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International application number:	PCT/US2022/036242
International filing date:	06 July 2022 (06.07.2022)
Document type:	Certified copy of priority document
Document details:	Country/Office: US
	Number: 63/203,135
	Filing date: 09 July 2021 (09.07.2021)
Date of receipt at the International Bureau:	27 July 2022 (27.07.2022)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-bis)

1217824

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July 26, 2022

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APPLICATION NUMBER: 63/203,135

FILING DATE: *July 09, 2021*

RELATED PCT APPLICATION NUMBER: *PCT/US22/36242*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US63/203,135*



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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	ALIG.072PR
		Application Number	
Title of Invention	ANTI-VIRAL COMPOUNDS		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

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Inventor Information:

Inventor	1				Remove
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All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button. Add			

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☐ An Address is being provided for the correspondence information of this application.	
Customer Number	20995
Email Address	efiling@knobbe.com Add Email Remove Email

Application Information:

Title of the Invention	ANTI-VIRAL COMPOUNDS		
Attorney Docket Number	ALIG.072PR	Small Entity Status Claimed	☒
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

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For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	ALIG.072PR
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Publication Information:

☐	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐	Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

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Please Select One:	☒ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number	20995		

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This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78. When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	ALIG.072PR
		Application Number	
Title of Invention	ANTI-VIRAL COMPOUNDS		

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Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Access Code ^j (if applicable)	
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Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013. NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	ALIG.072PR
		Application Number	
Title of Invention	ANTI-VIRAL COMPOUNDS		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

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NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

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The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

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☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	ALIG.072PR
		Application Number	
Title of Invention	ANTI-VIRAL COMPOUNDS		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant	1	Remove
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If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

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☒ Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.		Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Aligos Therapeutics, Inc.		
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Phone Number		Fax Number	
Email Address			

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	ALIG.072PR
		Application Number	
Title of Invention	ANTI-VIRAL COMPOUNDS		

Assignee	1
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Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

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If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

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See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Kimberly J. Miller/		Date (YYYY-MM-DD)	2021-07-09
First Name	Kimberly J.	Last Name	Miller	Registration Number
			61749	

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	ALIG.072PR
		Application Number	
Title of Invention	ANTI-VIRAL COMPOUNDS		

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ANTI-VIRAL COMPOUNDS**BACKGROUND**Field

[0001] The present application relates to the fields of chemistry, biochemistry and medicine. Disclosed herein are compounds of Formula (I), or pharmaceutically acceptable salt thereof, pharmaceutical compositions that include a compound described herein (including pharmaceutically acceptable salts of a compound described herein) and methods of synthesizing the same. Also disclosed herein are methods of treating diseases and/or conditions with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Description

[0002] A positive-sense single-stranded RNA virus ((+)ssRNA virus) is a virus that uses positive sense, single stranded, RNA as its genetic material. Positive-sense single-stranded RNA viruses can be enveloped or non-enveloped. Coronaviridae, Picornaviridae and Norviruses are each a (+)ssRNA virus. Each of the aforementioned viruses are known to infect mammals, including humans.

SUMMARY

[0003] Some embodiments disclosed herein relate to a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0004] Some embodiments disclosed herein relate to a pharmaceutical composition that can contain an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0005] Some embodiments described herein relate to a method of treating a coronavirus infection that can include administering to a subject identified as suffering from the coronavirus infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an

effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of treating a coronavirus infection.

[0006] Some embodiments disclosed herein relate to a method of inhibiting replication of a coronavirus that can include contacting a cell infected with the coronavirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of inhibiting the replication a coronavirus.

[0007] Some embodiments described herein relate to a method of treating a picornavirus infection that can include administering to a subject identified as suffering from the picornavirus infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of treating a picornavirus infection.

[0008] Some embodiments disclosed herein relate to a method of inhibiting replication of a picornavirus that can include contacting a cell infected with the picornavirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of inhibiting the replication a picornavirus.

[0009] Some embodiments described herein relate to a method of treating a norovirus infection that can include administering to a subject identified as suffering from the

norovirus infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of treating a norovirus infection.

[0010] Some embodiments disclosed herein relate to a method of inhibiting replication of a norovirus that can include contacting a cell infected with the norovirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for the use of inhibiting the replication a norovirus.

[0011] These are other embodiments are described in greater detail below.

