by SARS-CoV-2.

Example 9. Experimental methods.

Enzymatic PC-inhibition and cellular furin inhibition of furin-inhibitors

[00192] Biochemical assay: The proprotein convertases furin (108-574-Tev-Flag-6His), PC5A (PCSK5; 115-63-Tev-Flag-6His), PACE4 (PCSK6; 150-693-Tev-Flag-6His), and PC7 (PCSK7; 142-634-Tev-Flag-6His) enzymes were purified from BacMam transduced CHO cells. Reactions were performed in black 384-well polystyrene low volume plates (Greiner) at a final volume of 10 μL. Small-molecule inhibitors (e.g., Compound 93, Compound 219, and Compound 192) were dissolved in DMSO (1 mM) and serially diluted 1 to 3 with DMSO through eleven dilutions to provide a final compound concentration range from 0.00017 to 10

μM. 0.05 μl of each concentration was transferred to the corresponding well of an assay plate, and then 5 μl of enzyme (furin, PCSK5, PCSK6, and PCSK7) in assay buffer (100 mM HEPES pH 7.5, 1 mM $CaCl_2$ and 0.005% Triton X-100) was added using a Multidrop Combi (Thermo) to the compound plates to give a final protein concentration of 0.02, 0.5, 2.5, and 1.0 nM respectively. The plates were mixed by inversion, and following a 30 min preincubation of enzyme with compound at room temperature (~22 °C), the substrate FAM-QRVRRAVGIDK-TAMRA (AnaSpec # 808143, 5 μl of a 1, 0.25, 0.20, and 0.5 μM solution in assay buffer for furin, PCSK5, PCSK6, and PCSK7 respectively) was added using a Multidrop Combi to the entire assay plate. The plates were centrifuged at 500Xg for 1 minute and incubated at room temperature for two hours. Enzyme inhibition was then quantified using an Envision instrument (PerkinElmer). Data were normalized to maximal inhibition determined by 1 μM Decanoyl-Arg-Val-Lys-Arg-Chloromethylketone (Calbiochem #344930). Golgi imaging assay: This assay uses an image-based platform to evaluate the intracellular activity of furin inhibitors. Reactions were performed in black 384-well, tissue culture-treated, clear bottom plates (Greiner). Compounds under analysis were dissolved in DMSO (1.0 mM) and serially diluted 1 to 3 with DMSO through eleven dilutions. This creates a final compound concentration range from 0.00017 to 10 μM, and 0.1 μL of each concentration was transferred to the corresponding well of the assay plate.

[00193] Cellular assay: Analyses were initiated by the addition of U2OS cells simultaneously transduced with a BacMam-delivered construct containing a Golgi-targeting sequence followed by a 12-amino acid furin/PCSK cleavage site from Bone Morphogenic Protein 10 (BMP10) and then GFP at the C terminus. The dibasic furin cleavage site sequence was flanked by glycine rich linkers (GalNAc-T2-GGGGS-DSTARIRRNAKG-GGGGS-GFP). Briefly, frozen cells are thawed in assay media (Dulbecco's Modified Eagles Medium Nutritional Mixture F-12 (Ham) without phenol red containing 5% FBS) and diluted to deliver 6000 cells/well (50 μl) to the plate using a Multidrop Combi (Thermo). After a 24-hour incubation period at 37 °C, the cells are stained with Cell Mask Deep Red, fixed in paraformaldehyde and the nuclei stained using Ho33342. The Golgi-targeted GFP forms bright punctate clusters within the cell. In the absence of a furin/PCSK inhibitor, the endogenous protease cleaves GFP from its N-acetylgalactosaminyltransferase-2 Golgi tether, releasing GFP into the Golgi lumen where fluorescence is diluted below the threshold of assay sensitivity. In the presence of a cell permeable furin/PCSK inhibitor, GFP fluorescence increases as intra-Golgi protease activity is reduced. Cellular GFP intensity is determined by

image-based acquisition (Incell 2200, Perkin Elmer) at 40x magnification with 4 fields measured per well. Multi-scale top hat segmentation is used to identify the GFP-tagged puncta and to quantitate the average fluorescence of all puncta on a per cell basis. Cellular toxicity is determined in parallel.

[00194] Furin and TRMPSS2 fluorogenic assays: Recombinant furin was purchased from BioLegend (#719406), TRMPSS2 from Cusabio and the DABCYLGlu-EDANS labelled peptides encompassing the different cleavage sites (Supplementary Table 1) were purchased from Genscript. Reactions were performed at room temperature in black 384-well polystyrene low volume plates (CELLSTAR-Greiner Bio-One # 784476) at a final volume of 15 µL. The fluorescent peptides were used at 5 µM and the reactions were performed in 50 mM Tris buffer (pH 6.5 or 7.5), 0.2% Triton X-100, 1mM $CaCl_2$ and furin was added at a final concentration of 2-100 nM. Small-molecule inhibitors (Compound 93, Compound 219, and Compound 192) were dissolved in DMSO (1 mM) and serially diluted 1 to 2 with DMSO to provide a final compound concentration range from 50 µM to 0.01 nM with 5% DMSO in the enzymatic assay. For TMPRSS2, the fluorescent peptides were used at 5 µM and the reactions were performed in 50 mM Tris buffer (pH 6.5 or 7.5), 0.2% Triton X-100, 50 mM NaCl and TMPRSS2 was added at final concentrations of 25-100 nM. Cleavage of the synthetic peptides was quantitated by determining the increase of EDANS (493 nM) fluorescence following release of the DABCYL quencher, which is excited at 335 nM using a Safire 2 Tecan fluorimeter. The fluorescence was followed during 90 min, and the enzymatic activity was deduced by measurement of the increase of fluorescence during the linear phase of the reaction. Each reaction was performed in triplicate and the standard deviation was calculated using Excel-ecart type function ($\sqrt{\frac{\sum(x-\bar{x})^2}{(n-1)}}$).

Plasmids

[00195] C-terminal V5 tagged Spike glycoprotein of SARS-CoV-2 (optimized sequence) and its mutants were cloned into the pIRES-neo3 vector. Site-directed mutagenesis was achieved using a Quick-Change kit (Stratagene, CA) according to the manufacturer's instructions. The plasmids pCI-NEO-hACE2 received from DW Lambert (University of Leeds) and pIRES-NEO3-hTMPRSS2 from P Jolicoeur (IRCM). The ΔEnv Vpr Luciferase Reporter Vector (pNL4-3.Luc.R-E-) was obtained from Dr. Nathaniel Landau through the NIH AIDS Reagent Program whereas the pHIV-1NL4-3 ΔEnv-NanoLuc construct was a kind

gift from Dr. P Bieniasz. Plasmids encoding VSV-G, as HIV-1 Env and tat were previously described.

Cell culture and transfection

[00196] Monolayers of HeLa, HEK293T, HEK293T17 and Vero E6 cells were cultured in 5% CO_2 at 37°C in Dulbecco's modified Eagle's medium (DMEM; Invitrogen) supplemented with 10% (v/v) fetal bovine serum (FBS; Invitrogen). HEK293T-ACE2, a generous gift from Dr. Paul Bieniasz, were maintained in DMEM containing 10% FBS, 1% nonessential amino acids (NEAA) and 50 μg/ml blasticidin (Invivogen). Calu-3 were cultivated in F12K/DMEM containing 10% FBS. The cells were cultured in 5% CO_2 at 37°C in Dulbecco's modified Eagle's medium (DMEM; Invitrogen) supplemented with 10% (v/v) fetal bovine serum (FBS; Invitrogen). The cells were transfected with JetPrime transfection reagent according to the manufacturer's instructions (Polyplus transfection, New York, USA). At 24h post transfection the culture media were changed to serum-free DMEM and incubated for an additional 24h. To establish the stable HeLa cells over-expressing human ACE2, the cells were maintained in media containing 500 μg/mL of neomycin (G418, Wisent) for two weeks.

[00197] To generate HIV particles pseudotyped with SARS-CoV-2 S, 293T17 cells (600,000 cells plated in a 6-well vessel) were transfected with 1 μg pNL4-3.Luc.R-E- (or pHIV-1NLΔEnv-NanoLuc) in the presence or absence of 0.3 μg pIR-2019-nCoV-S V5 plasmids using Lipofectamine-3000 (Life Technologies). In certain experiments, 293T17 cells were treated with small-molecule inhibitors (e.g., Compound 93, 219, or 192) at 6 h post transfection. Pseudovirions expressing the nano- or firefly-luciferase were collected at 24 h or 48 h post transfection, respectively. Viral supernatants were clarified by centrifugation at 300 x *g*, passed through a 0.45-μm pore-size polyvinylidene fluoride (PVDF; Milipore) syringe filter (Millipore; SLGVR33RS), and aliquots frozen at −80°C. For WB analysis of purified pseudovirions, viral supernatants were concentrated by ultracentrifugation on a 20% sucrose cushion for 3h at 35,000 RPM; Beckman Couter OPTIMA XE; Ti70.1 rotor). HIV particles lacking the SARS-CoV-2 S glycoprotein served as a negative control in all experiments.

Cell viability assay using MTT

[00198] Cells, seeded in a 96-well plate, the day before, at 10,000 (HEK-293T and Vero E6) or 50,000 (Calu-3) cells, were treated with serial 10-fold dilutions of small-molecule inhibitors (e.g., Compound 93, 192, or 219) for up to 48h. Cells treated with vehicle alone

were used as negative control. MTT was subsequently added to the medium (final concentration: 2.5 mg/ml) and cells were further incubated for 4h at 37 ^{0}C. After removal of the culture media, DMSO was added and absorbance read at 595 nm using a microplate spectrophotometer. The data from two independent experiments done in triplicates was used to calculate the CC50 by nonlinear regression using GraphPad Prism V5.0 software.

Western blots

[00199] The cells were washed with PBS and then lysed using RIPA buffer (1% Triton X-100, 150 mM NaCl, 5 mM EDTA, and 50 mM Tris, pH 7.5) for 30 min at 4°C. The cell lysates were collected after centrifugation at 14,000 × g for 10 min. The proteins were separated on 7% tris-glycine or 8% tricine gels by SDS-PAGE and transferred to a PVDF membrane (Perkin Elmer). When specified, media from cultured and transfected cells were collected and concentrated 10x using Amicon Ultra 2 ml devices with a 10 kDa cut-off (Millipore; UFC 201024), as specified by the manufacturer, and analyzed by SDS-PAGE followed by Western blotting. The proteins were revealed using a V5-monoclonal antibody (V5-mAb V2660; 1:5000; Invitrogen), ACE2 antibody (rabbit monoclonal ab108252; 1:3,000; Abcam), TMPRSS2 antibody (rabbit polyclonal; 14427-1-AP; 1:1,000; Proteintech), Actin antibody (rabbit polyclonal A2066; 1:5,000; Sigma), or SARS-CoV-2 spike antibody (rabbit polyclonal GenTex GTX135356; 1:2,000; GenTex). The antigen-antibody complexes were visualized using appropriate HRP conjugated secondary antibodies and enhanced chemiluminescence kit (ECL; Amersham or Bio-Rad) and normalization was reported to β-actin. The quantification of the bands was performed using Image Lab software (Bio-Rad).

[00200] For analysis of SARS-CoV-2 S virions or pseudovirions, protein extracts of purified viral particles and corresponding producing cells (Calu-3 or 293T17, respectively) were resolved on 10% tris-glycine gels and immunoblotted for spike, nucleocapsid, HIV-1 Gag p24 or actin using anti-V5 (for pseudovirion detection; V2660)/anti-S2 (for virion detection; Sino Biologicals; 40590-T62), anti-N (Sino Biologicals; 40143-MM05), anti-p24 (MBS Hybridoma line 31-90-25) or anti-actin (MP Biomedicals, SKU 08691001), respectively.

Glycosidase treatment

[00201] 30 to 50 μg proteins were digested for 90 min at 37°C with endoglycosidase-H (Endo-H; P0702L) or endoglycosidase-F (Endo-F; P0705S) as recommended by the manufacturer (New England Biolabs).

Inhibitor treatment

[00202] At 24h post transfection, cells were incubated for 6h with two pan-PC inhibitors: the cell permeable decanoyl-RVKR-chloromethylketone (cmk; 50 mM; 4026850.001; Bachem) , or with the cell surface PC-inhibitor hexa-D-arginine (D6R; 20 μM; 344931; EMD). Culture media were then replaced with fresh ones containing the inhibitors for an additional 24h. For the selective cell-permeable furin-like inhibitors, the cells were treated with the inhibitors at the specified concentration starting at 5h pre-transfection and throughout the duration of the experiment.

Cell-to-cell fusion assay

[00203] HeLa or HeLa TZM-bl cells were plated at 200,000 cells in 12-well plates. HeLa cells were transiently transfected with different constructs of SARS-COV-2 Spike or NL4.3-HIV Env, or an empty vector and 0.2 μg of CMV-Tat plasmid. HeLa TZM-bl cells were transfected with human ACE2, TMPRSS2 or a combination of both. At 6h post-transfection, media were replaced with fresh ones containing furin-inhibitors, and 24h later the cells were detached with PBS-EDTA (1 μM). Different combinations of HeLa and HeLa-TZM-bl cells were placed in co-culture plate at a ratio of 1:1 for a total of 60,000 cells/well of a 96 well place. After 18-24h the media were removed and 50 μl of cell lysis reagent was added in each well. 20 μl of the cell lysate was used for luciferase reading using 50 μl of Renilla luciferase reagent (Promega, Madison, WI, USA). The relative light units (RLU) were measured using a Promega GLOMAX plate reader (Promega, Madison, WI, USA) and values were reported as fold increase over the RLU measured in co-culture of HeLa cells transfected EV with respective TZM-bl cells.

Microscopy

[00204] To establish the luciferase assay, cell co-cultures were plated on glass coverslips. After 18-24h, the cells were incubated with 488 CellMask™ to stain the membrane and then fixed with 4% PFA for 15 min at 4°C. The glass coverslips were mounted on glass slides

using ProLong™ Gold Antifade containing DAPI (Invitrogen). The number of syncytia were counted over 10 fields.

Immunofluorescence

[00205] Cell culture and transfection were performed on glass coverslips. Cells were washed twice with PBS and fixed with fresh 4% paraformaldehyde for 10 min at room temperature. Following washes, cells were either non-permeabilized or permeabilized with 0.2% Triton X-100 in PBS containing 2% BSA for 5 min, washed, and then blocking was performed with PBS containing 2% BSA for 1h. Cells were incubated with primary antibodies overnight at 4°C using an antibody against V5 (mouse monoclonal R960-25; 1:1000; Invitrogen), Spike (mouse monoclonal GTX632604; 1:500; GeneTex) and ACE2 (goat polyclonal AF933; 1:500; RnDsystems). Following wash, corresponding species-specific Alexa-Fluor (488 or 555)-tagged antibodies (Molecular Probes) were incubated for 1h at room temperature. Coverslips were mounted on a glass slide using ProLong Gold Reagent with DAPI (P36935, Life Technologies). Samples were visualized using a confocal laser-scanning microscope (LSM710, Carl Zeiss) with Plan-Apochromat 63x/1.40 Oil DIC M27 objective on ZEN software.

Pseudovirus entry

[00206] 293T-ACE2 or Calu-3 (10,000 cells/well plated in a 96-well dish the day before) were incubated with up to 200 µl filtered pseudovirions for overnight. Viral inoculum was removed, then fresh media were added and the cells cultured for up to 72h. Upon removal of spent media, 293T-ACE2 and Calu-3 cells were gently washed twice with PBS and analyzed for firefly- or nano- luciferase activity, respectively using Promega luciferase assay (Cat # E1501) or Nano-Glo luciferase system (Cat # N1110), respectively.

Live virus assays

Replication competent SARS-CoV-2 Viruses

[00207] SARS-CoV-2, which served as the viral source, was originally isolated from a COVID-19 patient in Quebec, Canada and was designated as LSPQ1. The clinical isolate was amplified, tittered in Vero E6 using a plaque assay as detailed below, and the integrity of the S-protein multi-basic protein convertase site validated by sequencing. All experiments involving infectious SARS-CoV-2 virus were performed in the designated areas of the Biosafety level 3 laboratory (IRCM) previously approved for SARS-CoV-2 work.

Plaque assay in Vero E6

[00208] Vero E6 cells (1.2 x 10^5 cells/well) were seeded in quadruplicate in 24-well tissue culture plates in DMEM supplemented with 10% FBS two days before infection. Cells were infected with up to six ten-fold serial dilutions (10^{-2}-10^{-6}) of viral supernatant containing SARS-CoV-2 for 1h at 37ºC (200 µl infection volume). The plates were manually rocked every 15 min during the 1-hour period. Subsequently, virus was removed, cells were washed and overlaying media (containing 0.6% low melt agarose in DMEM with 10% FBS) was added, and incubated undisturbed for 60-65h at 37ºC. Post incubation, cells were fixed with 4% formaldehyde and stained with 0.25% crystal violet (prepared in 30% methanol). High quality plaque pictures were taken using a high resolution DLSR camera (Nikon model: D80, objective: "AF Micro-Nikkor 60mm f/2.8D"). Plaques were counted manually and in parallel, imaged plaque plates were processed and plaques enumerated using an automated algorithm based Matlab software. Virus titer is expressed as plaque-forming units per ml (PFU/ml): (number of plaques x dilution factor of the virus) x 1000 / volume of virus dilution used for infection (in µl). Multiplicity of infection (MOI) expressed as: MOI = PFU of virus used for infection / number of cells.

Cell infections with fully replicative SARS-CoV-2

[00209] Vero E.6 and Calu-3 cells were seeded in duplicates in 12-well plates (2.3 x 10^5 cells/well) the day before. Cells were pre-treated with various concentrations (0.1-1µM) of the small-molecule inhibitor (e.g., Compound 93, 192, or 219) and vehicle alone (DMSO) for up to 24h. In certain experiments, Calu-3 were also pre-treated with Camostat for 1h. Thereafter, the cells were infected with SARS-CoV-2 virus at MOI of 0.001 for 1h (Vero E6) or 0.01 for 3h (Calu-3 cells) in 350 µl of serum-free DMEM at 37ºC with occasional manual rocking of plates. Cells plus media only were used as a control. After incubation, virus was removed, and the cell monolayer was washed twice successively with PBS and serum-free DMEM. New media (total 1ml) containing the aforementioned concentrations of the small molecule inhibitor was subsequently added to cells. Cell-free supernatant (250 µl) was removed at 12, 24 and 48h post infection. The drugs were replenished for 1 ml media at 24h post-infection. The virus supernatants were stored at -80°C until further use. Viral production in the supernatant was quantified using a plaque assay on Vero E6.1 cells as described above. In certain experiments, viral supernatants were harvested at the end of infection and purified on a 20% sucrose cushion using ultracentrifugation as described above. The resulting

concentrated virus and corresponding infected cells were analyzed by Western blotting as appropriate.

[00210] Quantification and statistical analysis: Virus titers quantified by plaque assay in triplicate were shown as mean ± standard deviation. The results from experiments done in triplicates were used to calculate the IC_{50} by nonlinear regression using GraphPad Prism V5.0 software. The difference between the control cells (virus with 0.001% DMSO) and the cells treated with the small-molecule inhibitors (e.g., Compound 93, 192, or 219) were evaluated by Student's t test. The P values of 0.05 or lower were considered statistically significant (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$).

EQUIVALENTS AND SCOPE

[00211] In the claims articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The disclosure includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[00212] Furthermore, the disclosure encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, e.g., in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the disclosure, or aspects of the disclosure, is/are referred to as comprising particular elements and/or features, certain embodiments of the disclosure or aspects of the disclosure consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms "comprising" and "containing" are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and

understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

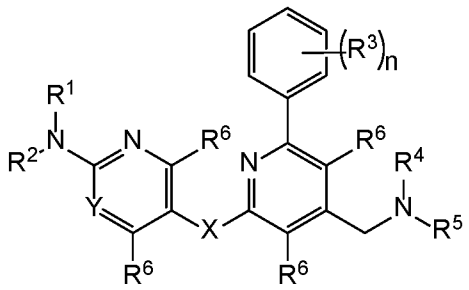
[00213] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present disclosure that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the disclosure can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[00214] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present disclosure, as defined in the following claims.