DETAILED DESCRIPTION

[0012] Coronaviridae viruses are a family of enveloped, positive-stranded, single-stranded, spherical RNA viruses. Coronaviruses are named for the crown-like spikes on their surface. The Coronaviridae family includes two sub-families, Coronavirus and Torovirus. The Coronavirus genus has a helical nucleocapsid, and Torovirus genus has a tubular nucleocapsid. The Coronaviridae family of viruses includes Middle East respiratory syndrome coronavirus (MERS-CoV), SARS and SARS-CoV-2.

[0013] Coronavirus disease 2019 (COVID-19) (also referred to as novel coronavirus pneumonia or 2019-nCoV acute respiratory disease) is an infectious disease caused by the virus severe respiratory syndrome coronavirus 2 (SARS-CoV-2) (also referred to as novel coronavirus 2019, or 2019-nCoV). The disease was first identified in December 2019 and spread globally, causing a pandemic. Symptoms of COVID-19 include fever, cough, shortness of breath, fatigue, headache, loss of smell, nasal congestion, sore throat,

coughing up sputum, pain in muscles or joints, chills, nausea, vomiting, and diarrhea. In severe cases, symptoms can include difficulty waking, confusion, blueish face or lips, coughing up blood, decreased white blood cell count, and kidney failure. Complications can include pneumonia, viral sepsis, acute respiratory distress syndrome, and kidney failure.

[0014] COVID-19 is especially threatening to public health. The virus is highly contagious, and studies currently indicate that it can be spread by asymptomatic carriers or by those who are pre-symptomatic. Likewise, the early stage of the disease is slow-progressing enough that carriers do not often realize they are infected, leading them to expose numerous others to the virus. The combination of COVID-19's ease of transmission, its high rate of hospitalization of victims, and its death rate make the virus a substantial public health risk, especially for countries without a healthcare system equipped to provide supportive care to pandemic-level numbers of patients. There is not yet a vaccine or specific antiviral treatment for COVID-19 and accordingly, there is a pressing need for treatments or cures.

[0015] SARS-CoV-2 is not the only coronavirus that causes disease. It is a β -coronavirus, a genus of coronaviruses that includes other human pathogens, including SARS-CoV (the causative agent of SARS), MERS-CoV (the causative agent of MERS), and HCoV-OC43 (a causative agent of the common cold). The infectivity of these viruses, and the severity of the diseases they cause, varies widely. β -coronavirus can also manifest as zoonotic infections, spread to and from humans and animals. Additionally, non-human species such as camels, bats, tigers, non-human primates, and rabbits can be susceptible to β -coronavirus. Accordingly, there is a pressing need for treatments or cures to multiple coronaviruses.

[0016] The present disclosure provides molecules useful against coronaviruses, and especially SARS-CoV-2, the causative agent of COVID-19 in humans. Accordingly, the present disclosure fulfills the need in the art for compounds that can be safely and effectively treat or prevent coronavirus infections in humans.

[0017] Picornaviruses are a family of positive strand RNA, nonenveloped viruses. A picornavirus has 60 identical subunits (vertices) which contain five protomers. Each protomer is made up of one copy of four proteins, named VP1, VP2, VP3 and VP4. There are several genera of picornaviruses, including, Enterovirus, Aphthovirus, Cardiovirus, and

Hepatovirus. Enteroviruses known to infect human include, but are not limited to, Rhinovirus A, Rhinovirus B, Rhinovirus C, Cocksackievirus A, Cocksackievirus B and Poliovirus. There is no specific treatment for a picornavirus infection.

[0018] Noroviruses are single-stranded positive-sense RNA, non-enveloped viruses belonging to the Caliciviridae family. Noroviruses are often spread by the fecal-oral route, and are a common cause of gastroenteritis. Infected subjects can experience nausea, non-bloody diarrhea, vomiting and/or abdominal pain. Those suffering from a norovirus infection can become severely dehydrated and require medical attention. As with a picornavirus infection, there is no specific treatment for a norovirus infection. Accordingly, there is a need for compounds that effectively treat or prevent a picornavirus and/or a norovirus infection.

Definitions

[0019] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0020] Whenever a group is described as being “optionally substituted” that group may be unsubstituted or substituted with one or more of the indicated substituents. Likewise, when a group is described as being “unsubstituted or substituted” if substituted, the substituent(s) may be selected from one or more of the indicated substituents. If no substituents are indicated, it is meant that the indicated “optionally substituted” or “substituted” group may be substituted with one or more group(s) (such as 1, 2 or 3) individually and independently selected from deuterium, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, C-amido(alkyl), isocyanato, thiocyanato, nitro, azido, silyl, sulfenyl,

sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, an amino, a mono-substituted amine and a di-substituted amine.

[0021] As used herein, “C_a to C_b” in which “a” and “b” are integers refer to the number of carbon atoms in an alkyl, alkenyl or alkynyl group, or the number of carbon atoms in the ring of a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocyclyl group. That is, the alkyl, alkenyl, alkynyl, ring of the cycloalkyl, ring of the cycloalkenyl, ring of the aryl, ring of the heteroaryl or ring of the heterocyclyl can contain from “a” to “b”, inclusive, carbon atoms. Thus, for example, a “C₁ to C₄ alkyl” group refers to all alkyl groups having from 1 to 4 carbons, that is, CH₃-, CH₃CH₂-, CH₃CH₂CH₂-, (CH₃)₂CH-, CH₃CH₂CH₂CH₂-, CH₃CH₂CH(CH₃)- and (CH₃)₃C-. If no “a” and “b” are designated with regard to an alkyl, alkenyl, alkynyl, cycloalkyl cycloalkenyl, aryl, heteroaryl or heterocyclyl group, the broadest range described in these definitions is to be assumed.

[0022] As used herein, “alkyl” refers to a straight or branched hydrocarbon chain that comprises a fully saturated (no double or triple bonds) hydrocarbon group. The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as “1 to 20” refers to each integer in the given range; *e.g.*, “1 to 20 carbon atoms” means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. The alkyl group of the compounds may be designated as “C₁-C₄ alkyl” or similar designations. By way of example only, “C₁-C₄ alkyl” indicates that there are one to four carbon atoms in the alkyl chain, *i.e.*, the alkyl chain is selected from methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl and hexyl. The alkyl group may be substituted or unsubstituted.

[0023] As used herein, “alkenyl” refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more double bonds. The length of an alkenyl can vary. For example, the alkenyl can be a C₂₋₄ alkenyl, C₂₋₆ alkenyl or C₂₋₈ alkenyl. Examples of alkenyl groups include allenyl, vinylmethyl and ethenyl. An alkenyl group may be unsubstituted or substituted.

[0024] As used herein, “alkynyl” refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more triple bonds. The length of an alkynyl can vary. For example, the alkynyl can be a C₂₋₄ alkynyl, C₂₋₆ alkynyl or C₂₋₈ alkynyl. Examples of alkynyls include ethynyl and propynyl. An alkynyl group may be unsubstituted or substituted.

[0025] As used herein, “cycloalkyl” refers to a completely saturated (no double or triple bonds) mono- or multi- cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused- or spiro-fashion. Cycloalkyl groups can contain 3 to 10 atoms in the ring(s). 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). A cycloalkyl group may be unsubstituted or substituted. Typical cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[0026] As used herein, “cycloalkenyl” refers to a mono- or multi- cyclic hydrocarbon ring system that contains one or more double bonds in at least one ring; although, if there is more than one, the double bonds cannot form a fully delocalized pi-electron system throughout all the rings (otherwise the group would be “aryl,” as defined herein). When composed of two or more rings, the rings may be connected together in a fused- or spiro-fashion. A cycloalkenyl can contain 3 to 10 atoms in the ring(s) or 3 to 8 atoms in the ring(s). A cycloalkenyl group may be unsubstituted or substituted.

[0027] As used herein, “aryl” refers to a carbocyclic (all carbon) monocyclic or polycyclic aromatic ring system (including fused ring systems where two carbocyclic rings share a chemical bond) that has a fully delocalized pi-electron system throughout all the rings. The number of carbon atoms in an aryl group can vary. For example, the aryl group can be a C₆-C₁₄ aryl group, a C₆-C₁₀ aryl group, or a C₆ aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0028] As used herein, “heteroaryl” refers to a monocyclic, bicyclic and tricyclic aromatic ring system (a ring system with fully delocalized pi-electron system) that contain(s) one or more heteroatoms (for example, 1 to 5 heteroatoms), that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur. The number of atoms in the ring(s) of a heteroaryl group can vary. For example, the heteroaryl group can contain 4 to 14