CLAIMS

What is claimed is:

1. A method of treating a viral infection resulting from coronaviridae family virus in a subject in need thereof comprising administering to the subject a compound of Formula (**I**), wherein the compound of Formula (**I**) is of the formula:



(**I**),

or a pharmaceutically acceptable salt thereof, wherein:

X is –O– or –N(R^8)–;

Y is –N= or –C(R^6)=;

R^1 and R^2 are each independently H or optionally substituted (C_1-C_4)alkyl; optionally, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, –OCONR^{8}R^9, –CO_2R^8, –C(O)CO_2R^8, –R^7, –OR^7, –NHR^8, –NR^7R^8, –C(O)R^7, –$CONHR^8$,
–$CONR^7R^8$, or –SO_2R^7;

each R^3 is independently halogen, –CN, –O(C_1-C_4)alkyl, or optionally substituted (C_1-C_4)alkyl;

R^4 and R^5 are each independently H or optionally substituted (C_1-C_4)alkyl; optionally, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, –OCONR^{8}R^9, –CO_2R^8, –C(O)CO_2R^8, –SO_2(C_1 C_4)alkyl, –R^7, –OR^7, –NHR^8, –NR^7R^8,
–N(R^8)C(O)R^9, –N(R^8)SO_2R^9, –N(R^8)CONR^{8}R^9, –N(R^8)CON(R^8)SO_2R^9, –C(O)R^7, –

$CONHR^8$,

$–CONR^7R^8$, or $–P(O)R^8R^9$;

each R^6 is independently H, halogen, optionally substituted $(C_1\text{-}C_4)$alkyl, –OH, or optionally substituted $(C_1\text{-}C_4)$alkoxy;

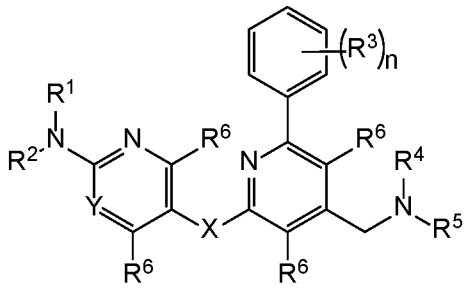
each R^7 is independently $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, or $(C_1\text{-}C_4)$alkyl$(C_3\text{-}C_6)$cycloalkyl, each of which is optionally substituted with one or two of triazolyl, tetrazolyl, $–CO_2R^8$, $–CONR^8R^9$, $–CON(R^8)CO_2(C_1\text{-}C_4)$alkyl, hydroxyl, oxo, $–(C_1\text{-}C_4)$alkoxy, $–OCONR^8R^9$, $–OCON(R^8)C(O)R^9$, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkylOH,

$–NR^8R^9$, $–N(O)R^8R^9$, $–N(R^8)C(O)R^9$, $–N(R^8)CO_2(C_1\text{-}C_4)$alkyl, $–N(R^8)CH_2CO_2R^9$, $–N(R^8)CONR^8R^9$, $–N(R^8)CON(R^8)C(O)R^9$, $–N(R^8)CON(R^8)CO_2(C_1\text{-}C_4)$alkyl, $–N(R^8)SO_2R^9$, $–N(R^8)CON(R^8)SO_2R^9$, $–SO(C_1\text{-}C_4)$alkyl, $–SO_2(C_1\text{-}C_4)$alkyl, $–SO_3R^8$, $–SO_2NR^8R^9$, $–B(OH)_2$, $–P(O)R^8R^9$, or $–P(O)(OR^8)(OR^9)$;

each of R^8 and R^9 is independently H, optionally substituted $(C_1\text{-}C_4)$alkyl, or optionally substituted $(C_3\text{-}C_6)$cycloalkyl; and

n is 1, 2, 3, or 4.

2. A method of inhibiting the entry of a coronaviridae family virus into a cell in a subject in need thereof, comprising administering to the subject an effective amount of a compound of Formula (**I**), wherein the compound of Formula (**I**) is of the formula:



(**I**),

or a pharmaceutically acceptable salt thereof, wherein:

X is –O– or $–N(R^8)–$;

Y is –N= or $–C(R^6)=$;

R^1 and R^2 are each independently H or optionally substituted $(C_1\text{-}C_4)$alkyl; optionally, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of

halogen, hydroxyl, oxo, –$OCONR^8R^9$, –CO_2R^8, –$C(O)CO_2R^8$, –R^7, –OR^7, –NHR^8, –NR^7R^8, –$C(O)R^7$, –$CONHR^8$,
–$CONR^7R^8$, or –SO_2R^7;

each R^3 is independently halogen, –CN, –$O(C_1$-$C_4)$alkyl, or optionally substituted (C_1-C_4)alkyl;

R^4 and R^5 are each independently H or optionally substituted (C_1-C_4)alkyl; optionally, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, –$OCONR^8R^9$, –CO_2R^8, –$C(O)CO_2R^8$, –$SO_2(C_1$ $C_4)$alkyl, –R^7, –OR^7, –NHR^8, –NR^7R^8,
–$N(R^8)C(O)R^9$, –$N(R^8)SO_2R^9$, –$N(R^8)CONR^8R^9$, –$N(R^8)CON(R^8)SO_2R^9$, –$C(O)R^7$, –$CONHR^8$, –$CONR^7R^8$, or –$P(O)R^8R^9$;

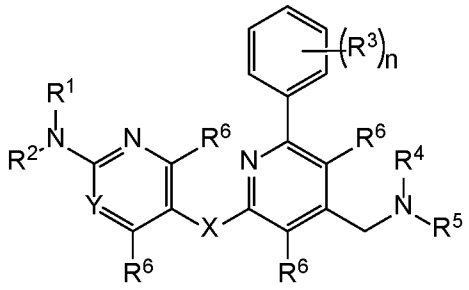
each R^6 is independently H, halogen, optionally substituted (C_1-C_4)alkyl, –OH, or optionally substituted (C_1-C_4)alkoxy;

each R^7 is independently (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, or (C_1-C_4)alkyl(C_3-C_6)cycloalkyl, each of which is optionally substituted with one or two of triazolyl, tetrazolyl, –CO_2R^8, –$CONR^8R^9$, –$CON(R^8)CO_2(C_1$-$C_4)$alkyl, hydroxyl, oxo, –(C_1-C_4)alkoxy, –$OCONR^8R^9$, –$OCON(R^8)C(O)R^9$, (C_1-C_4)alkyl, (C_1-C_4)alkylOH, –NR^8R^9, –$N(O)R^8R^9$, –$N(R^8)C(O)R^9$, –$N(R^8)CO_2(C_1$-$C_4)$alkyl, –$N(R^8)CH_2CO_2R^9$, –$N(R^8)CONR^8R^9$, –$N(R^8)CON(R^8)C(O)R^9$, –$N(R^8)CON(R^8)CO_2(C_1$-$C_4)$alkyl, –$N(R^8)SO_2R^9$, –$N(R^8)CON(R^8)SO_2R^9$, –$SO(C_1$-$C_4)$alkyl, –$SO_2(C_1$-$C_4)$alkyl, –SO_3R^8, –$SO_2NR^8R^9$, –$B(OH)_2$, –$P(O)R^8R^9$, or –$P(O)(OR^8)(OR^9)$;

each of R^8 and R^9 is independently H, optionally substituted (C_1-C_4)alkyl, or optionally substituted (C_3-C_6)cycloalkyl; and

n is 1, 2, 3, or 4.

3. A method of inhibiting the maturation of a coronaviridae family virus in a subject in need thereof, comprising administering to the subject an effective amount of a compound of Formula (**I**), wherein the compound of Formula (**I**) is of the formula:



(**I**),

or a pharmaceutically acceptable salt thereof, wherein:

X is –O– or –N(R^8)–;

Y is –N= or –C(R^6)=;

R^1 and R^2 are each independently H or optionally substituted (C_1-C_4)alkyl;

optionally, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, –OCONR^{8}R^9, –CO_2R^8, –C(O)CO_2R^8, –R^7, –OR^7, –NHR^8, –NR^7R^8, –C(O)R^7, –$CONHR^8$, –$CONR^7R^8$, or –SO_2R^7;

each R^3 is independently halogen, –CN, –O(C_1-C_4)alkyl, or optionally substituted (C_1-C_4)alkyl;

R^4 and R^5 are each independently H or optionally substituted (C_1-C_4)alkyl;

optionally, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, –OCONR^{8}R^9, –CO_2R^8, –C(O)CO_2R^8, –SO_2(C_1 C_4)alkyl, –R^7, –OR^7, –NHR^8, –NR^7R^8, –N(R^8)C(O)R^9, –N(R^8)SO_2R^9, –N(R^8)CONR^{8}R^9, –N(R^8)CON(R^8)SO_2R^9, –C(O)R^7, –$CONHR^8$, –$CONR^7R^8$, or –P(O)R^{8}R^9;

each R^6 is independently H, halogen, optionally substituted (C_1-C_4)alkyl, –OH, or optionally substituted (C_1-C_4)alkoxy;

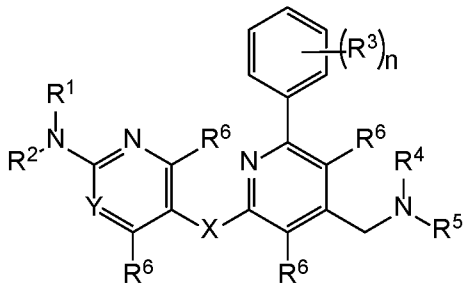
each R^7 is independently (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, or (C_1-C_4)alkyl(C_3-C_6)cycloalkyl, each of which is optionally substituted with one or two of triazolyl, tetrazolyl, –CO_2R^8, –CONR^{8}R^9, –CON(R^8)CO_2(C_1-C_4)alkyl, hydroxyl, oxo, –(C_1-

C_4)alkoxy, –$OCONR^8R^9$, –$OCON(R^8)C(O)R^9$, (C_1-C_4)alkyl, (C_1-C_4)alkylOH, –NR^8R^9, –$N(O)R^8R^9$, –$N(R^8)C(O)R^9$, –$N(R^8)CO_2$(C_1-C_4)alkyl, –$N(R^8)CH_2CO_2R^9$, –$N(R^8)CONR^8R^9$, –$N(R^8)CON(R^8)C(O)R^9$, –$N(R^8)CON(R^8)CO_2$(C_1-C_4)alkyl, –$N(R^8)SO_2R^9$, –$N(R^8)CON(R^8)SO_2R^9$, –SO(C_1-C_4)alkyl, –SO_2(C_1-C_4)alkyl, –SO_3R^8, –$SO_2NR^8R^9$, –$B(OH)_2$, –$P(O)R^8R^9$, or –$P(O)(OR^8)(OR^9)$;

each of R^8 and R^9 is independently H, optionally substituted (C_1-C_4)alkyl, or optionally substituted (C_3-C_6)cycloalkyl; and

n is 1, 2, 3, or 4.

4. A compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, for use in treating and/or preventing a viral infection resulting from a coronaviridae family virus in a subject in need thereof, wherein the compound of Formula (**I**) is of the formula:



(**I**),

or a pharmaceutically acceptable salt thereof, wherein:

X is –O– or –$N(R^8)$–;

Y is –N= or –$C(R^6)$=;

R^1 and R^2 are each independently H or optionally substituted (C_1-C_4)alkyl;

optionally, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, –$OCONR^8R^9$, –CO_2R^8, –$C(O)CO_2R^8$, –R^7, –OR^7, –NHR^8, –NR^7R^8, –$C(O)R^7$, –$CONHR^8$, –$CONR^7R^8$, or –SO_2R^7;

each R^3 is independently halogen, –CN, –O(C_1-C_4)alkyl, or optionally substituted (C_1-C_4)alkyl;

R^4 and R^5 are each independently H or optionally substituted (C_1-C_4)alkyl;

optionally, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen,

nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, –OCONR^{8}R^9, –CO$_2$R^8, –C(O)CO$_2$R^8, –SO$_2$(C$_1$ C$_4$)alkyl, –R^7, –OR^7, –NHR^8, –NR^{7}R^8, –N(R^8)C(O)R^9, –N(R^8)SO$_2$R^9, –N(R^8)CONR^{8}R^9, –N(R^8)CON(R^8)SO$_2$R^9, –C(O)R^7, –CONHR^8, –CONR^{7}R^8, or –P(O)R^{8}R^9;

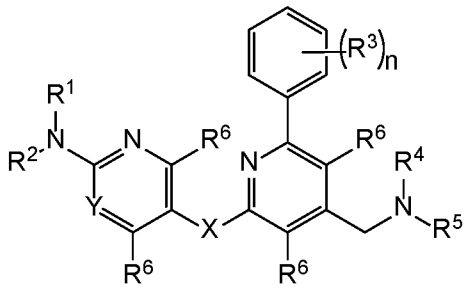
each R^6 is independently H, halogen, optionally substituted (C$_1$-C$_4$)alkyl, –OH, or optionally substituted (C$_1$-C$_4$)alkoxy;

each R^7 is independently (C$_1$-C$_6$)alkyl, (C$_2$-C$_6$)alkenyl, halo(C$_1$-C$_6$)alkyl, (C$_3$-C$_6$)cycloalkyl, or (C$_1$-C$_4$)alkyl(C$_3$-C$_6$)cycloalkyl, each of which is optionally substituted with one or two of triazolyl, tetrazolyl, –CO$_2$R^8, –CONR^{8}R^9, –CON(R^8)CO$_2$(C$_1$-C$_4$)alkyl, hydroxyl, oxo, –(C$_1$-C$_4$)alkoxy, –OCONR^{8}R^9, –OCON(R^8)C(O)R^9, (C$_1$-C$_4$)alkyl, (C$_1$-C$_4$)alkylOH, –NR^{8}R^9, –N(O)R^{8}R^9, –N(R^8)C(O)R^9, –N(R^8)CO$_2$(C$_1$-C$_4$)alkyl, –N(R^8)CH$_2$CO$_2$R^9, –N(R^8)CONR^{8}R^9, –N(R^8)CON(R^8)C(O)R^9, –N(R^8)CON(R^8)CO$_2$(C$_1$-C$_4$)alkyl, –N(R^8)SO$_2$R^9, –N(R^8)CON(R^8)SO$_2$R^9, –SO(C$_1$-C$_4$)alkyl, –SO$_2$(C$_1$-C$_4$)alkyl, –SO$_3$R^8, –SO$_2$NR^{8}R^9, –B(OH)$_2$, –P(O)R^{8}R^9, or –P(O)(OR^8)(OR^9);

each of R^8 and R^9 is independently H, optionally substituted (C$_1$-C$_4$)alkyl, or optionally substituted (C$_3$-C$_6$)cycloalkyl; and

n is 1, 2, 3, or 4.

5. Use of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment and/or prevention of a viral infection resulting from a coronaviridae family virus in a subject in need thereof, wherein the compound of Formula (**I**) is of the formula:



(**I**),

or a pharmaceutically acceptable salt thereof, wherein:

X is –O– or –N(R^8)–;

Y is –N= or –C(R^6)=;

R^1 and R^2 are each independently H or optionally substituted (C$_1$-C$_4$)alkyl; optionally, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring,

optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, $–OCONR^8R^9$, $–CO_2R^8$, $–C(O)CO_2R^8$, $–R^7$, $–OR^7$, $–NHR^8$, $–NR^7R^8$, $–C(O)R^7$, $–CONHR^8$, $–CONR^7R^8$, or $–SO_2R^7$;

each R^3 is independently halogen, –CN, $–O(C_1\text{-}C_4)$alkyl, or optionally substituted $(C_1\text{-}C_4)$alkyl;

R^4 and R^5 are each independently H or optionally substituted $(C_1\text{-}C_4)$alkyl;

optionally, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, $–OCONR^8R^9$, $–CO_2R^8$, $–C(O)CO_2R^8$, $–SO_2(C_1\ C_4)$alkyl, $–R^7$, $–OR^7$, $–NHR^8$, $–NR^7R^8$, $–N(R^8)C(O)R^9$, $–N(R^8)SO_2R^9$, $–N(R^8)CONR^8R^9$, $–N(R^8)CON(R^8)SO_2R^9$, $–C(O)R^7$, $–CONHR^8$, $–CONR^7R^8$, or $–P(O)R^8R^9$;

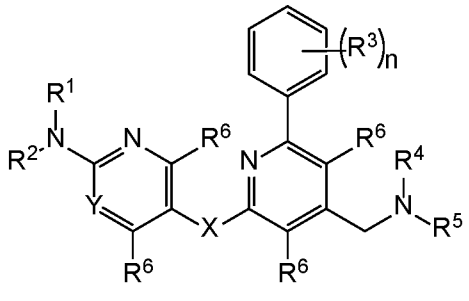
each R^6 is independently H, halogen, optionally substituted $(C_1\text{-}C_4)$alkyl, –OH, or optionally substituted $(C_1\text{-}C_4)$alkoxy;

each R^7 is independently $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, or $(C_1\text{-}C_4)$alkyl$(C_3\text{-}C_6)$cycloalkyl, each of which is optionally substituted with one or two of triazolyl, tetrazolyl, $–CO_2R^8$, $–CONR^8R^9$, $–CON(R^8)CO_2(C_1\text{-}C_4)$alkyl, hydroxyl, oxo, $–(C_1\text{-}C_4)$alkoxy, $–OCONR^8R^9$, $–OCON(R^8)C(O)R^9$, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkylOH, $–NR^8R^9$, $–N(O)R^8R^9$, $–N(R^8)C(O)R^9$, $–N(R^8)CO_2(C_1\text{-}C_4)$alkyl, $–N(R^8)CH_2CO_2R^9$, $–N(R^8)CONR^8R^9$, $–N(R^8)CON(R^8)C(O)R^9$, $–N(R^8)CON(R^8)CO_2(C_1\text{-}C_4)$alkyl, $–N(R^8)SO_2R^9$, $–N(R^8)CON(R^8)SO_2R^9$, $–SO(C_1\text{-}C_4)$alkyl, $–SO_2(C_1\text{-}C_4)$alkyl, $–SO_3R^8$, $–SO_2NR^8R^9$, $–B(OH)_2$, $–P(O)R^8R^9$, or $–P(O)(OR^8)(OR^9)$;

each of R^8 and R^9 is independently H, optionally substituted $(C_1\text{-}C_4)$alkyl, or optionally substituted $(C_3\text{-}C_6)$cycloalkyl;

n is 1, 2, 3, or 4.

6. A pharmaceutical composition comprising a compound of Formula (**I**), for use in the methods of any one of the preceding claims, wherein the compound of Formula (**I**) is of the formula:



(**I**),

or a pharmaceutically acceptable salt thereof, wherein:

X is –O– or –N(R^8)–;

Y is –N= or –C(R^6)=;

R^1 and R^2 are each independently H or optionally substituted (C_1-C_4)alkyl;

optionally, R^1 and R^2 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, –OCONR^{8}R^9, –CO_2R^8, –C(O)CO_2R^8, –R^7, –OR^7, –NHR^8, –NR^7R^8, –C(O)R^7, –$CONHR^8$, –$CONR^7R^8$, or –SO_2R^7;

each R^3 is independently halogen, –CN, –O(C_1-C_4)alkyl, or optionally substituted (C_1-C_4)alkyl;

R^4 and R^5 are each independently H or optionally substituted (C_1-C_4)alkyl;

optionally, R^4 and R^5 taken together with the nitrogen atom to which they are attached form a 4-11 membered monocyclic, fused bicyclic, bridged, or spiro-bicyclic saturated ring, optionally containing one or two additional heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, –OCONR^{8}R^9, –CO_2R^8, –C(O)CO_2R^8, –SO_2(C_1 C_4)alkyl, –R^7, –OR^7, –NHR^8, –NR^7R^8, –N(R^8)C(O)R^9, –N(R^8)SO_2R^9, –N(R^8)CONR^{8}R^9, –N(R^8)CON(R^8)SO_2R^9, –C(O)R^7, –$CONHR^8$, –$CONR^7R^8$, or –P(O)R^{8}R^9;

each R^6 is independently H, halogen, optionally substituted (C_1-C_4)alkyl, –OH, or optionally substituted (C_1-C_4)alkoxy;

each R^7 is independently (C_1-C_6)alkyl, (C_2-C_6)alkenyl, halo(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, or (C_1-C_4)alkyl(C_3-C_6)cycloalkyl, each of which is optionally substituted with one or two of triazolyl, tetrazolyl, –CO_2R^8, –CONR^{8}R^9, –CON(R^8)CO_2(C_1-C_4)alkyl,

hydroxyl, oxo, –(C_1-C_4)alkoxy, –$OCONR^8R^9$, –$OCON(R^8)C(O)R^9$, (C_1-C_4)alkyl, (C_1-C_4)alkylOH, –NR^8R^9, –$N(O)R^8R^9$, –$N(R^8)C(O)R^9$, –$N(R^8)CO_2$(C_1-C_4)alkyl, –$N(R^8)CH_2CO_2R^9$, –$N(R^8)CONR^8R^9$, –$N(R^8)CON(R^8)C(O)R^9$, –$N(R^8)CON(R^8)CO_2$(C_1-C_4)alkyl, –$N(R^8)SO_2R^9$, –$N(R^8)CON(R^8)SO_2R^9$, –SO(C_1-C_4)alkyl, –SO_2(C_1-C_4)alkyl, –SO_3R^8, –$SO_2NR^8R^9$, –$B(OH)_2$, –$P(O)R^8R^9$, or –$P(O)(OR^8)(OR^9)$;

each of R^8 and R^9 is independently H, optionally substituted (C_1-C_4)alkyl, or optionally substituted (C_3-C_6)cycloalkyl; and

n is 1, 2, 3, or 4.

7. The method, compound, pharmaceutical composition, or use of any one of claims 1-6, further comprising administering an additional pharmaceutical agent.

8. The method, compound, pharmaceutical composition, or use of claim 7, wherein the additional pharmaceutical agent is an antiviral agent.

9. The method, compound, pharmaceutical composition, or use of claim 8, wherein the antiviral agent is Abacavir, Acyclovir, Amantadine, Atazanavir, Chloroquine, Darunavir, Elvitegravir, Fosamprenavir, Ganciclovir, Indinavir, Ledipasvir, Lopinavir, Nitazoxanide, Oseltamivir, Penciclovir, Peramivir, Raltegravir, Ribavirin, Rimantadine, Ritonavir, Saquinavir, Sofosbuvir, Tipranavir, Velpatasvir, Zanamivirfavipiravir, remdesivir, Oya1, galidesivir, umifenovir, or hydroxychloroquine.

10. The method, compound, pharmaceutical composition, or use of claim any one of claims 1-6, wherein the additional pharmaceutical agent is an antibacterial agent.

11. The method, compound, pharmaceutical composition, or use of claim 10, wherein the antibacterial agent is azithromycin.

12. The method, compound, pharmaceutical composition, or use of claim 7, wherein the additional pharmaceutical agent is an anti-inflammatory agent.

13. The method, compound, pharmaceutical composition, or use of claim 12, wherein the anti-inflammatory agent is Gimsilumab, IL-6 antibodies, actemra, paracetamol, or non-steroidal anti-inflammatory drugs (NSAIDs).

14. The method, compound, pharmaceutical composition, or use of claim 7, wherein the additional pharmaceutical agent is human antibodies to SARS-CoV-2.

15. The method, compound, pharmaceutical composition, or use of claim 7, wherein the additional pharmaceutical agent is antibodies that bind the S-spike protein of SARS-CoV-2.

16. The method, compound, pharmaceutical composition, or use of claim 7, wherein the additional pharmaceutical agent is a serine protease inhibitor.

17. The method, compound, pharmaceutical composition, or use of claim 16, wherein the serine protease inhibitor is a TMPRSS2 inhibitor.

18. The method, compound, pharmaceutical composition, or use of claim 16 or 17, wherein the serine protease inhibitor is camostat.

19. The method, compound, pharmaceutical composition, or use of claim 7, wherein the additional pharmaceutical agent is an ACE2 inhibitor.

20. The method, compound, pharmaceutical composition, or use of claim 19, wherein the ACE2 inhibitor is benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, or trandolapril.

21. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 20, wherein the coronaviridae family virus is an alphacoronavirus.

22. The method, compound, pharmaceutical composition, or use of claim 21, wherein the alphacoronavirus is HCoV-NL63.

23. The method, compound, pharmaceutical composition, or use of claim 21, wherein the alphacoronavirus is HCoV-229E.

24. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 20, wherein the coronaviridae family virus is a betacoronavirus.

25. The method, compound, pharmaceutical composition, or use of claim 24, wherein the betacoronavirus is SARS-CoV.

26. The method, compound, pharmaceutical composition, or use of claim 24, wherein the betacoronavirus is SARS-CoV-2.

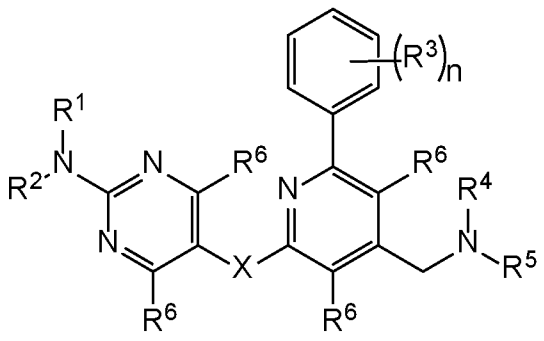
27. The method, compound, pharmaceutical composition, or use of claim 24, wherein the betacoronavirus is MERS-CoV.

28. The method, compound, pharmaceutical composition, or use of claim 24, wherein the betacoronavirus is HCoV-OC43.

29. The method, compound, pharmaceutical composition, or use of claim 24, wherein the betacoronavirus is HCoV-HKU1.

30. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 29, wherein Y is –N=.

31. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 30, wherein the compound of Formula (**I**) is of Formula (**II**):

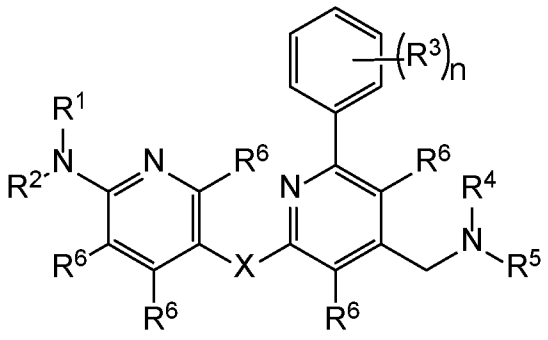


(**II**),

or a pharmaceutically acceptable salt thereof.

32. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 30, wherein Y is –C(R^6)=.

33. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 30, or 31, wherein the compound of Formula (**I**) is of Formula (**III**):



(**III**),

or a pharmaceutically acceptable salt thereof.

34. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 33, wherein R^3 is halogen.

35. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 34, wherein R^3 is –Cl.

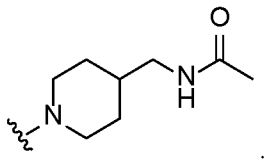
36. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 35, wherein n is 2.

37. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 36, wherein X is –O–.

38. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 37, wherein R^4 and R^5 taken together with the nitrogen atom to which they are attached form a 4-11 membered heterocyclic ring, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, $–OCONR^8R^9$, $–CO_2R^8$, $–C(O)CO_2R^8$, $–SO_2(C_1\ C_4)$alkyl, $–R^7$, $–OR^7$, $–NHR^8$, $–NR^7R^8$, $–N(R^8)C(O)R^9$, $–N(R^8)SO_2R^9$, $–N(R^8)CONR^8R^9$, $–N(R^8)CON(R^8)SO_2R^9$, $–C(O)R^7$, $–CONHR^8$, $–CONR^7R^8$, or $–P(O)R^8R^9$.

39. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 38, wherein R^4 and R^5 taken together with the nitrogen atom to which they are attached form an optionally substituted pyrrolidine, pyrazolidine, imidazolidine, piperidine, piperazine, or morpholine ring.

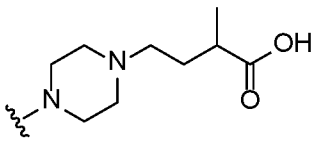
40. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 39, wherein R^4 and R^5 taken together with the nitrogen atom to which they are attached form a heterocyclic ring of the formula:



41. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 40, wherein R^1 and R^2 taken together with the nitrogen atom to which they are attached form a 4-11 membered heterocyclic ring, wherein said ring is optionally substituted with one, two, or three of halogen, hydroxyl, oxo, $-OCONR^8R^9$, $-CO_2R^8$, $-C(O)CO_2R^8$, $-R^7$, $-OR^7$, $-NHR^8$, $-NR^7R^8$, $-C(O)R^7$, $-CONHR^8$, $-CONR^7R^8$, or $-SO_2R^7$.

42. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 37, wherein R^1 and R^2 taken together with the nitrogen atom to which they are attached form an optionally substituted an optionally substituted pyrrolidine, pyrazolidine, imidazolidine, piperidine, piperazine, or morpholine ring.

43. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 31 or 34 to 42, wherein R^1 and R^2 taken together with the nitrogen atom to which they are attached form a piperazine ring of the formula:



44. The method, compound, pharmaceutical composition, or use of any claims 1 to 31, or 34 to 43, wherein the compound, or pharmaceutically acceptable salt thereof, is:

1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfinyl)butyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(4-(methylsulfonyl)butan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(4-(methylsulfonyl)butan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(4-hydroxybutan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(1-hydroxypropan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-hydroxycyclobutyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(1,3-dihydroxypropan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-((1s,3s)-3-hydroxy-3-methylcyclobutyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-((1r,3r)-3-hydroxy-3-methylcyclobutyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

1-(2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)-N-methylmethanamine;

1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propane-1-sulfonamide;

methyl((1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-fluoro-4-(((methoxycarbonyl)amino)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)ethanol;

2-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)oxy)acetic acid;

3-(4-(5-((4-((4-(2-(carbamoyloxy)ethyl)piperazin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid;

3-(3-(5-((6-(3,5-dichlorophenyl)-4-((4-(((methoxycarbonyl)amino)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)propanoic acid;

4-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(2-hydroxyethyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylbutanoic acid;

4-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(propionamidomethyl)piperidin-1-yl)methyl) pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylbutanoic acid;

4-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-fluoropiperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)butan-2-ol;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3-chloro-5-(difluoromethyl)phenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(((methoxycarbonyl)amino)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid;

methyl ((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate;

N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate;

1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

N-((1-((2-(3,5-dichlorophenyl)-6-((2-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

5-((4-((4-((1H-tetrazol-5-yl)methyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)-2-(4-methylpiperazin-1-yl)pyrimidine;

(1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate;

1-((1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

3-(4-(5-((4-((4-(3-amino-3-oxopropyl)piperazin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid;

3-(4-(5-((4-((4-(2-amino-2-oxoethyl)piperazin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-(((1R,7S,8r)-8-(methylsulfonamido)-4-azabicyclo[5.1.0]octan-4-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid;

4-(4-(5-((6-(3,5-dichlorophenyl)-4-(((1R,7S,8r)-8-(methylsulfonamido)-4-azabicyclo[5.1.0]octan-4-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylbutanoic acid;

4-(4-(5-((4-(((1R,7S,8r)-8-acetamido-4-azabicyclo[5.1.0]octan-4-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylbutanoic acid;

4-(4-(5-((6-(3,5-dichlorophenyl)-4-(pyrrolidin-1-ylmethyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylbutanoic acid;

3-(4-(5-((4-((4-(cyclopropanecarboxamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetamide;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)ethanesulfonamide;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-N-methylpropanamide;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)butanamide;

4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)butanamide;

N-((1-((2-((2-(1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-((2-(4-aminopiperidin-1-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

2-((1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)oxy)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(6-hydroxy-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-((2-(4-amino-4-(2-hydroxyethyl)piperidin-1-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

((1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)dimethylphosphineoxide;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

3-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)azetidin-3-yl)butanoic acid;

2-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)pyrrolidin-3-yl)oxy)acetic acid;

2-(2-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)octahydrocyclopenta[c]pyrrol-5-yl)acetic acid;

3-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)propanoic acid;

3-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)-2-methylpropanoic acid;

2-(1-((2-((2-(1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

(S)-3-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)-2-methylpropanoic acid;

1-(7-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-hydroxyethanone;

(R)-3-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)-2-methylpropanoic acid;

1-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)propan-2-ol;

3-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)-2-hydroxypropanoic acid;

2-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)oxy)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetamide;

1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)oxy)cyclopropanecarboxylic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(6-methoxy-4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(6-hydroxy-4,6-dimethyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(6-fluoro-4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((4-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(3-(methylamino)pyrrolidin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

(S)-2-(4-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)-1,4-oxazepan-7-yl)ethanol;

N-((1R,5S,6r)-3-((2-(3,5-dichlorophenyl)-6-((2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)-3-azabicyclo[3.1.0]hexan-6-yl)acetamide;

1-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)propan-2-one;

2-(1-((2-((2-(4-aminopiperidin-1-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

(S)-2-(1-((2-(3,5-dichlorophenyl)-6-((2-(3-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(3,3-dimethylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-((2-(3,6-diazabicyclo[3.1.1]heptan-3-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-((2-(3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-((2-(4,7-diazaspiro[2.5]octan-7-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-((2-(4-amino-4-(hydroxymethyl)piperidin-1-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

methyl (3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoyl)carbamate;

1-(2-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)ethyl)cyclopropanecarboxylic acid;

methyl (3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoyl)carbamate;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2,3-dihydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfinyl)butyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)butyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

4-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(((methylcarbamoyl)oxy)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)pentanoic acid;

(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(4-hydroxybutan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate;

(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(((methylcarbamoyl)oxy)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)cyclobutanecarboxylic acid;

N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)butyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)pentanoic acid;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)cyclobutanecarboxylic acid;

1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)butyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)cyclobutanecarboxylic acid;

4-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(((methoxycarbonyl)amino)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)pentanoic acid;

methyl ((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate;

2-((1R,7S,8r)-4-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)-4-azabicyclo[5.1.0]octan-8-yl)acetic acid;

2-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)oxy)-2-methylpropanoic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(6-hydroxy-4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(dimethylamino)piperidin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-((1-hydroxycyclopropyl)methyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-ethyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-((1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-((2-(4-cyclopropylpiperazin-1-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-ethylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-isopropylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-fluoroethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-hydroxybutyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(4-hydroxybutan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(4-(methylamino)butan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(4-(dimethylamino)butan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-((methylcarbamoyl)oxy)ethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-methoxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-sulfamoylpropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-methoxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(((methylcarbamoyl)oxy)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid;

N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-sulfamoylpropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid;

1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanamide;

1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-methoxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-hydroxy-4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanamide;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(((ethoxycarbonyl)amino)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(2-(ethylamino)-2-oxoethyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid;

3-(1-((2-(3,5-dichlorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)-2-methylpropanoic acid;

3-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)propanoic acid;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3-chloro-4,5-difluorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanamide;

1-((1-((2-(3-chloro-5-fluorophenyl)-6-((2-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

methyl ((1-((2-(3-chloro-5-fluorophenyl)-6-((2-(piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-(1-hydroxycyclopropyl)ethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-hydroxy-3-methylbutyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-hydroxy-2,2-dimethylpropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)butanoic acid;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylpropanoic acid;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylpropanamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-sulfamoylethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylpropanamide;

(S)-3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(((methoxycarbonyl)amino)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)-2-methylpiperazin-1-yl)propanoic acid;

1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-hydroxybutyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

3-(3-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)propanoic acid;

methyl3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoate;

(R)-2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

3-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-((R)-2-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)-2-methylpropanoic acid;

(R)-N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxy-2-methylpropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(3-fluoro-2-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate;

(R)-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate;

(R)-1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

methyl ((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate;

(R)-methyl ((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate;

N-((1-((2-(3-chloro-5-fluorophenyl)-6-((2-(4-(2-hydroxyethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-hydroxypropanoic acid;

(R)-2-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-(2-hydroxypropyl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)oxy)acetic acid;

((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)boronic acid;

(2-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)ethyl)boronic acid;

((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)dimethylphosphineoxide;

(1R,7S,8r)-4-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)-4-azabicyclo[5.1.0]octane-8-carboxylic acid;

((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)boronic acid;

(2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)ethyl)boronic acid;

(1-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylacetylcarbamate;

N-1-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-N'-methoxylcarbonylurea;

N-(((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamoyl)methanesulfonamide;

N-(((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamoyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)carbamoyl)methanesulfonamide;

1-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)urea;

(S)-(4-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)-1,4-oxazepan-7-yl)methanol;

(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)dimethylphosphineoxide;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)amino)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-((2-(1,4-diazabicyclo[3.2.1]octan-4-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

N-((1-((2-((2-(3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

methyl ((1-((2-((2-(1,4-diazabicyclo[3.2.1]octan-4-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate;

4-((2-((2-(1,4-diazabicyclo[3.2.1]octan-4-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)-4-azabicyclo[5.1.0]octane-8-carboxylic acid;

4-(5-((6-(3,5-dichlorophenyl)-4-((4-fluoropiperidin-1-yl)methyl)pyridin-2-yl)oxy)pyrimidin-2-yl)-1,4-diazabicyclo[3.2.1]octane;

3-(4-(5-((4-(((1R,7S,8r)-8-acetamido-4-azabicyclo[5.1.0]octan-4-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)propanoic acid;

methyl4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylbutanoate;

4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylbutanoic acid;

4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2,2-dimethylbutanoic acid;

N-((1-((2-(3-chloro-5-fluorophenyl)-6-((2-(4-(4-(methylsulfonyl)butan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

1-((1-((2-(3-chloro-5-fluorophenyl)-6-((2-(4-(4-(methylsulfonyl)butan-2-yl)piperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

2-(1-((2-(3-chloro-5-fluorophenyl)-6-((2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-(isopropyl(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)amino)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((6-(3,5-dichlorophenyl)-3-fluoro-2-((2-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((6-(3,5-dichlorophenyl)-3-fluoro-2-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((6-(3,5-dichlorophenyl)-3-fluoro-2-((4-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)-3-fluoropyridin-2-yl)oxy)pyrimidin-2-yl)piperazin-1-yl)-2-methylbutanoic acid;

2-(1-((2-((2-(3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)-3-fluoropyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-((2-(4-((1H-1,2,3-triazol-5-yl)methyl)piperazin-1-yl)pyrimidin-5-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-(methyl(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)amino)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-(ethyl(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)amino)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

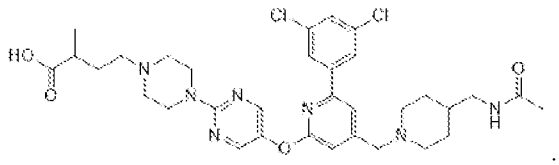
(1R,7S,8r)-4-((2-(3,5-dichlorophenyl)-6-((2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)-4-azabicyclo[5.1.0]octane-8-carboxylic acid;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid; or

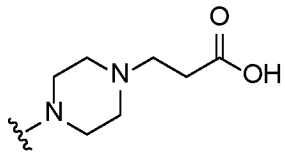
2-(1-((2-(3,5-dichlorophenyl)-6-((2-(6-fluoro-1,4-diazepan-1-yl)pyrimidin-5-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetic acid;

or a pharmaceutically acceptable salt thereof.

45. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 31 or 34 to 44, wherein the compound, or pharmaceutically acceptable salt thereof, is of the formula:



46. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 29 or 32 to 37, wherein R^1 and R^2 taken together with the nitrogen atom to which they are attached form a piperazine ring of the formula:



47. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 29, 32 to 42 or 46, wherein the compound, or pharmaceutically acceptable salt thereof, is:

2-(4-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperazin-1-yl)-N-methylacetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)-4-hydroxypiperidin-4-yl)methyl)acetamide;

3-(1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)propanoicacid;

2-(1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid;

1-((1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)-4-hydroxypiperidin-4-yl)methyl)-3-methylurea;

methyl((1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)-4-hydroxypiperidin-4-yl)methyl)carbamate;

2-(1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)ethanesulfonicacid;

(1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methanesulfonicacid;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

2-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)aceticacid;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanamide;

N-((1-((2-((6-(4-(2-(1H-tetrazol-5-yl)ethyl)piperazin-1-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-(methylsulfinyl)ethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(4-(methylsulfonyl)butan-2-yl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-((trans)-3-(methylsulfonamido)cyclobutyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-((cis)-3-(methylsulfonamido)cyclobutyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-((6-(4-(2-aminoethyl)piperazin-1-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2,4-dihydroxybutyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

(2-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)ethyl)phosphonicacid;

2-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)ethylcarbamate;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-(N-methylmethylsulfonamido)ethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-((1-(hydroxymethyl)cyclopropyl)methyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-((1-hydroxycyclopropyl)methyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)-N-ethylacetamide;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(sulfamoylmethyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((methylsulfonyl)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid;

1-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-hydroxyethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(methylsulfonamidomethyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((methylamino)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid;

3-(4-(5-((4-((4-(2-(carbamoyloxy)ethyl)piperazin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid;

3-(4-(5-((4-((4-(cyclopropanecarboxamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid;

methyl((1-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate;

(1-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate;

1-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

(1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate;

methyl((1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(((methylcarbamoyl)oxy)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((dimethylphosphoryl)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid;

N-((1-((2-(3,5-dichlorophenyl)-6-((5-fluoro-6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)-4-hydroxypiperidin-4-yl)methyl)acetamide;

1-(5-((6-(3-chloro-5-methylphenyl)-4-((methylamino)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperidin-4-amine;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3-chloro-5-fluorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3-bromo-5-fluorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid;

2-(1-((2-(3,5-dichlorophenyl)-6-((6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)-N,N-dimethylethanamineoxide;

N-((1-((2-(3,5-dichlorophenyl)-6-((5-fluoro-6-(piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

(1R,7S,8r)-4-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)-4-azabicyclo[5.1.0]octane-8-carboxylicacid;

9-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)-2-oxa-4,9-diazaspiro[5.5]undecan-3-one;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(6-fluoro-4-methyl-1,4-diazepan-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

2-(1-((2-(3,5-dichlorophenyl)-6-((2-methyl-6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid;

2-(1-((2-(3,5-dichlorophenyl)-6-((5-fluoro-6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid;

2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-methyl-1,4-diazepan-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid;

2-(1-((2-((6-(1,4-diazepan-1-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid;

4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)-2-methylbutanoicacid;

methyl(3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoyl)carbamate;

4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)-1-methylpiperazine1-oxide;

4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)-1,1-bis(2-hydroxyethyl)piperazin-1-ium;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-hydroxyethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)-1,1-dimethylpiperazin-1-ium;

N-((1-((2-((6-(4-amino-3-fluoropiperidin-1-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-((1S,4S)-5-(2-(methylsulfonyl)ethyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-((6-((3S,4R)-3-(aminomethyl)-4-hydroxypyrrolidin-1-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

3-((1R,5S)-3-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)propanoicacid;

(S)-3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)-2-methylpiperazin-1-yl)propanoicacid;

2-(1-((2-((6-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid;

4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)-2-ethylbutanoicacid;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)-2,2-dimethylpropanoicacid;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)-1,4-diazepan-1-yl)propanoicacid;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)-2,2-dimethylpiperazin-1-yl)propanoicacid;

N-((1-((2-((6-(1,4-diazepan-1-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(methylamino)piperidin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(3-(hydroxymethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-((6-(4-aminopiperidin-1-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(3,3-dimethylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-((6-(4-amino-3,3-dimethylpiperidin-1-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-((6-(2,7-diazaspiro[4.4]nonan-2-yl)pyridin-3-yl)oxy)-6-(3,5-dichlorophenyl)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

2-(1-((2-(3,5-dichlorophenyl)-6-((6-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid;

2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid;

3-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)-2-methylpropanoicacid;

methyl((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)carbamate;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)butyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

1-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)butyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid;

2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-methoxyethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid;

4-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)butanoicacid;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-methoxyethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-sulfamoylpropyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid;

1-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-methoxyethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

1-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propane-1-sulfonamide;

2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)acetamide;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)-3-fluoropyridin-2-yl)piperazin-1-yl)propanoicacid;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-((3-methylureido)methyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)-3-fluoropyridin-2-yl)piperazin-1-yl)propanoicacid;

3-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(3-(methylsulfonyl)propyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)propanoicacid;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(2-(methylsulfonyl)ethyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid;

3-(4-(5-((6-(3,5-dichlorophenyl)-4-((4-(2-sulfamoylethyl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoicacid;

3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)butanoicacid;

2-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)ethanesulfonicacid;

2-((4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)methyl)butanoicacid;

N-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-sulfamoylethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)acetamide;

1-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

(R)-2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-hydroxypropyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid;

2-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-hydroxyethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid;

(R)-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-hydroxypropyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methylmethylcarbamate;

(R)-1-((1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-hydroxypropyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)methyl)-3-methylurea;

3-(1-((2-(3,5-dichlorophenyl)-6-((6-(4-(2-hydroxyethyl)piperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)propanoicacid;

2-(1-((6-(3,5-dichlorophenyl)-3-fluoro-2-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid;

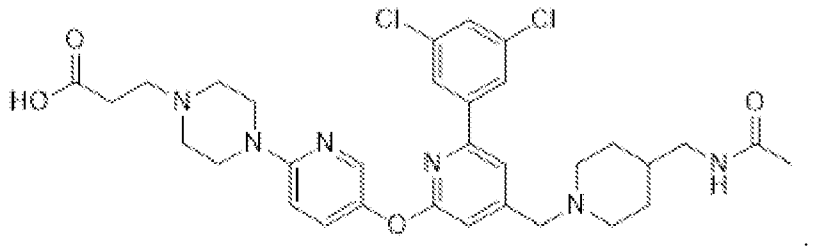
2-(1-((6-(3,5-dichlorophenyl)-3-fluoro-2-((2-methyl-6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid;

methyl3-(4-(5-((4-((4-(acetamidomethyl)piperidin-1-yl)methyl)-6-(3,5-dichlorophenyl)pyridin-2-yl)oxy)pyridin-2-yl)piperazin-1-yl)propanoate; or

2-(1-((6-(3,5-dichlorophenyl)-3-methyl-2-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)oxy)pyridin-4-yl)methyl)piperidin-4-yl)aceticacid;

or a pharmaceutically acceptable salt thereof.

48. The method, compound, pharmaceutical composition, or use of any one of claims 1 to 29, 32 to 42, 46, or 47, wherein the compound, or pharmaceutically acceptable salt thereof, is of the formula:



49. A method of identifying a compound useful for treating or preventing a viral infection resulting from a coronaviridae family virus, the method comprising:

(i) providing a test compound or a pharmaceutically acceptable salt thereof;

(ii) contacting a cell with the compound, wherein the cell expresses the pro-(S) protein of the virus; and

(iii) determining if the pro-(S) protein has been processed by furin or an endogenous furin-like enzyme.

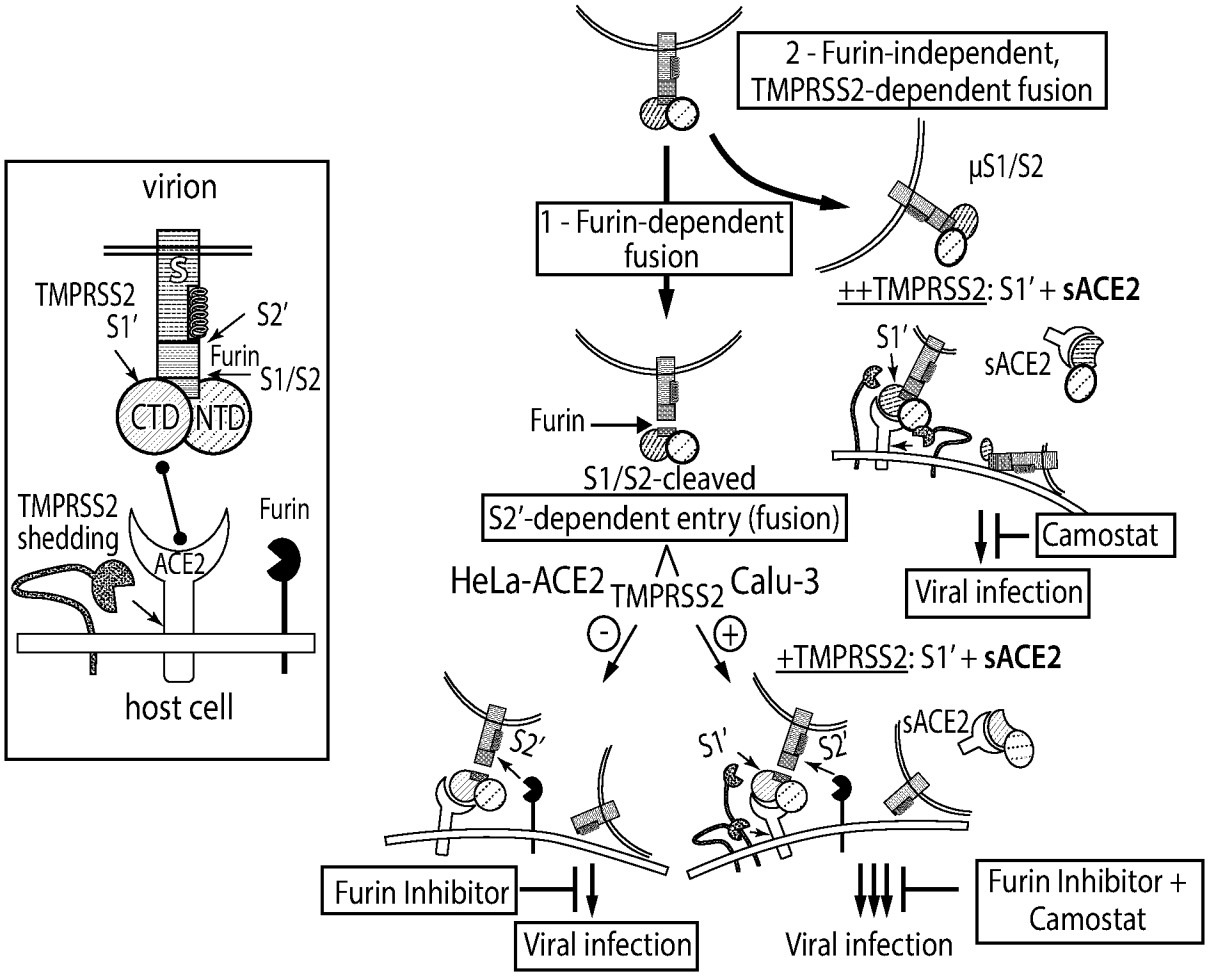

virion
S
TMPRSS2
S1′
S2′
Furin
S1/S2
CTD
NTD
TMPRSS2
shedding
ACE2
Furin
host cell
2 - Furin-independent,
TMPRSS2-dependent fusion
μS1/S2
1 - Furin-dependent
fusion
++TMPRSS2: S1′ + sACE2
S1′
sACE2
Furin
S1/S2-cleaved
S2′-dependent entry (fusion)
Camostat
HeLa-ACE2
TMPRSS2
Calu-3
Viral infection
+TMPRSS2: S1′ + sACE2
S2′
S1′
S2′
sACE2
Furin Inhibitor
Viral infection
Viral infection
Furin Inhibitor +
Camostat
Furin inhibitor + Camostat

Figure 1

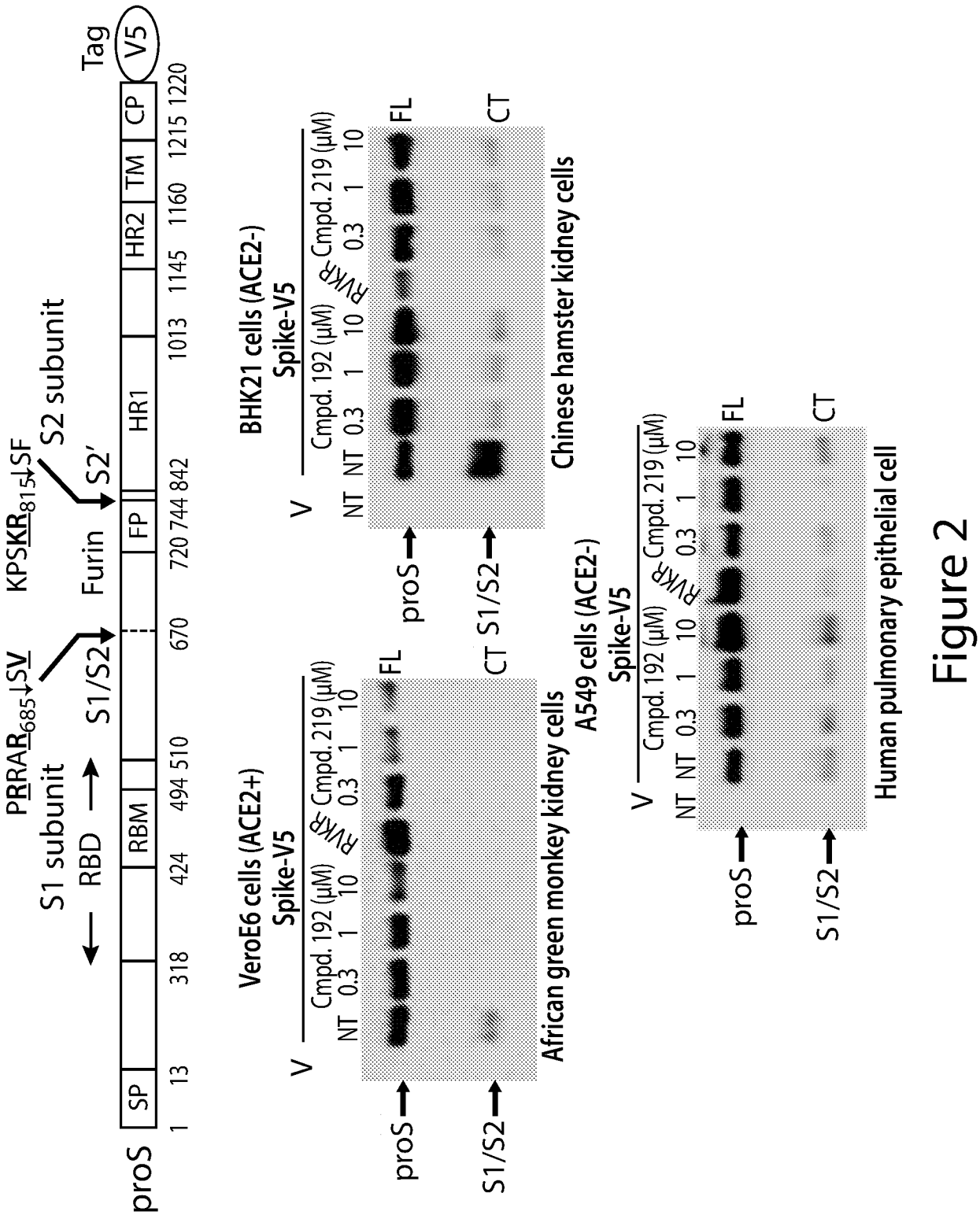

proS
SP
RBM
HR1
FP
HR2
TM
CP
Tag
V5
S1 subunit
RBD
S1/S2
Furin
S2 subunit
S2′
PRRAR685↓SV
KPSKR815↓SF
1 13 318 424 494 510 670 720 744 842 1013 1145 1160 1215 1220
VeroE6 cells (ACE2+)
Spike-V5
African green monkey kidney cells
BHK21 cells (ACE2-)
Spike-V5
Chinese hamster kidney cells
A549 cells (ACE2-)
Spike-V5
Human pulmonary epithelial cell
V
NT NT 0.3 1 10 RVKR 0.3 1 10
Cmpd. 192 (μM)
Cmpd. 219 (μM)
FL
CT
proS
S1/S2