atoms in the ring(s), 5 to 10 atoms in the ring(s) or 5 to 6 atoms in the ring(s). Furthermore, the term “heteroaryl” includes fused ring systems where two rings, such as at least one aryl ring and at least one heteroaryl ring, or at least two heteroaryl rings, share at least one chemical bond. Examples of heteroaryl rings include, but are not limited to, furan, furazan, thiophene, benzothiophene, phthalazine, pyrrole, oxazole, benzoxazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, thiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, benzothiazole, imidazole, benzimidazole, indole, indazole, pyrazole, benzopyrazole, isoxazole, benzoisoxazole, isothiazole, triazole, benzotriazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, purine, pteridine, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline and triazine. A heteroaryl group may be substituted or unsubstituted.

[0029] As used herein, “heterocyclyl” refers to a monocyclic, bicyclic and tricyclic ring system wherein carbon atoms together with from 1 to 5 heteroatoms constitute said ring system. A heterocycle may optionally contain one or more unsaturated bonds situated in such a way, however, that a fully delocalized pi-electron system does not occur throughout all the rings. The number of atoms in the ring(s) of a heterocyclyl group can vary. For example, the heterocyclyl group can contain 4 to 14 atoms in the ring(s), 5 to 10 atoms in the ring(s) or 5 to 6 atoms in the ring(s). The heteroatom(s) is an element other than carbon including, but not limited to, oxygen, sulfur and nitrogen. A heterocycle may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems and thio-systems such as lactams, lactones, cyclic imides, cyclic thioimides and cyclic carbamates. When composed of two or more rings, the rings may be joined together in a fused fashion. Additionally, any nitrogens in a heterocyclyl may be quaternized. Heterocyclyl groups may be unsubstituted or substituted. Examples of such “heterocyclyl groups include but are not limited to, 1,3-dioxin, 1,3-dioxane, 1,4-dioxane, 1,2-dioxolane, 1,3-dioxolane, 1,4-dioxolane, 1,3-oxathiane, 1,4-oxathiin, 1,3-oxathiolane, 1,3-dithiole, 1,3-dithiolane, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, trioxane, hexahydro-1,3,5-triazine, imidazoline, imidazolidine, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, morpholine, oxirane, piperidine *N*-Oxide, piperidine, piperazine, pyrrolidine, pyrrolidone, pyrrolidione, 4-piperidone, pyrazoline, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, 4H-pyran,

tetrahydrothiopyran, thiamorpholine, thiamorpholine sulfoxide, thiamorpholine sulfone and their benzo-fused analogs (e.g., benzimidazolidinone, tetrahydroquinoline and 3,4-methylenedioxyphenyl).

[0030] As used herein, “aryl(alkyl)” refer to an aryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and aryl group of an aryl(alkyl) may be substituted or unsubstituted. Examples include but are not limited to benzyl, 2-phenyl(alkyl), 3-phenyl(alkyl), and naphthyl(alkyl).

[0031] As used herein, “heteroaryl(alkyl)” refer to a heteroaryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and heteroaryl group of heteroaryl(alkyl) may be substituted or unsubstituted. Examples include but are not limited to 2-thienyl(alkyl), 3-thienyl(alkyl), furyl(alkyl), thienyl(alkyl), pyrrolyl(alkyl), pyridyl(alkyl), isoxazolyl(alkyl), imidazolyl(alkyl), and their benzo-fused analogs.

[0032] A “(heterocyclyl)alkyl” refer to a heterocyclic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocyclyl of a heterocyclyl(alkyl) may be substituted or unsubstituted. Examples include but are not limited tetrahydro-2H-pyran-4-yl(methyl), piperidin-4-yl(ethyl), piperidin-4-yl(propyl), tetrahydro-2H-thiopyran-4-yl(methyl) and 1,3-thiazinan-4-yl(methyl).

[0033] “Lower alkylene groups” are straight-chained $\text{-CH}_2\text{-}$ tethering groups, forming bonds to connect molecular fragments via their terminal carbon atoms. Examples include but are not limited to methylene ($\text{-CH}_2\text{-}$), ethylene ($\text{-CH}_2\text{CH}_2\text{-}$), propylene ($\text{-CH}_2\text{CH}_2\text{CH}_2\text{-}$) and butylenc ($\text{-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{-}$). A lower alkylenc group can be substituted by replacing one or more hydrogen of the lower alkylene group with a substituent(s) listed under the definition of “substituted.” Further, when a lower alkylene group is substituted, the lower alkylene can be substituted by replacing both hydrogens on the same carbon with a

cycloalkyl group (e.g., ).