Figure 2

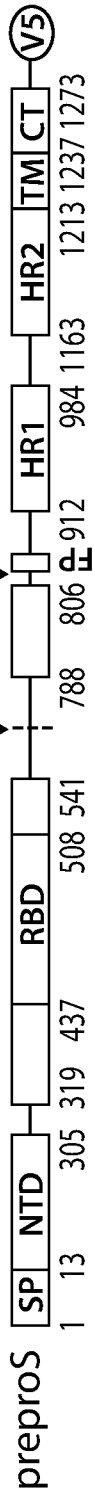


Figure 3A

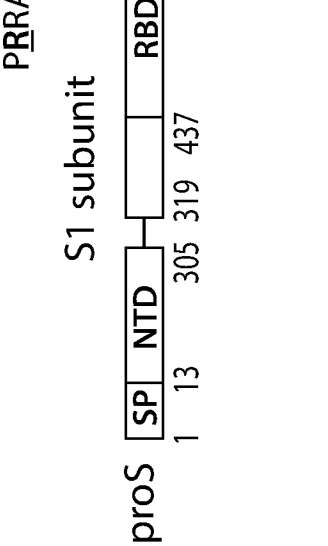


Figure 3B

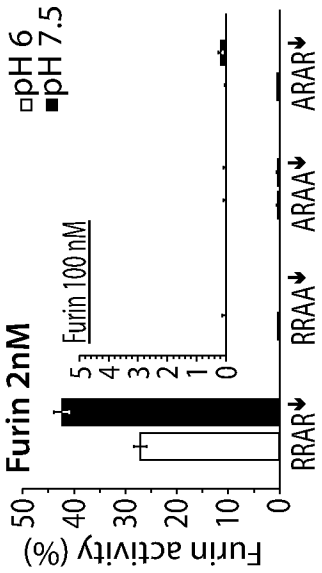


Figure 3C

Figure 3D

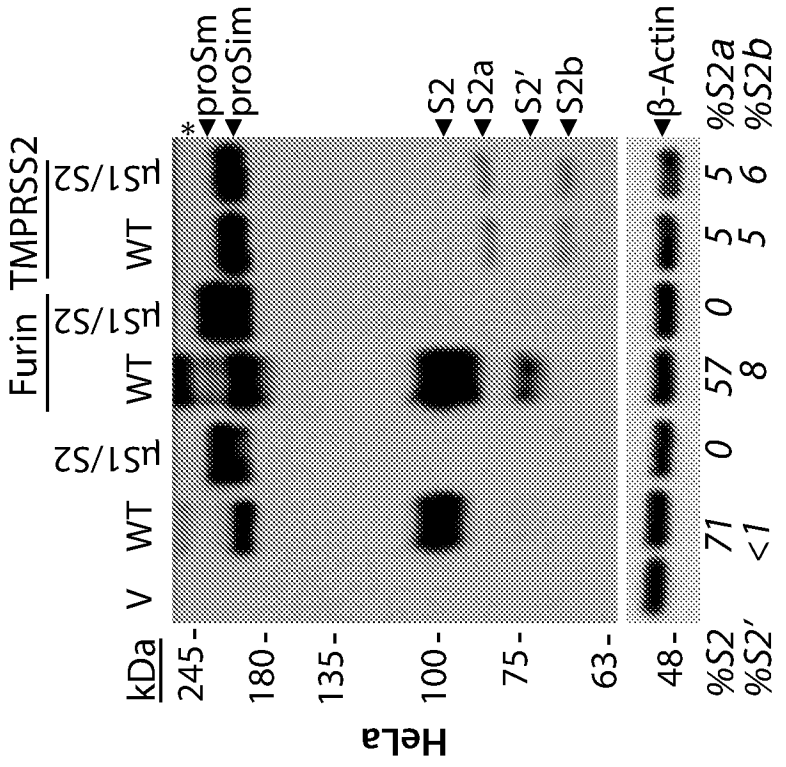


Figure 3F

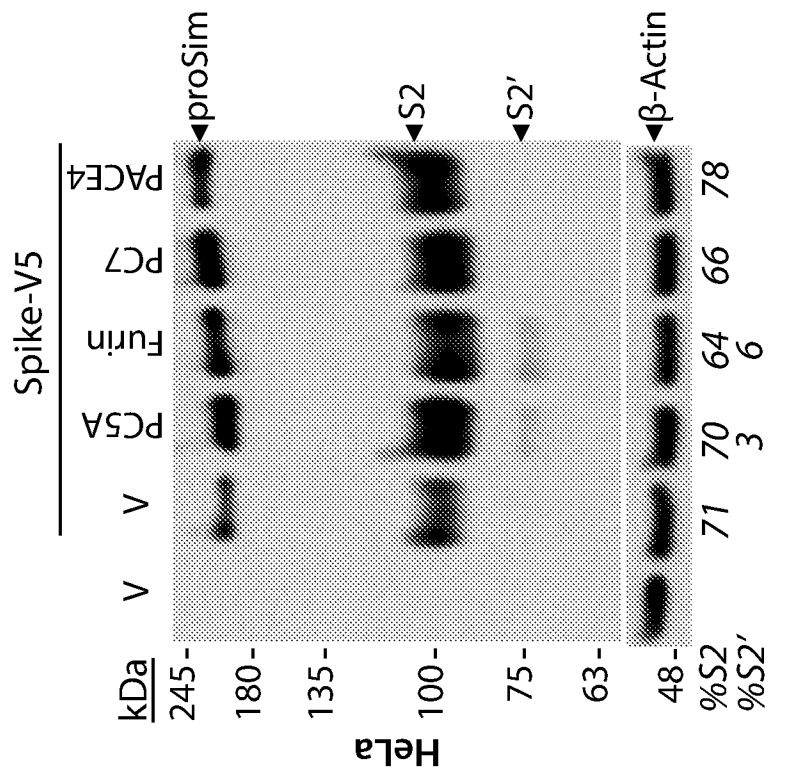


Figure 3E

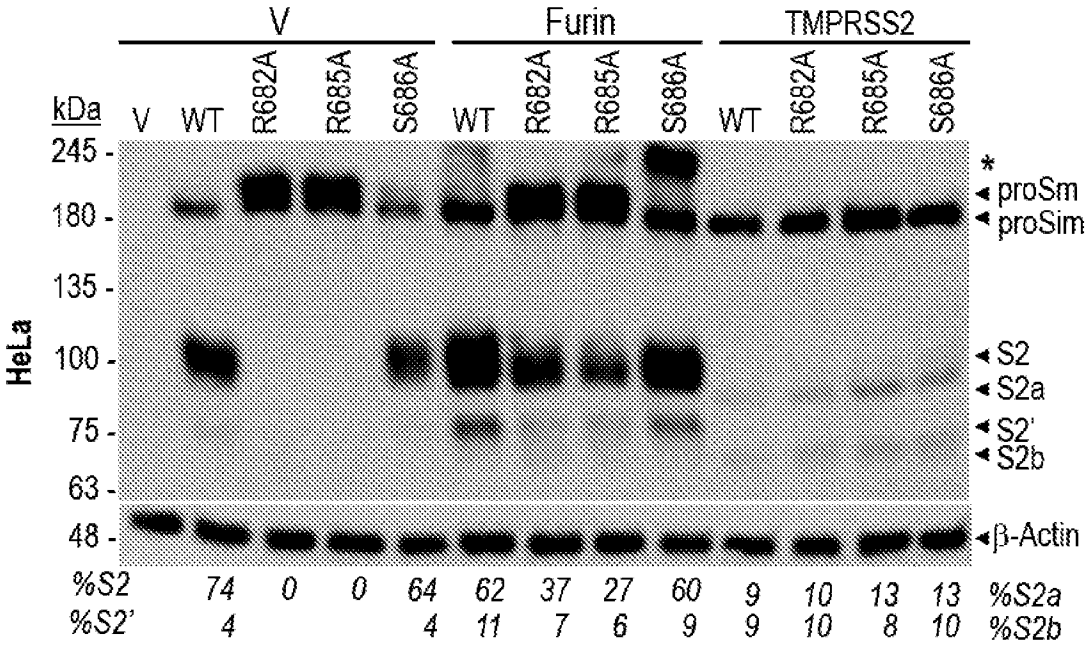


Figure 4A

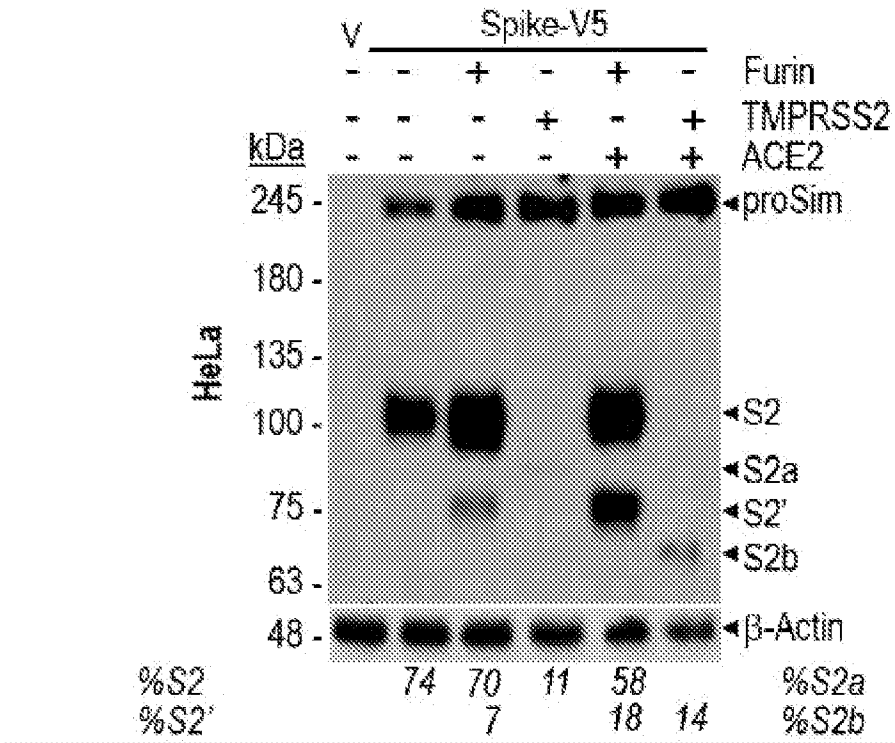
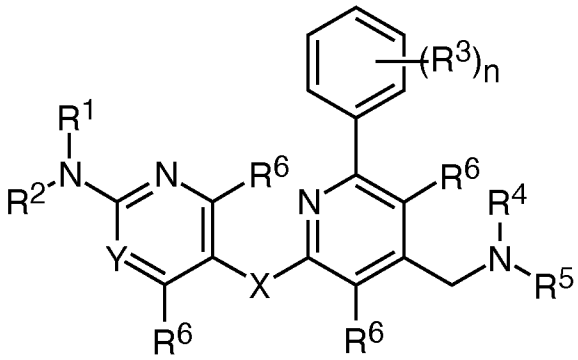
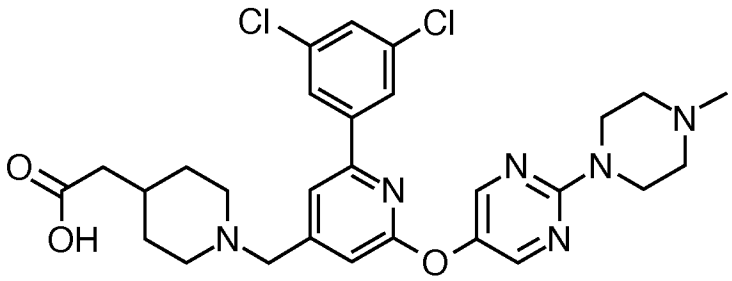


Figure 4B



Structure of Furin inhibitors

Figure 5A



Compound 93

Figure 5B

	Furin pIC50	PCSK5 pIC50	PCSK6 pIC50	PCSK7 pIC50	Golgi pIC50 (U2OS)
Compound 93	8.8 ± 0.4 (n = 10)	7.6 ± 0.09 (n = 8)	6.7 ± 0.15 (n = 6)	7.4 ± 0.22 (n = 8)	7.7 ± 0.24 (n = 22)
Compound 192	9.3 ± 0.5 (n = 10)	7.5 ± 0.22 (n = 10)	6.9 ± 0.1 (n = 4)	6.9 ± 0.2 (n = 8)	8.3 ± 0.25 (n = 12)
Compound 219	9.4 ± 0.3 (n = 10)	7.6 ± 0.1 (n = 10)	6.7 ± 0.24 (n = 5)	6.9 ± 0.3 (n = 8)	7.6 ± 0.2 (n = 12)
Decanoyl-RVKR-CMK "Furin Inhibitor I"	9.1 ± 0.43 (n = 447)	9.9 ± 0.38 (n = 162)	9.2 ± 0.24 (n = 214)	9.62 ± 0.63 (n = 198)	5.1 ± 0.33 (n = 8)