[0034] As used herein, “alkoxy” refers to the formula -OR wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl) is defined herein. A non-limiting list of alkoxys are methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, phenoxy and benzyloxy. In some instances, an alkoxy can

be -OR, wherein R is an unsubstituted C₁₋₄ alkyl. An alkoxy may be substituted or unsubstituted.

[0035] As used herein, “acyl” refers to a hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl) connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl and acryl. An acyl may be substituted or unsubstituted.

[0036] As used herein, “haloalkyl” refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkyl, di-haloalkyl and tri-haloalkyl). Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-chloro-2-fluoromethyl and 2-fluoroisobutyl. A haloalkyl may be substituted or unsubstituted.

[0037] As used herein, “haloalkoxy” refers to a O-alkyl group and O-monocyclic cycloalkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkoxy, di- haloalkoxy and tri- haloalkoxy). Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-chloro-2-fluoromethoxy, 2-fluoroisobutoxy, chloro-substituted cyclopropyl, fluoro-substituted cyclopropyl, chloro-substituted cyclobutyl and fluoro-substituted cyclobutyl. In some instances, a haloalkoxy can be -OR, wherein R is a C₁₋₄ alkyl substituted by 1, 2 or 3 halogens. A haloalkoxy may be substituted or unsubstituted.

[0038] A “sulfenyl” group refers to an “-SR” group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A sulfenyl may be substituted or unsubstituted.

[0039] A “sulfinyl” group refers to an “-S(=O)-R” group in which R can be the same as defined with respect to sulfenyl. A sulfinyl may be substituted or unsubstituted.

[0040] A “sulfonyl” group refers to an “SO₂R” group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[0041] An “O-carboxy” group refers to a “RC(=O)O-” group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. An O-carboxy may be substituted or unsubstituted.

[0042] The terms “ester” and “C-carboxy” refer to a “-C(=O)OR” group in which R can be the same as defined with respect to O-carboxy. An ester and C-carboxy may be substituted or unsubstituted.

[0043] A “thiocarbonyl” group refers to a “-C(=S)R” group in which R can be the same as defined with respect to O-carboxy. A thiocarbonyl may be substituted or unsubstituted.

[0044] A “trihalomethanesulfonyl” group refers to an “X₃CSO₂-” group wherein each X is a halogen.

[0045] A “trihalomethanesulfonamido” group refers to an “X₃CS(O)₂N(R_A)-” group wherein each X is a halogen, and R_A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl).

[0046] The term “amino” as used herein refers to a -NH₂ group.

[0047] As used herein, the term “hydroxy” refers to a -OH group.

[0048] A “cyano” group refers to a “-CN” group.

[0049] The term “azido” as used herein refers to a -N₃ group.

[0050] An “isocyanato” group refers to a “-NCO” group.

[0051] A “thiocyanato” group refers to a “-CNS” group.

[0052] An “isothiocyanato” group refers to an “-NCS” group.

[0053] A “mercapto” group refers to an “-SH” group.

[0054] A “carbonyl” group refers to a -C(=O)- group.

[0055] An “S-sulfonamido” group refers to a “-SO₂N(R_AR_B)-” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An S-sulfonamido may be substituted or unsubstituted.

[0056] An “N-sulfonamido” group refers to a “RSO₂N(R_A)-” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-sulfonamido may be substituted or unsubstituted.

[0057] An “O-carbamyl” group refers to a “-OC(=O)N(R_AR_B)-” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl,

aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-carbamyl may be substituted or unsubstituted.

[0058] An “N-carbamyl” group refers to an “ $\text{ROC(=O)N(R}_A\text{)-}$ ” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-carbamyl may be substituted or unsubstituted.

[0059] An “O-thiocarbamyl” group refers to a “ $\text{-OC(=S)-N(R}_A\text{R}_B\text{)-}$ ” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-thiocarbamyl may be substituted or unsubstituted.

[0060] An “N-thiocarbamyl” group refers to an “ $\text{ROC(=S)N(R}_A\text{)-}$ ” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-thiocarbamyl may be substituted or unsubstituted.

[0061] A “C-amido” group refers to a “ $\text{-C(=O)N(R}_A\text{R}_B\text{)-}$ ” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A C-amido may be substituted or unsubstituted.

[0062] An “N-amido” group refers to a “ $\text{RC(=O)N(R}_A\text{)-}$ ” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-amido may be substituted or unsubstituted.

[0063] A “mono-substituted amine” refers to a “ -NHR_A ” in which R_A can be independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A mono-substituted amine may be substituted or unsubstituted. In some instances, a mono-substituted amine can be -NHR_A , wherein R_A can be an unsubstituted C_{1-6} alkyl or an unsubstituted or a substituted benzyl.

[0064] A “di-substituted amine” refers to a “ $\text{-NR}_A\text{R}_B$ ” in which R_A and R_B can be independently can be independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A mono-substituted amine may be substituted or unsubstituted. In some instances, a

mono-substituted amine can be $\text{-NR}_\text{A}\text{R}_\text{B}$, wherein R_A and R_B can be independently an unsubstituted C_{1-6} alkyl or an unsubstituted or a substituted benzyl.

[0065] A “ketoamide” group refers to a $\text{-C(=O)-C(=O)N(R}_\text{A}\text{R}_\text{B})$ group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A ketoamide may be substituted or unsubstituted.

[0066] The term “halogen atom” or “halogen” as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, such as, fluorine, chlorine, bromine and iodine.

[0067] Where the numbers of substituents is not specified (e.g. haloalkyl), there may be one or more substituents present. For example “haloalkyl” may include one or more of the same or different halogens. As another example, “ $\text{C}_1\text{-C}_3$ alkoxyphenyl” may include one or more of the same or different alkoxy groups containing one, two or three atoms.

[0068] As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (See, Biochem. 11:942-944 (1972)).

[0069] The term “pharmaceutically acceptable salt” refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), sulfuric acid, nitric acid and phosphoric acid. Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, salicylic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine,

tris(hydroxymethyl)methylamine, C₁-C₇ alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine.

[0070] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term ‘including’ should be read to mean ‘including, without limitation,’ ‘including but not limited to,’ or the like; the term ‘comprising’ as used herein is synonymous with ‘including,’ ‘containing,’ or ‘characterized by,’ and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term ‘having’ should be interpreted as ‘having at least;’ the term ‘includes’ should be interpreted as ‘includes but is not limited to;’ the term ‘example’ is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof. In addition, the term “comprising” is to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a compound or composition, the term "comprising" means that the compound or composition includes at least the recited features or components, but may also include additional features or components.

[0071] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article “a” or “an” does not exclude a plurality.

[0072] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of (R)-configuration or (S)-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, racemic mixture, diastereomerically pure, diastereomerically enriched, or a stereoisomeric mixture. In addition it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof. Likewise, it is understood that, in any compound described, all tautomeric forms are also intended to be included.

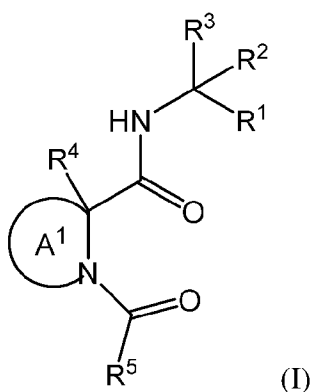
[0073] It is to be understood that where compounds disclosed herein have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof, e.g., hydrogen-1 (protium) and hydrogen-2 (deuterium).

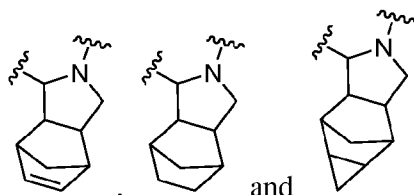
[0074] It is understood that the compounds described herein can be labeled isotopically. Substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

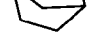
[0075] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