Figure 5C

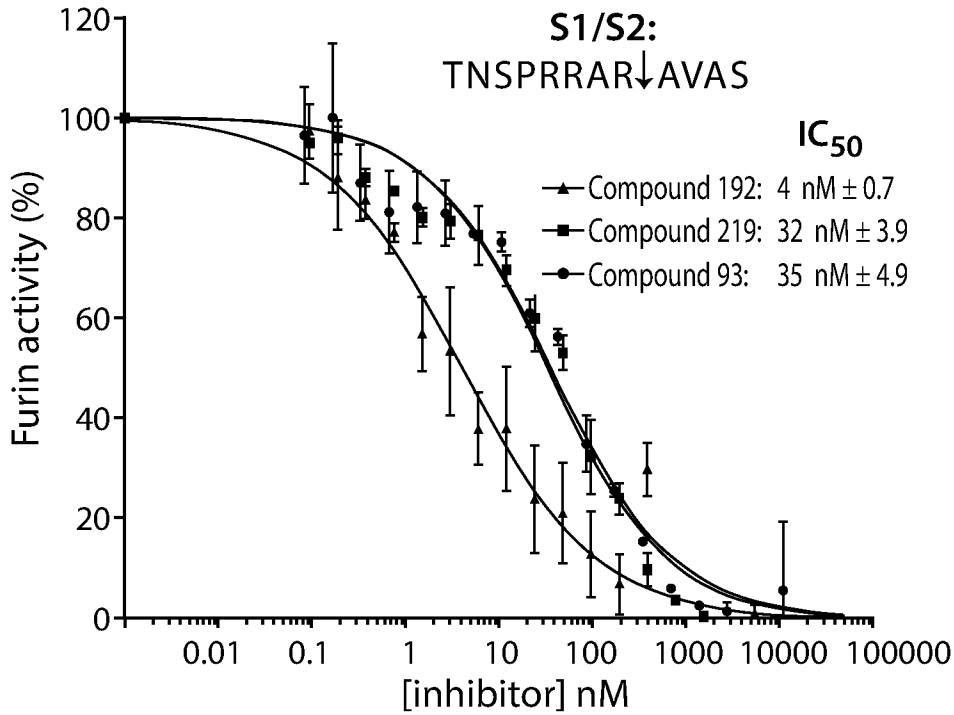


Figure 5D

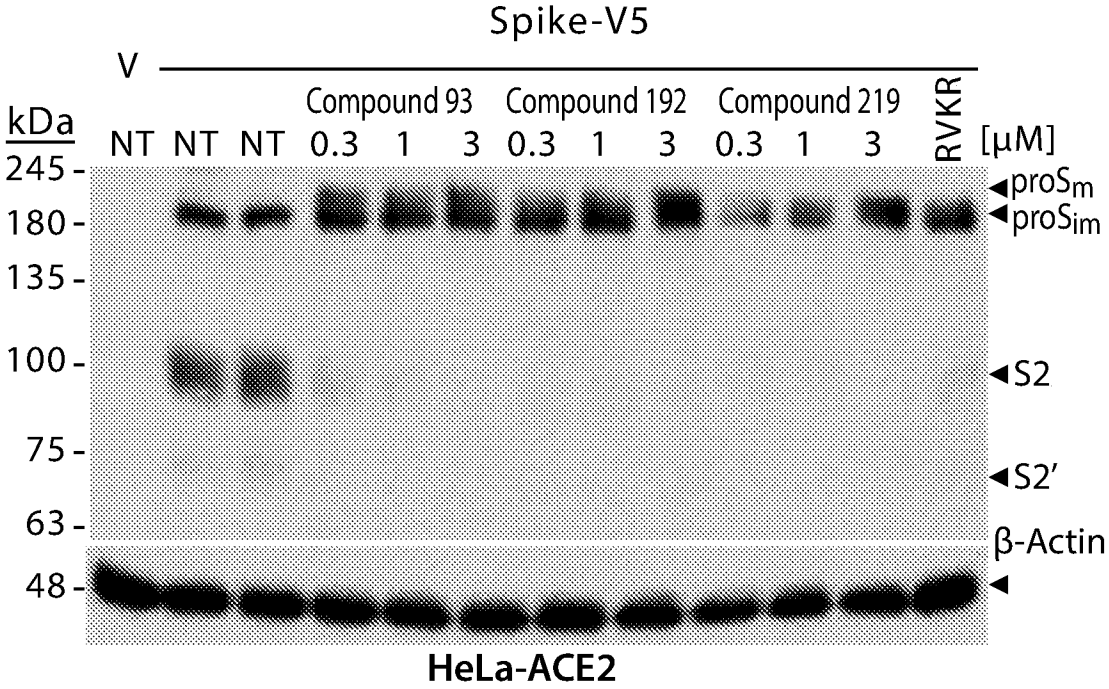


Figure 5E

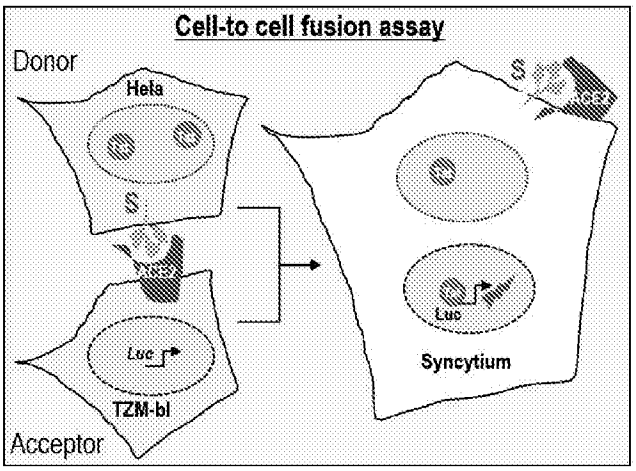


Figure 6A

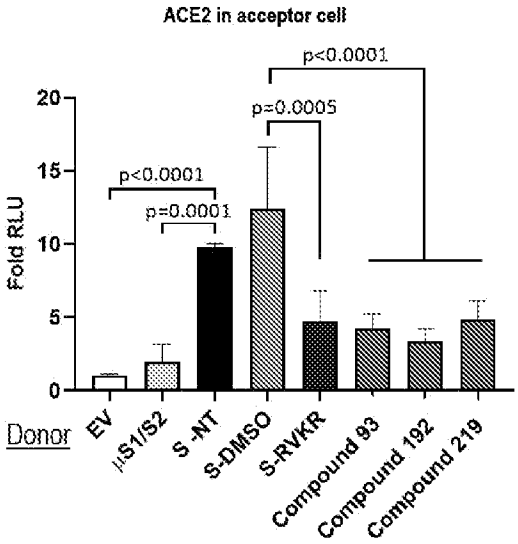


Figure 6B

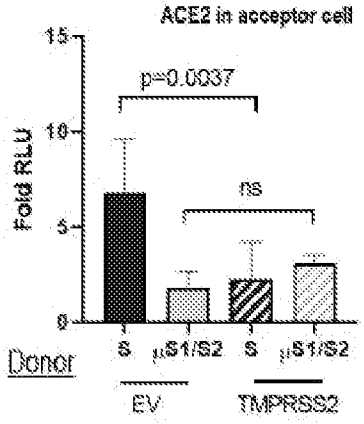


Figure 6C

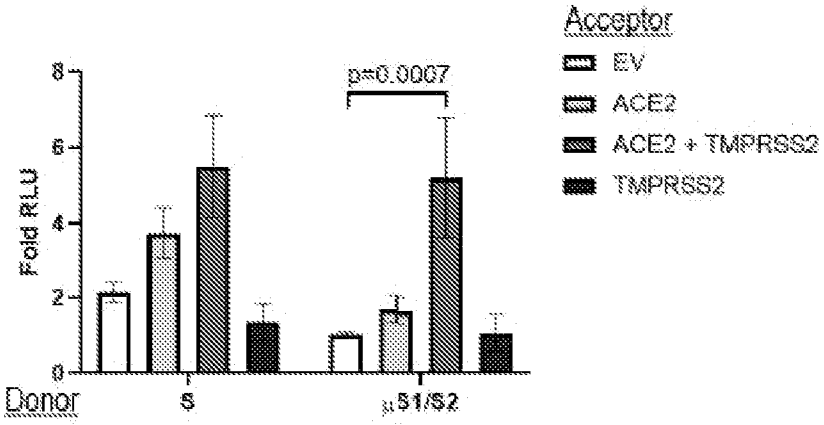


Figure 6D

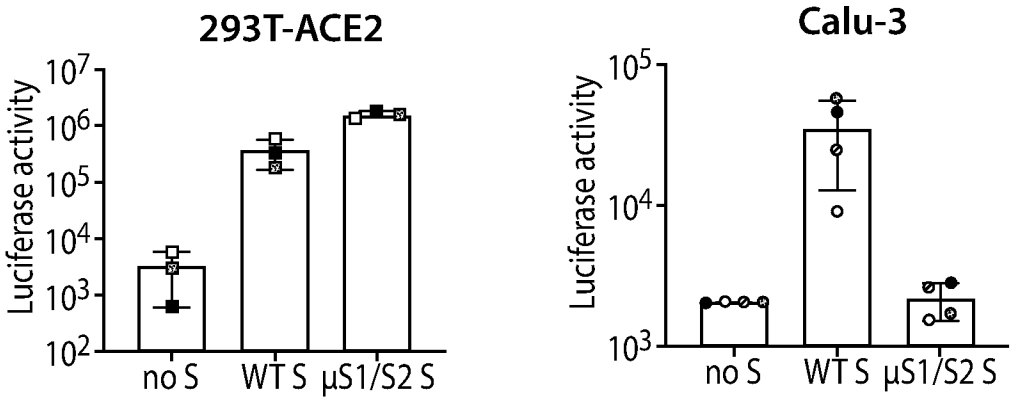


Figure 7A

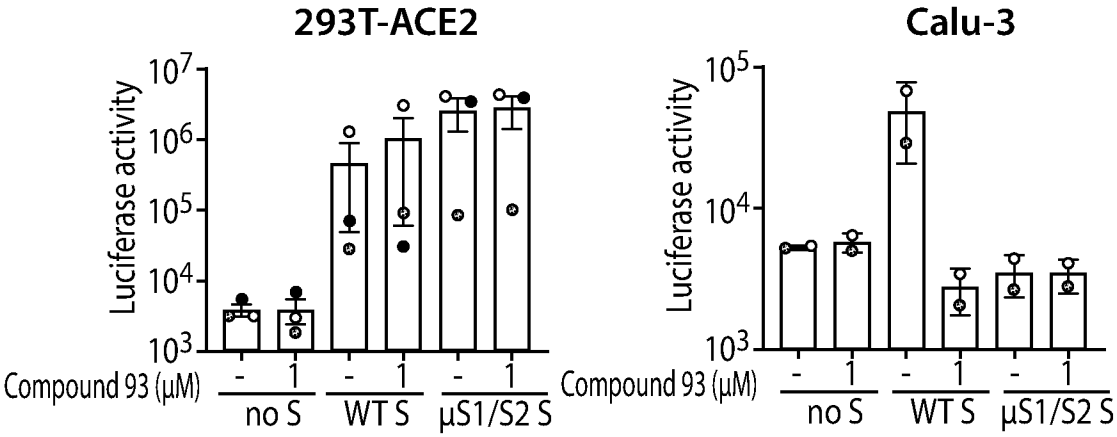


Figure 7B

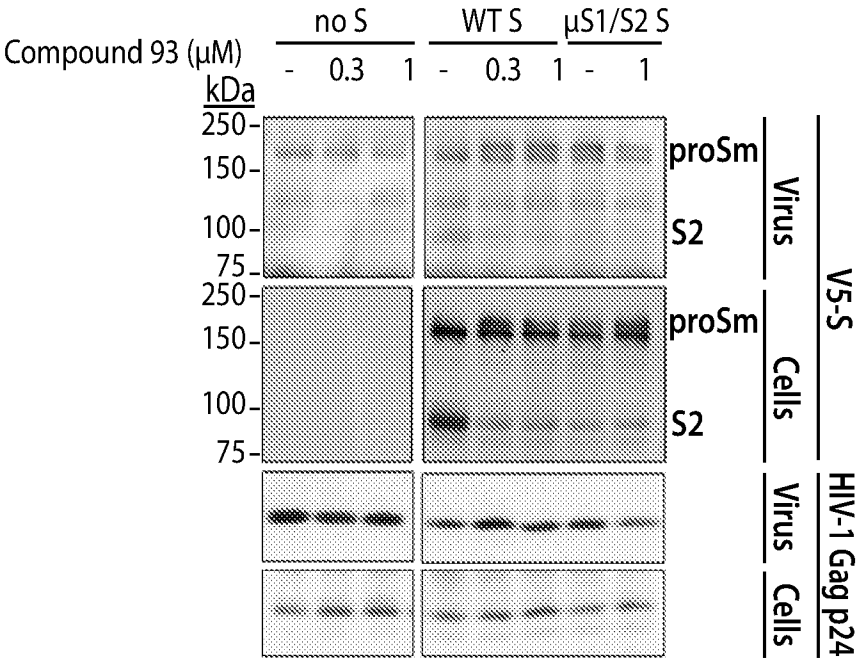


Figure 7C

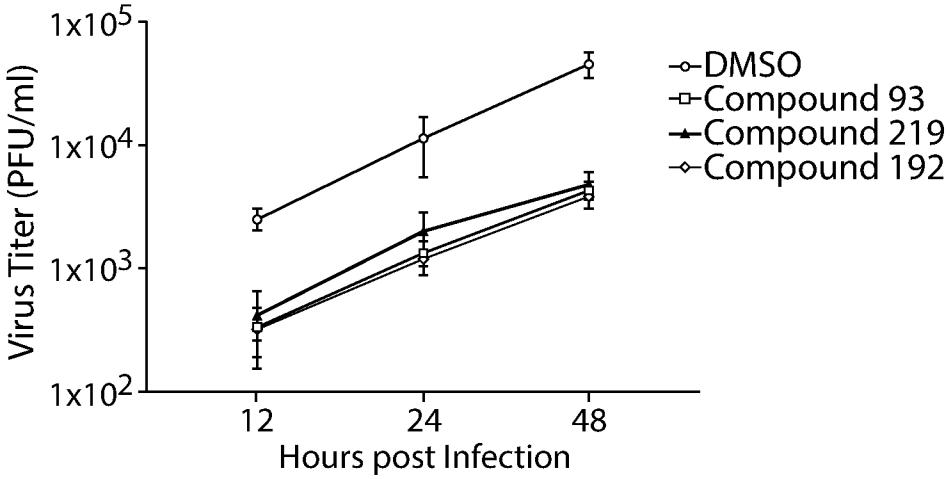


Figure 8A

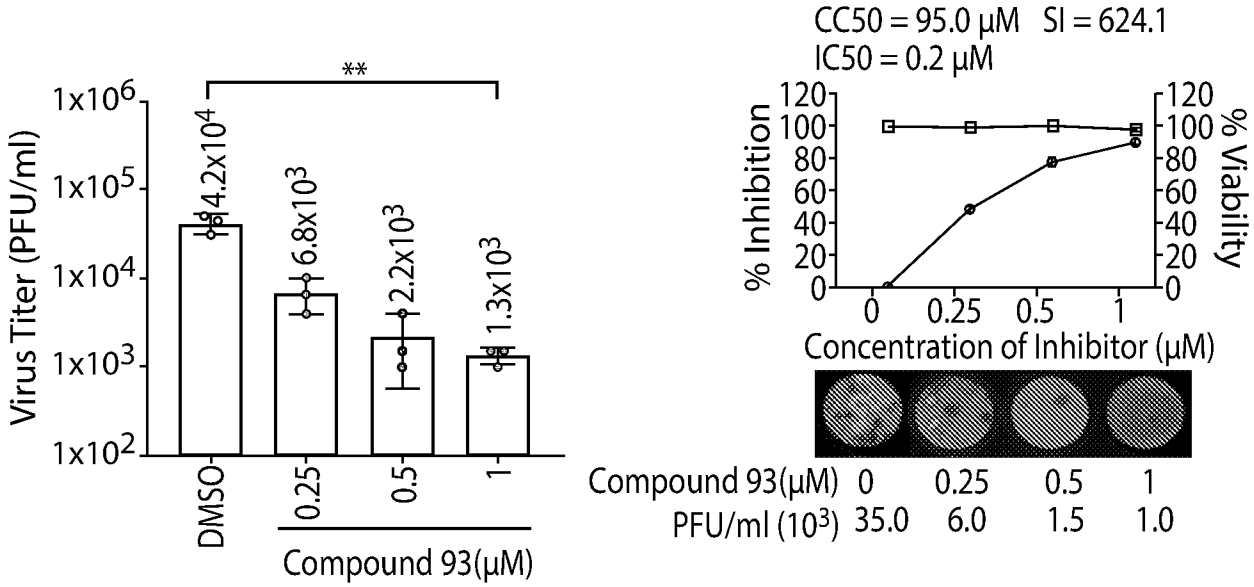


Figure 8B

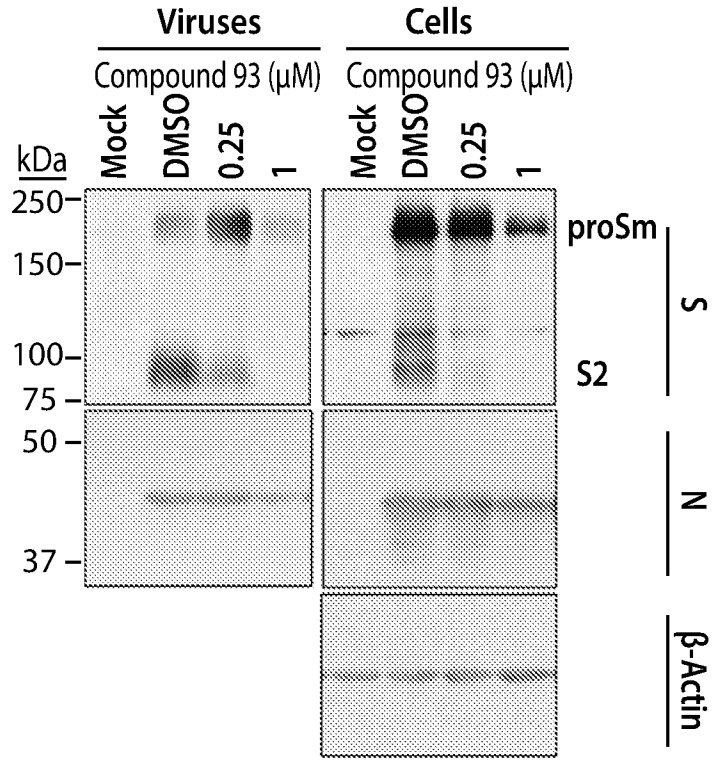


Figure 8C

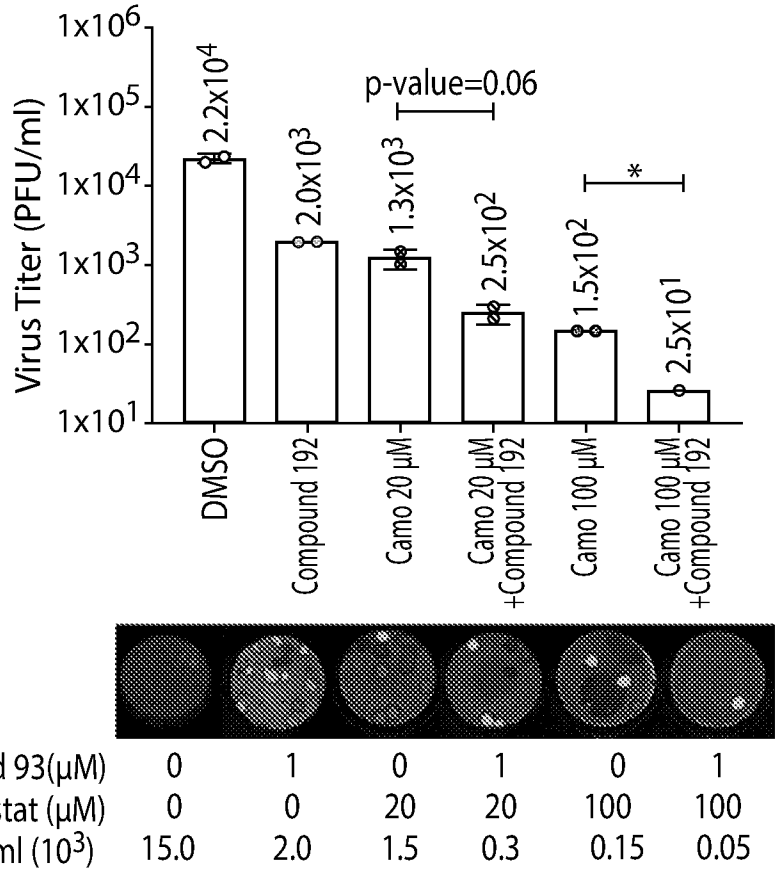


Figure 8D

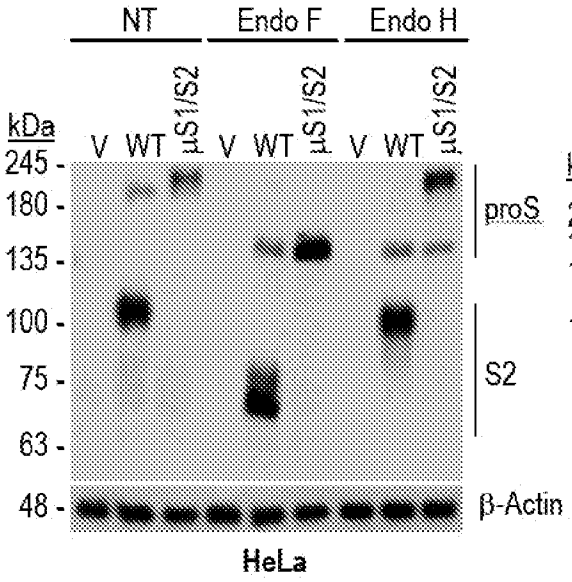


Figure 9A

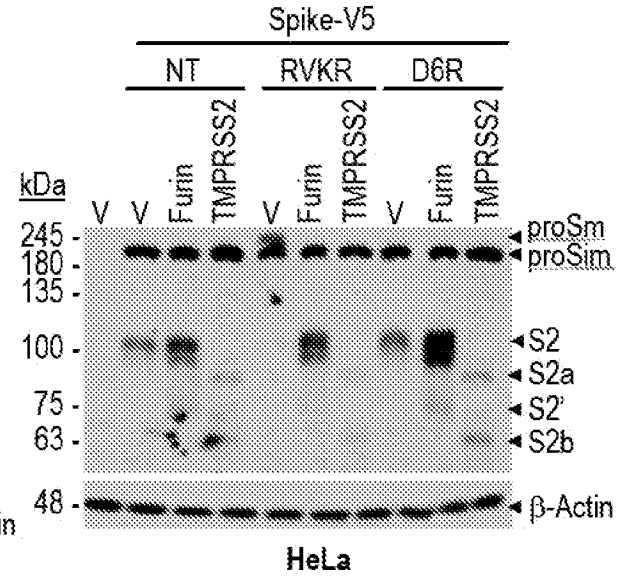


Figure 9B

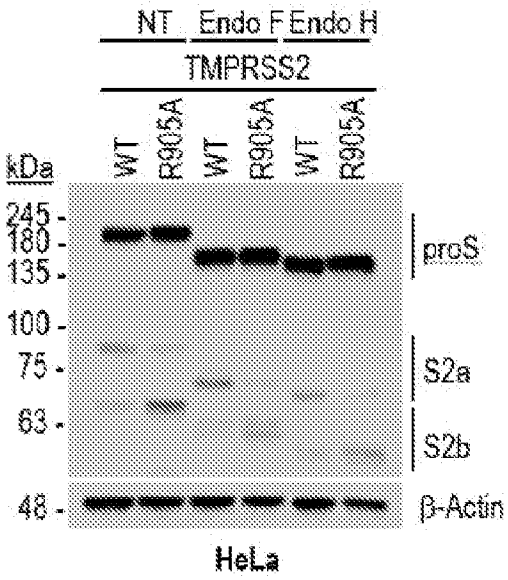


Figure 9C

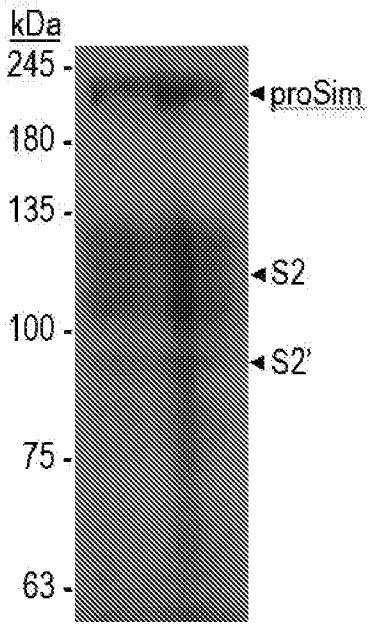


Figure 10

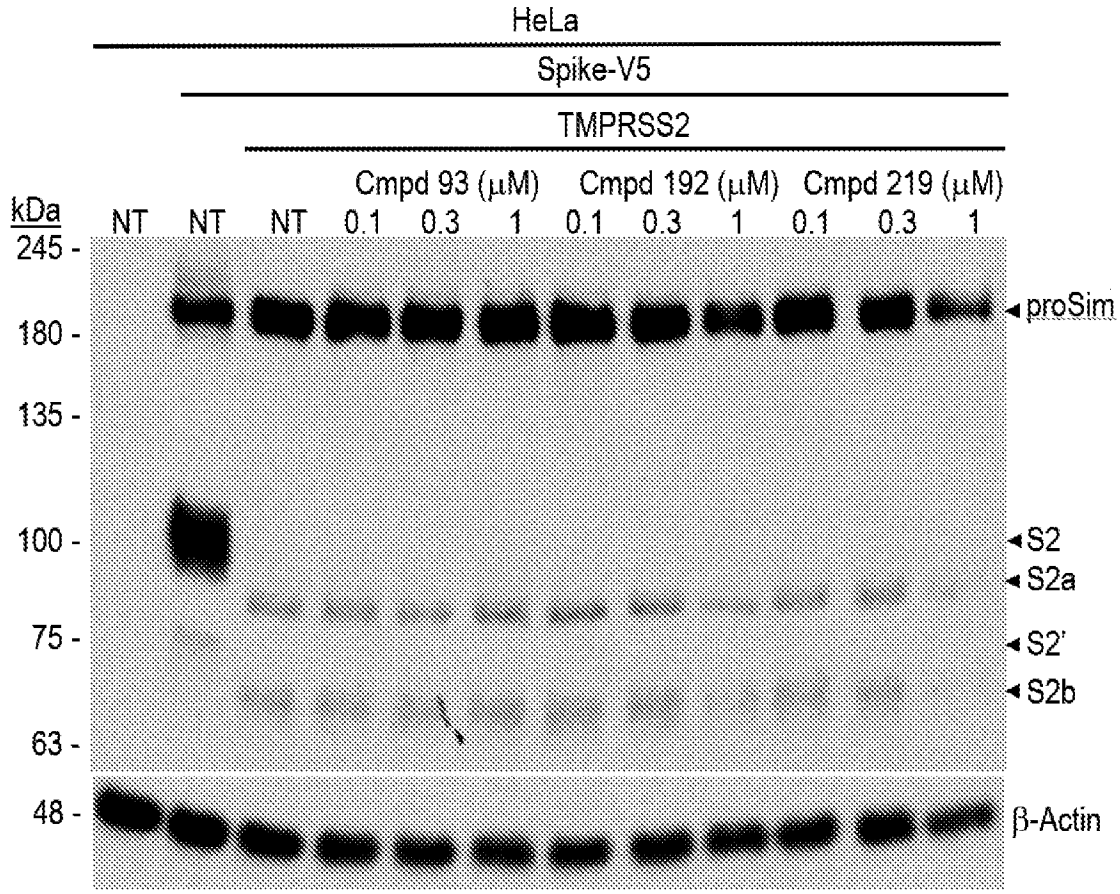


Figure 11

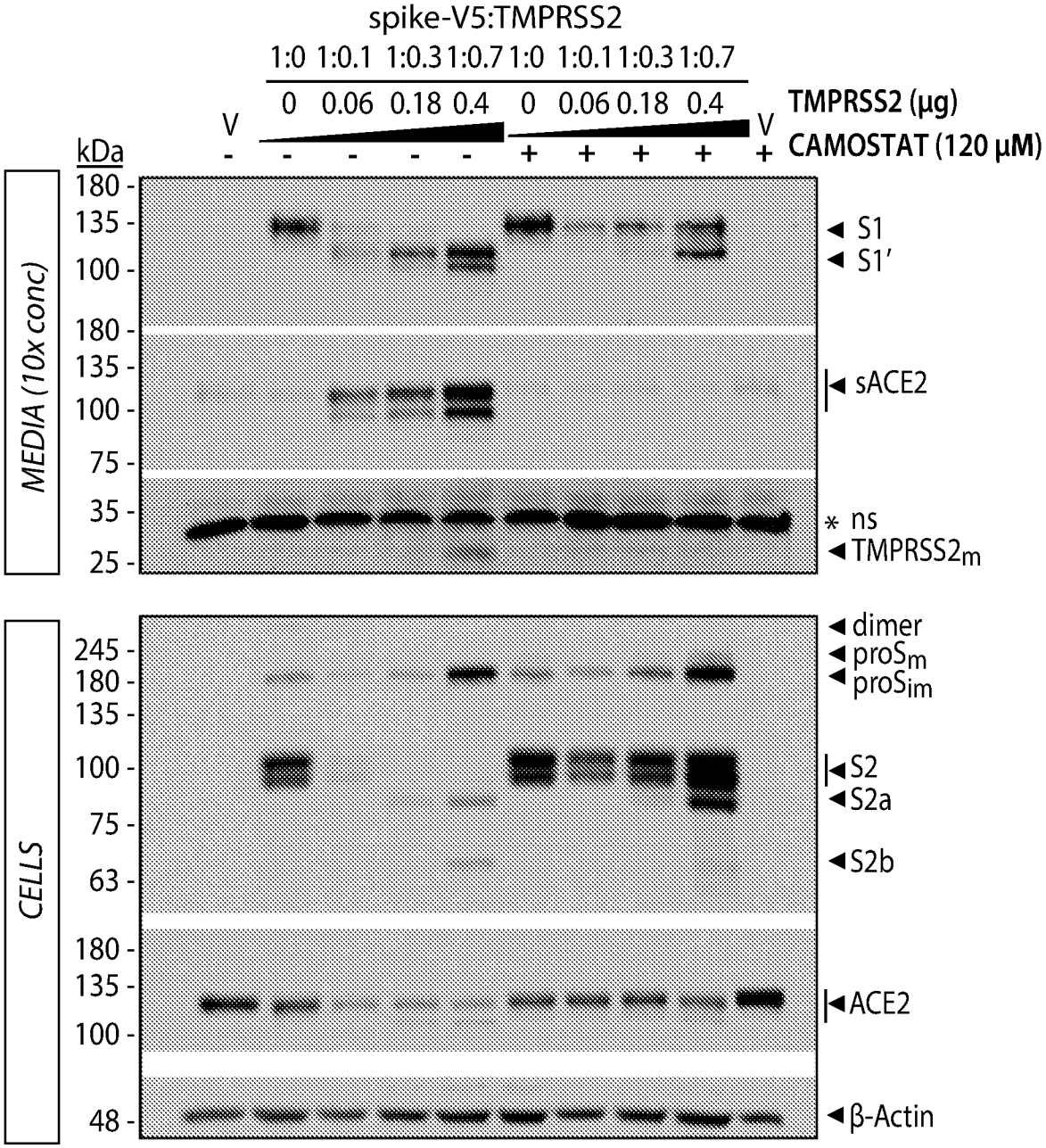

spike-V5:TMPRSS2
1:0 1:0.1 1:0.3 1:0.7 1:0 1:0.1 1:0.3 1:0.7
0 0.06 0.18 0.4 0 0.06 0.18 0.4
TMPRSS2 (µg)
V V
CAMOSTAT (120 µM)
kDa
MEDIA (10x conc)
180
135
100
75
35
25
S1
S1′
sACE2
* ns
TMPRSS2m
CELLS
245
180
135
100
75
63
48
dimer
proSm
proSim
S2
S2a
S2b
ACE2
β-Actin