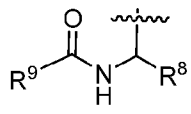
Compounds

[0076] Some embodiments disclosed herein relate to a compound of Formula (I), or a pharmaceutically acceptable salt thereof:





wherein: Ring A¹ can be ,  and , and wherein Ring A¹ can be optionally substituted with one or more moieties independently selected from halogen, an unsubstituted C₁₋₄ alkyl, an unsubstituted C₁₋₄ haloalkyl, an unsubstituted C₂₋₄ alkenyl and an unsubstituted or a substituted C₃₋₆ monocyclic cycloalkyl; R¹ can be selected from cyano, an unsubstituted or a substituted C₂₋₅ alkynyl, an unsubstituted or a substituted acyl, an unsubstituted or a substituted ketoamide, -CH(OH)-(S(=O)₂-O⁻), -CH(OH)((P=O)(OR⁶)₂) and -C(=O)CH₂-O-((P=O)(OR⁷)₂); each R⁶ and each R⁷ can be independently hydrogen, an unsubstituted C₁₋₆ alkyl, an unsubstituted C₂₋₆ alkenyl, an unsubstituted C₁₋₆ haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C₁₋₄ alkyl); R² can be hydrogen, deuterium or halogen; R³ can be an unsubstituted or a substituted monocyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl) or an unsubstituted or a substituted bicyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl); R⁴ can be hydrogen, deuterium or halogen; and

R⁵ can be ; R⁸ can be selected from an unsubstituted or a substituted C₂₋₆ alkyl, an unsubstituted or a substituted C₂₋₆ alkenyl, an unsubstituted or a substituted C₂₋₆ alkynyl, an unsubstituted or a substituted monocyclic C₃₋₆ cycloalkyl, an unsubstituted or a substituted bicyclic C₅₋₈ cycloalkyl and an unsubstituted or a substituted monocyclic 4- to 6-membered heterocyclyl, wherein when the C₂₋₆ alkyl is substituted, the C₂₋₆ alkyl can be substituted 1, 2, 3 or 4 times with a substituent independently selected from halogen and an unsubstituted C₁₋₄ alkoxy; wherein when the C₂₋₆ alkenyl, the C₂₋₆ alkynyl, the monocyclic C₃₋₆ cycloalkyl, the bicyclic C₅₋₈ cycloalkyl and the monocyclic 4- to 6-membered heterocyclyl are substituted, the C₂₋₆ alkenyl, the C₂₋₆ alkynyl, the monocyclic C₃₋₆ cycloalkyl, the bicyclic C₅₋₈ cycloalkyl and the monocyclic 4- to 6-membered heterocyclyl can be substituted 1, 2, 3 or 4 times with a substituent independently selected from halogen, an unsubstituted C₁₋₄ alkyl and an unsubstituted C₁₋₄ alkoxy; and R⁹ can be selected from an unsubstituted C₁₋₆ alkyl, an unsubstituted C₁₋₆ haloalkyl and a substituted monocyclic C₃₋₆ cycloalkyl, wherein the substituted monocyclic C₃₋₆ cycloalkyl is substituted 1, 2, 3 or 4

times with a substituent independently selected from halogen, an unsubstituted C₁₋₄ alkyl and an unsubstituted C₁₋₄ haloalkyl.

[0077] The substituent R¹ can be various moieties. In some embodiments, R¹ can be an unsubstituted ketoamide. In some embodiments, R¹ can be a substituted ketoamide. The ketoamide can have the structure –C(=O)–C(=O)NR^{y1}R^{z1}. In some embodiments, R¹ can be an acyl, for example, R¹ can be –C(=O)H, –C(=O)(an unsubstituted C₁₋₄ alkyl), –C(=O)(an unsubstituted to a substituted benzyl), –C(=O)(an unsubstituted to a substituted monocyclic heteroaryl) or –C(=O)(an unsubstituted to a substituted bicyclic heteroaryl). In some embodiments, R¹ can be a substituted acyl. The acyl for R¹ can have the structure –C(=O)R^{y2}. When the acyl is substituted, the possible groups that can be present on the acyl include hydroxy, a substituted or an unsubstituted alkoxy (such as –O–(an unsubstituted C₁₋₄ alkyl), –O–(an unsubstituted C₃₋₆ cycloalkyl), a substituted or an unsubstituted phenoxy or a substituted or an unsubstituted benzyloxy) or –O–(C=O)–(an unsubstituted C₁₋₆ alkyl). In some embodiments, R¹ can be an unsubstituted can be –C(=O)–N-sulfonamido.