Figure 12A

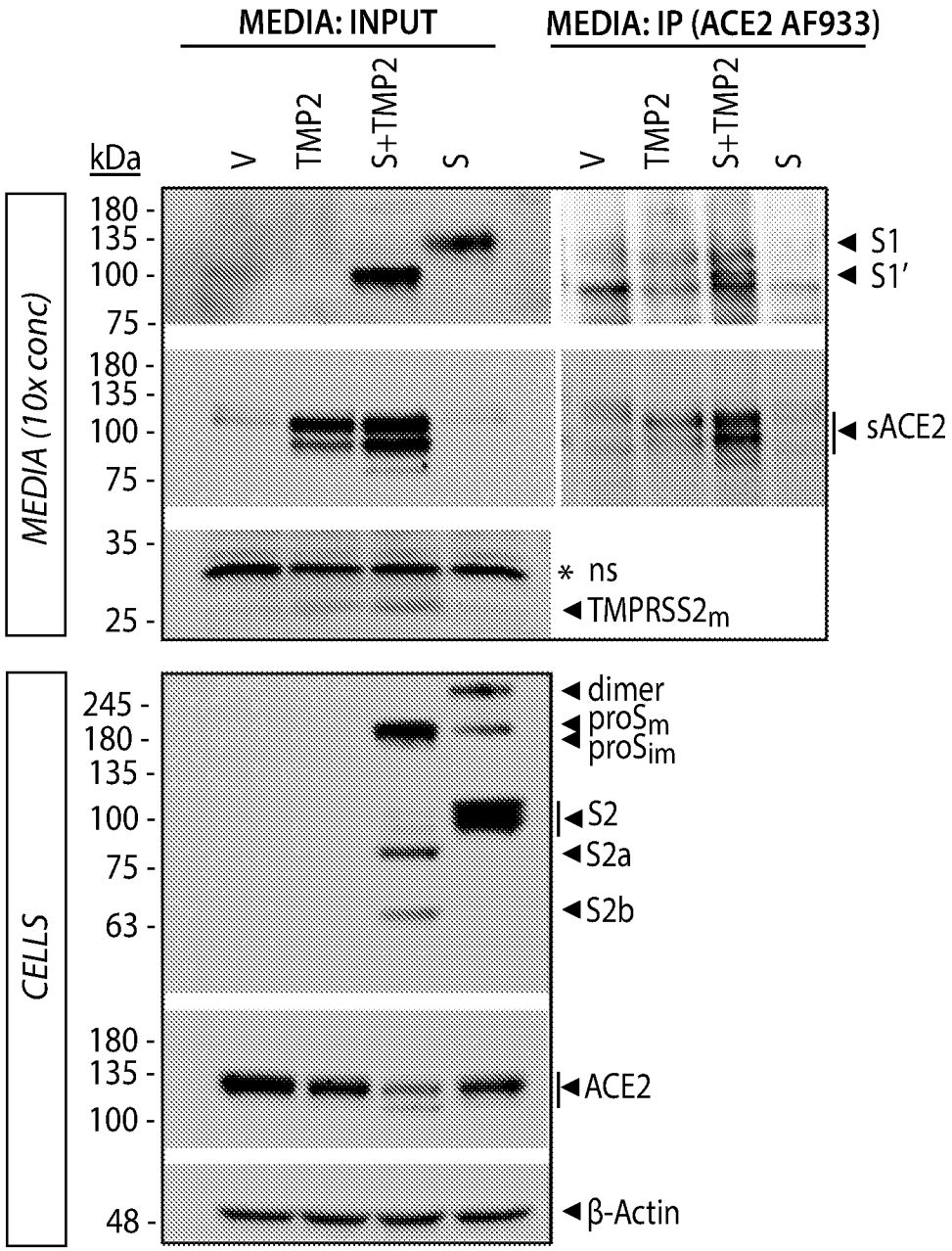

MEDIA: INPUT
MEDIA: IP (ACE2 AF933)
V
TMP2
S+TMP2
S
kDa
MEDIA (10x conc)
180 -
135 -
100 -
75 -
35 -
25 -
S1
S1′
sACE2
* ns
TMPRSS2m
CELLS
245 -
63 -
48 -
dimer
proSm
proSim
S2
S2a
S2b
ACE2
β-Actin

Figure 12B

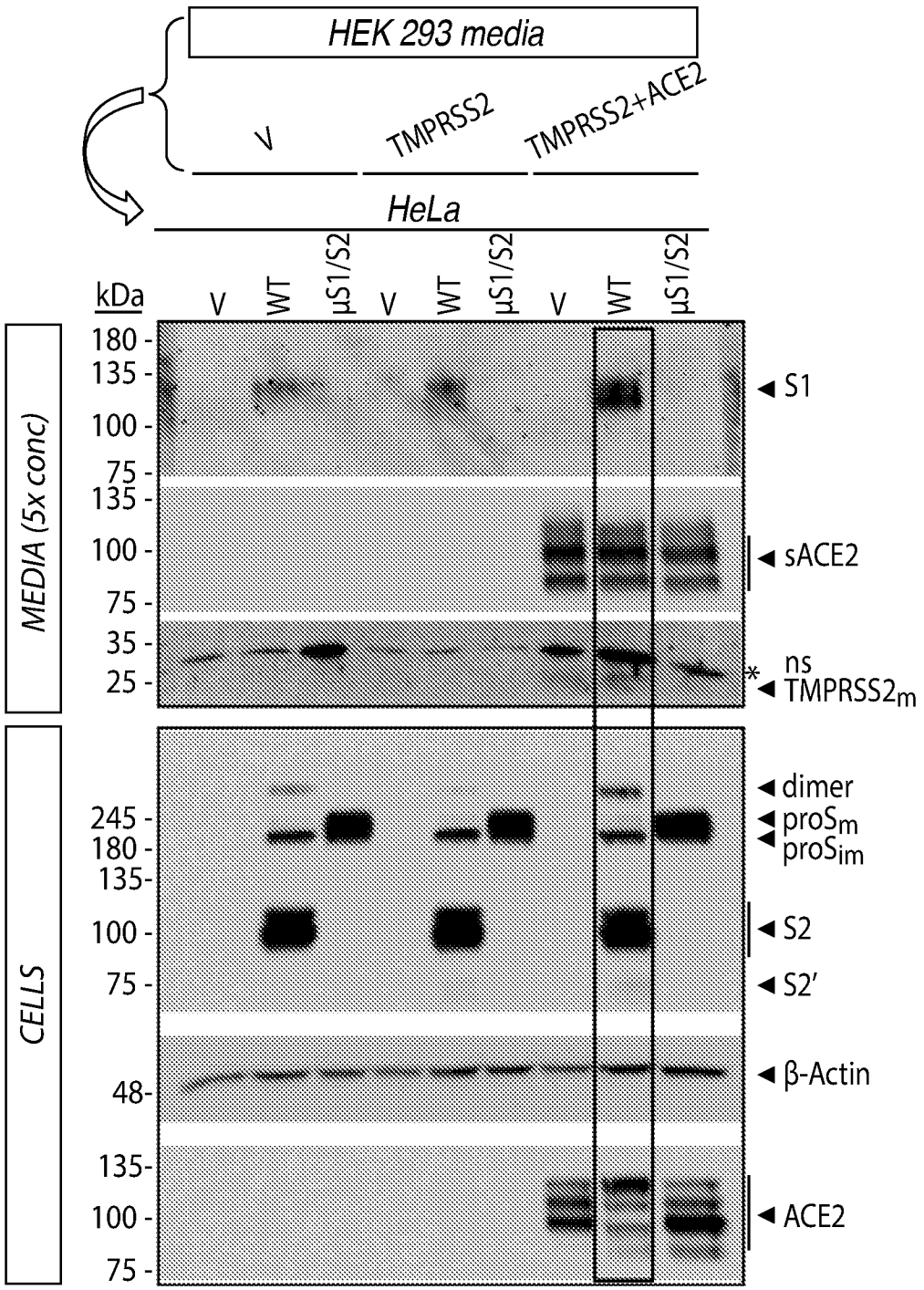

HEK 293 media
V
TMPRSS2
TMPRSS2+ACE2
HeLa
kDa
V
WT
µS1/S2
V
WT
µS1/S2
V
WT
µS1/S2
MEDIA (5x conc)
180 -
135 -
100 -
75 -
135 -
100 -
75 -
35 -
25 -
S1
sACE2
ns
TMPRSS2m
CELLS
245 -
180 -
135-
100 -
75 -
48-
135-
100 -
75 -
dimer
proSm
proSim
S2
S2′
β-Actin
ACE2

Figure 13A

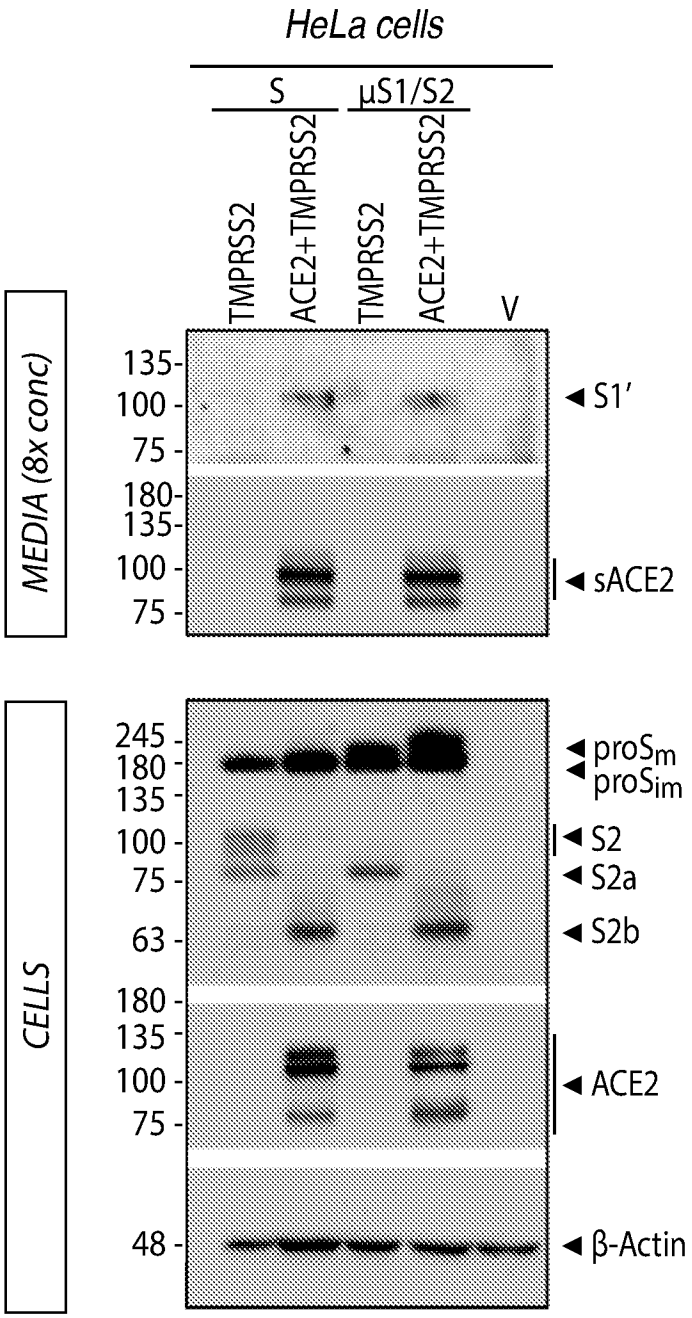

HeLa cells
S
μS1/S2
TMPRSS2
ACE2+TMPRSS2
TMPRSS2
ACE2+TMPRSS2
V
MEDIA (8x conc)
135-
100 -
75 -
180-
135-
100 -
75 -
S1'
sACE2
CELLS
245 -
180 -
135 -
100 -
75 -
63 -
180 -
135 -
100 -
75 -
48 -
proSm
proSim
S2
S2a
S2b
ACE2
β-Actin

Figure 13B

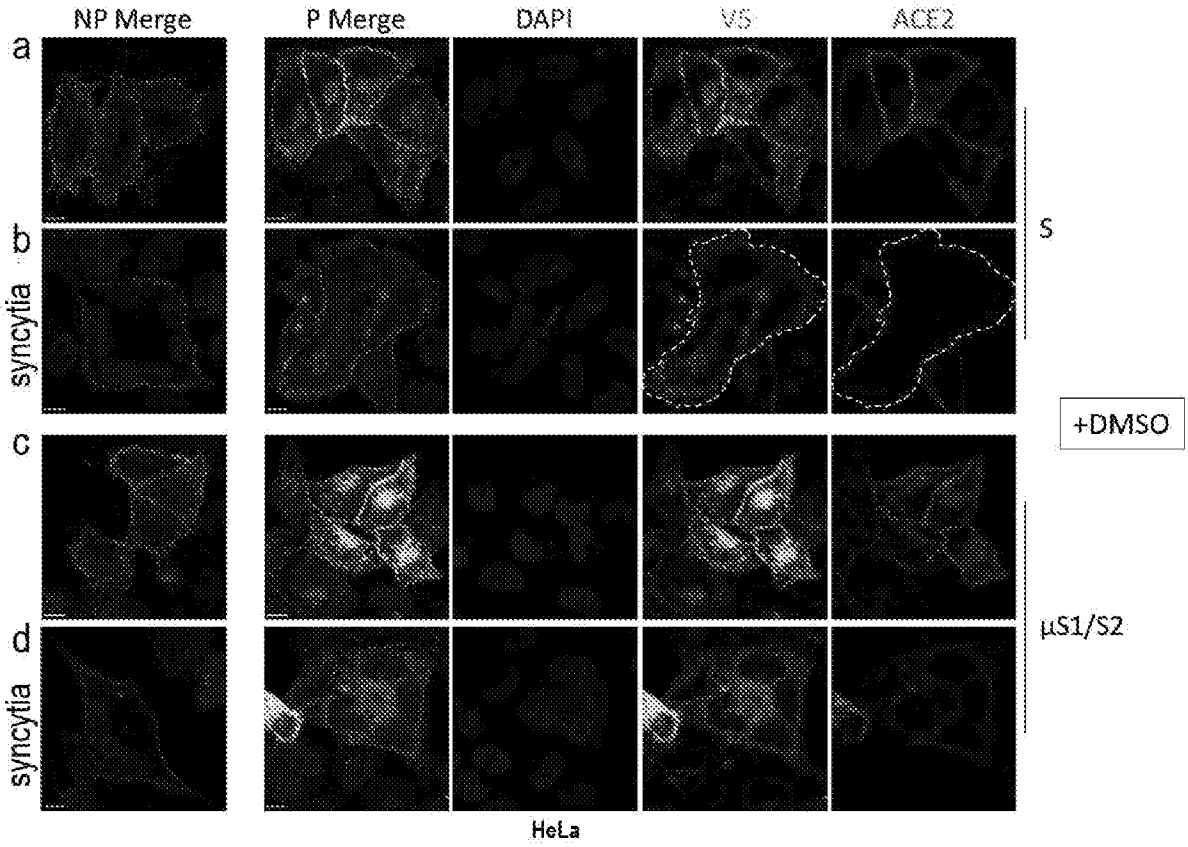


Figure 14

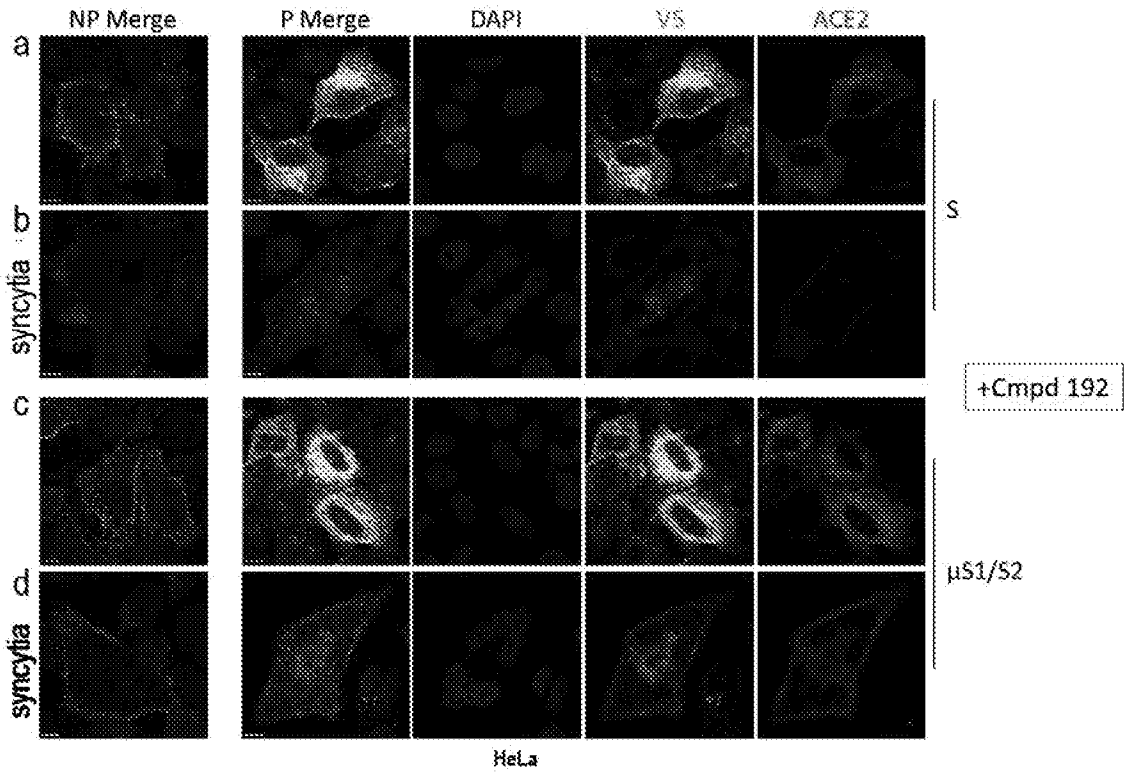


Figure 15

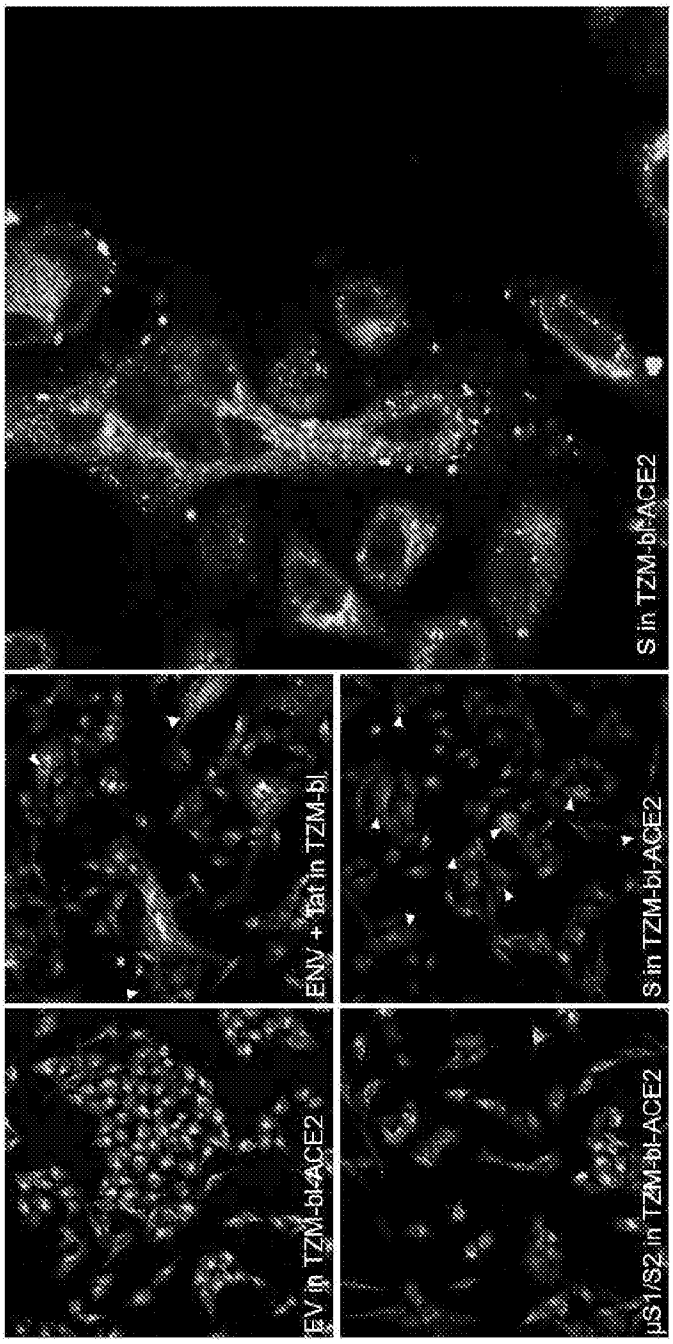

EV in TZM-bl-ACE2
ENV + Tat in TZM-bl
S in TZM-bl-ACE2
μS1/S2 in TZM-bl-ACE2
S in TZM-bl-ACE2

Figure 16A

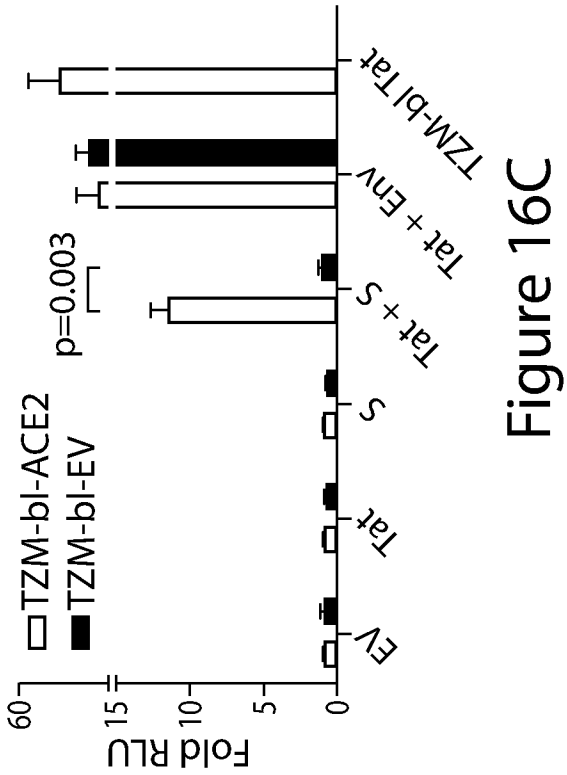


Figure 16C

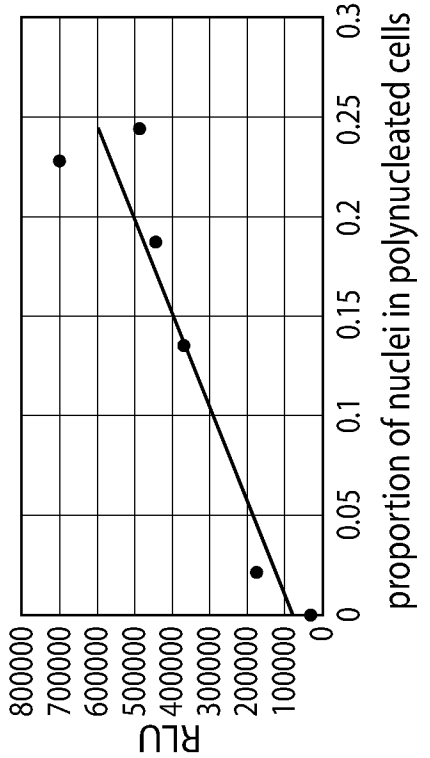


Figure 16B

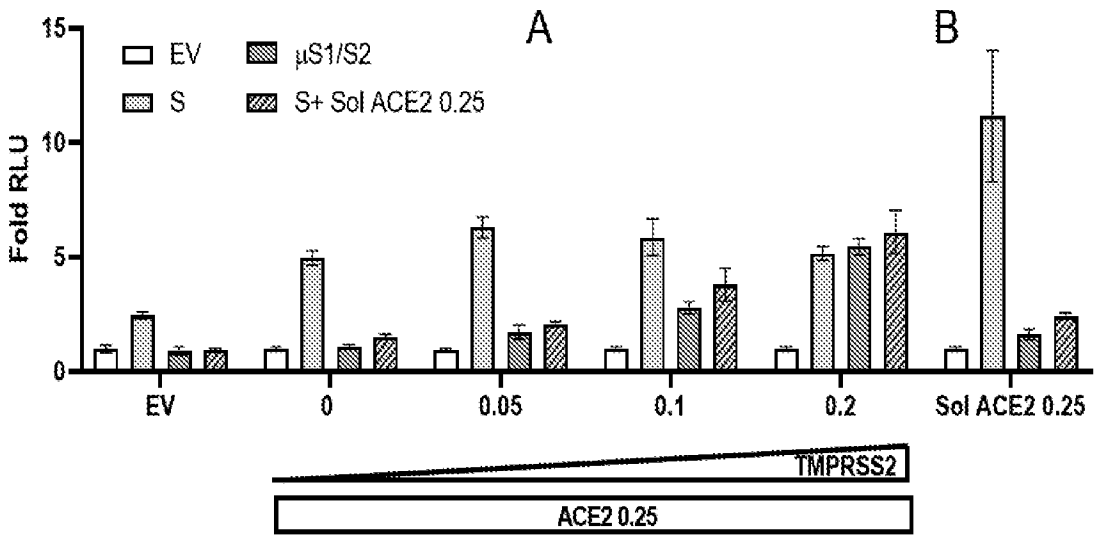

A
B
EV
S
µS1/S2
S+ Sol ACE2 0.25
Fold RLU
15
10
5
0
EV
0
0.05
0.1
0.2
Sol ACE2 0.25
TMPRSS2
ACE2 0.25

Figure 17

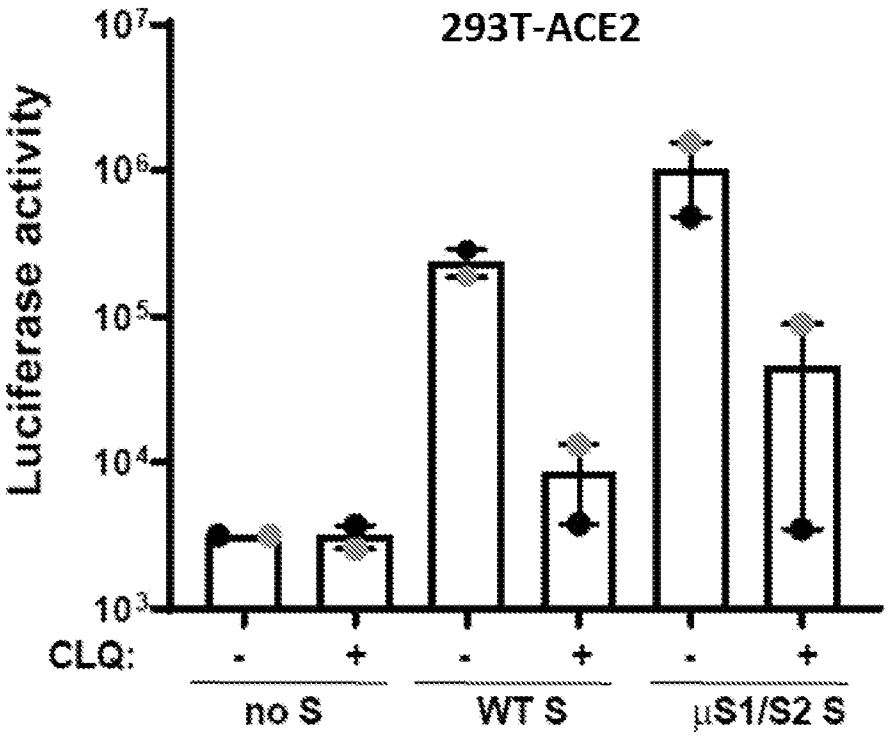

293T-ACE2
Luciferase activity
10^7
10^6
10^5
10^4
10^3
CLQ:
-
+
-
+
-
+
no S
WT S
μS1/S2 S

Figure 18

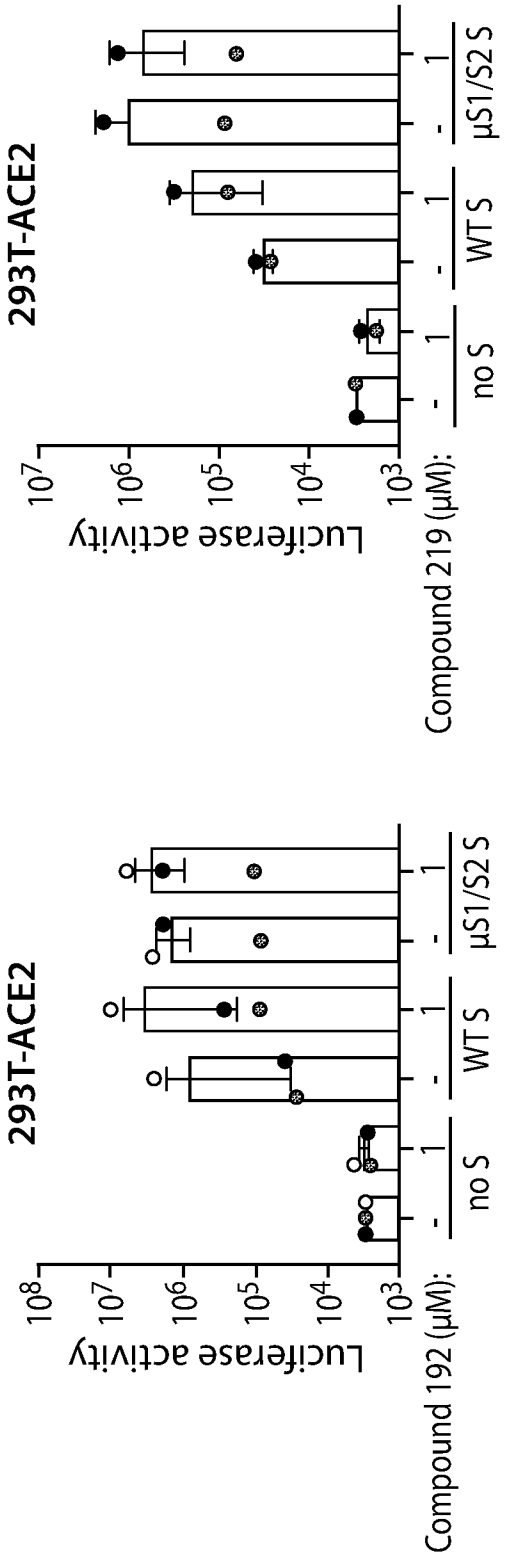
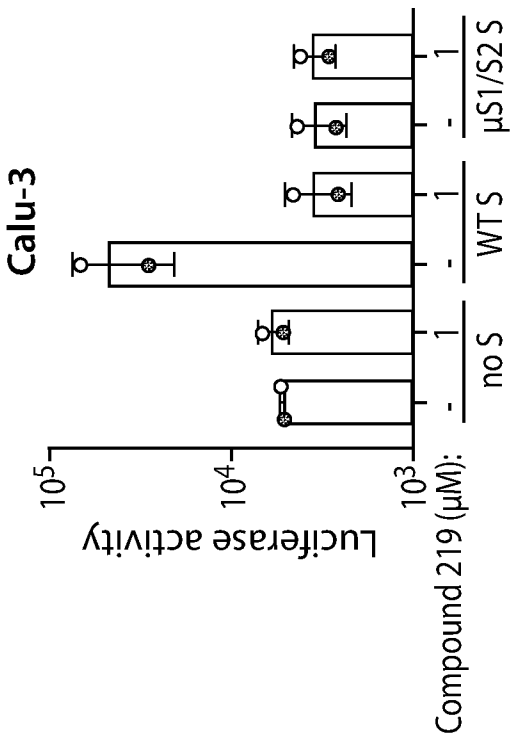


Figure 19A



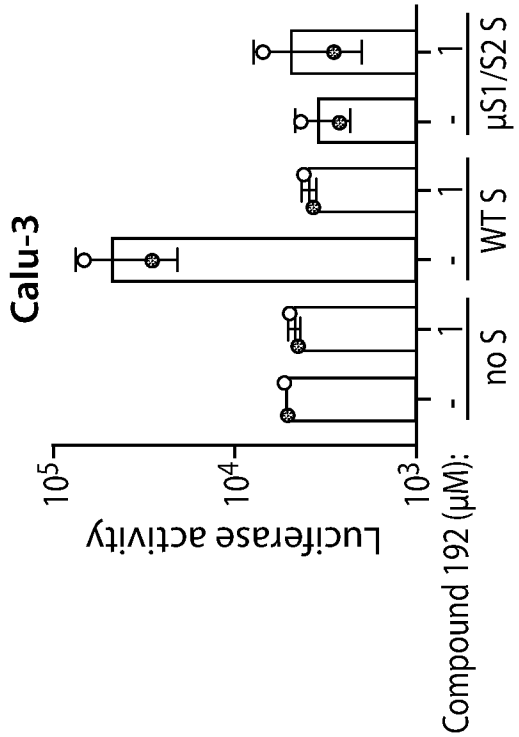


Figure 19B

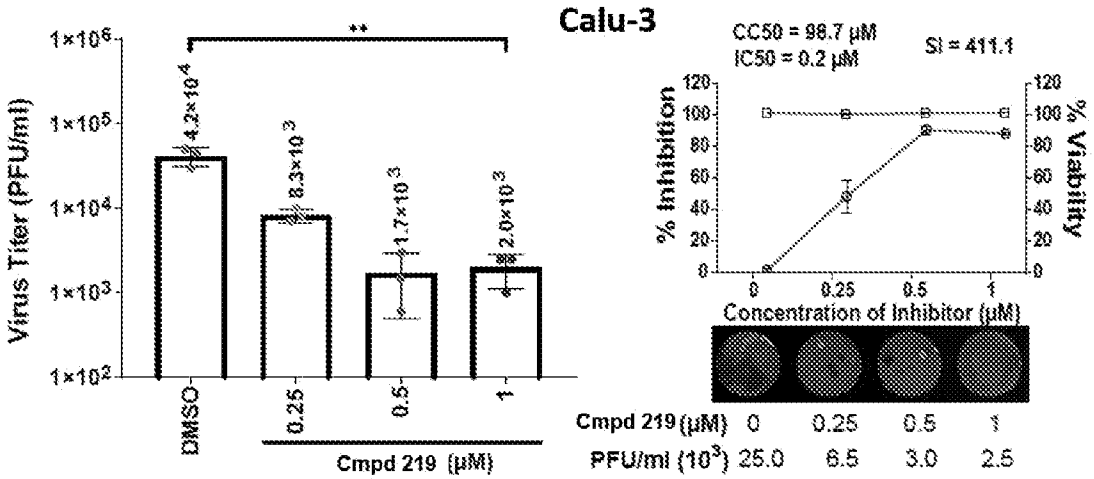


Figure 20A

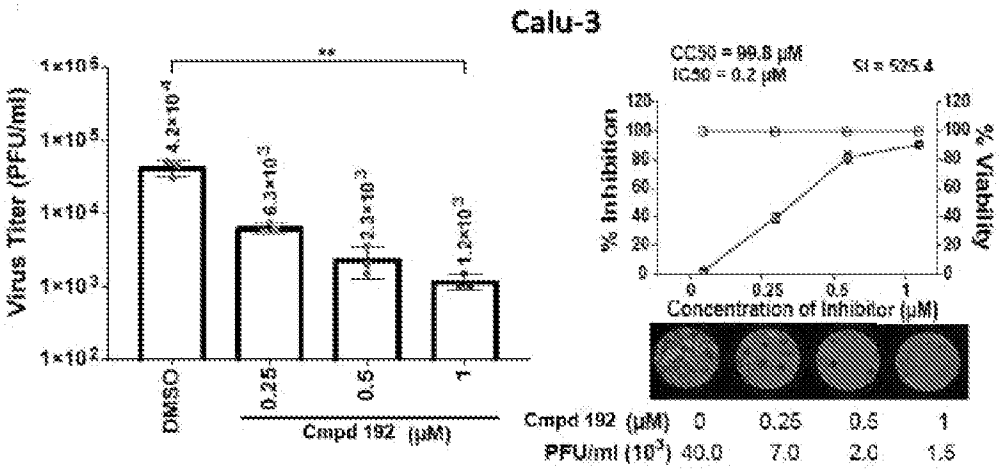


Figure 20B

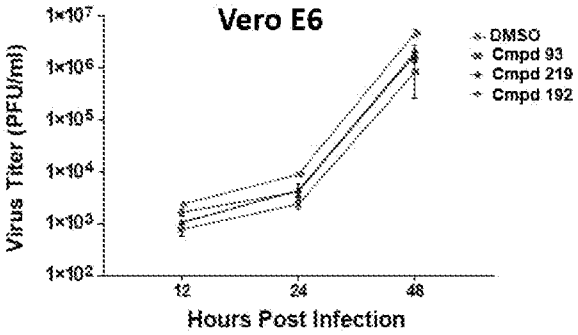


Figure 21A

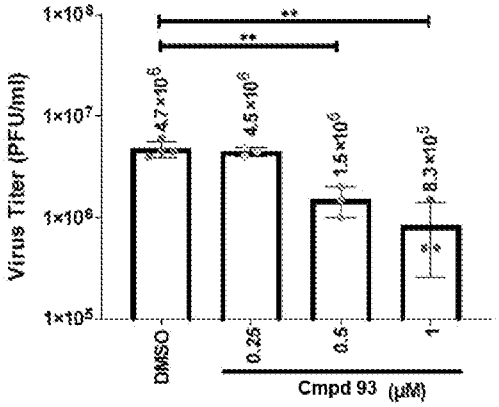


Figure 21B

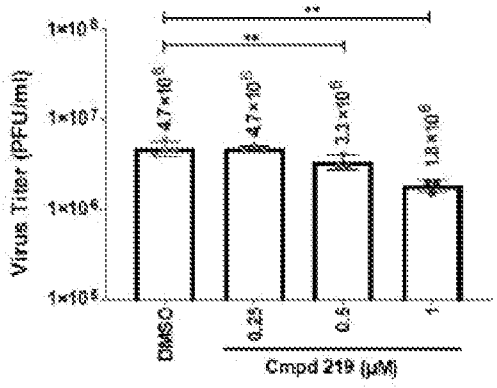


Figure 21C

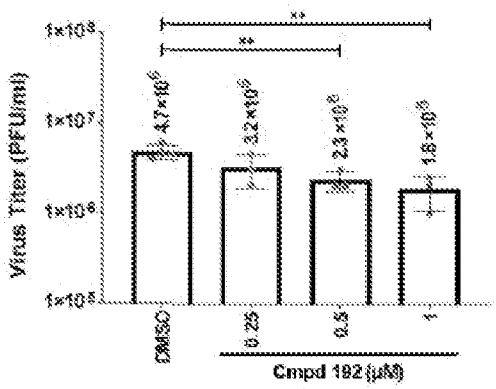


Figure 21D