[0078] R^{y1}, R^{y2} and R^{z1} can be a variety of groups. In some embodiments, R^{y1}, R^{y2} and R^{z1} can be independently selected from hydrogen, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl (for example, a monocyclic C₃₋₈ cycloalkyl), C₃₋₈ cycloalkenyl (such as a monocyclic C₃₋₈ cycloalkenyl), aryl (such as phenyl or naphthyl), heteroaryl (including a monocyclic or a bicyclic heteroaryl), heterocyclyl (for example, a monocyclic or a bicyclic heterocyclyl), aryl(alkyl) (such as benzyl), heteroaryl(alkyl) (including a monocyclic heteroaryl(CH₂)– and a monocyclic (heteroaryl(CH₂CH₂)–) or heterocyclyl(alkyl) (such as a monocyclic heterocyclyl(CH₂)– and a monocyclic heterocyclyl(CH₂CH₂)–), wherein each of the aforementioned R^{y1}, R^{y2} and R^{z1} groups can be unsubstituted or substituted. In some embodiments, R^{y1}, R^{y2} and R^{z1} can be independently selected from H, C₁₋₈ alkyl, an unsubstituted C₁₋₄ haloalkyl (including –CF₃, –CCl₃, –CHF₂, –C(CH₃)F₂, –CHCl₂, –CH₂F, –CH(CH₃)F, –CH₂CF₃, –CH₂Cl, –CH₂CH₂F, –CH₂CH₂Cl, –CH₂CH₂CH₂F and –CH₂CH₂CH₂Cl), –C₁₋₄ alkyl(OH) (including –CH₂OH, –CH₂CH₂OH and –CH(CH₃)OH), –C₁₋₄ alkyl(C₁₋₄ alkoxy) (such as –CH₂O(an unsubstituted C₁₋₄ alkyl) and –CH₂CH₂O(an unsubstituted C₁₋₄ alkyl)), –C₁₋₄ alkyl-O-(a monocyclic C₃₋₆ cycloalkyl) (such as –CH₂O(a monocyclic C₃₋₆ cycloalkyl), –CH₂CH₂O(a monocyclic C₃₋₆ cycloalkyl)), –C₁₋₄ alkyl-O-(phenyl) (for example, –CH₂O(phenyl) and –CH₂CH₂O(phenyl)), –C₁₋₄ alkyl-O-(5- to 6-

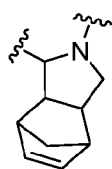
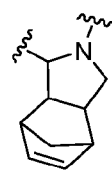
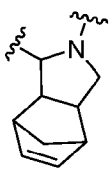
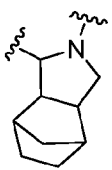
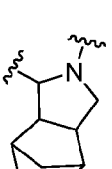
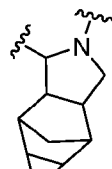
membered monocyclic heteroaryl) (such as $-\text{CH}_2\text{O}$ (5- to 6-membered monocyclic heteroaryl) and $-\text{CH}_2\text{CH}_2\text{O}$ (5- to 6-membered monocyclic heteroaryl)), $-\text{C}_{1-4}$ alkyl-O-(5- to 6-membered monocyclic heterocyclyl) (for example, $-\text{CH}_2\text{O}$ (5- to 6-membered monocyclic heterocyclyl) and $-\text{CH}_2\text{CH}_2\text{O}$ (5- to 6-membered monocyclic heterocyclyl)), $-\text{C}_{1-4}$ alkyl-O-(a monocyclic C_{3-6} cycloalkyl(C_{1-4} alkyl) (such as $-\text{C}_{1-4}$ alkyl-O- CH_2 -(monocyclic C_{3-6} cycloalkyl) and $-\text{C}_{1-4}$ alkyl-O- CH_2CH_2 -(monocyclic C_{3-6} cycloalkyl)), $-\text{C}_{1-4}$ alkyl-O-(benzyl) (for example, $-\text{CH}_2\text{O}$ (benzyl) and $-\text{CH}_2\text{CH}_2\text{O}$ (benzyl)), $-\text{C}_{1-4}$ alkyl-O-(5- to 6-membered monocyclic heteroaryl(C_{1-4} alkyl), $-\text{C}_{1-4}$ alkyl-O-(5- to 6-membered monocyclic heterocyclyl(C_{1-4} alkyl), $-\text{C}_{1-4}$ alkyl-O($\text{C}=\text{O}$)(an unsubstituted C_{1-6} alkyl) (for example, $-\text{CH}_2\text{O}$ ($\text{C}=\text{O}$)(an unsubstituted C_{1-6} alkyl)), a monocyclic C_{3-8} cycloalkyl (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl), a monocyclic heteroaryl (such as imidazole, 1,3,4-oxadiazole and pyridinyl), a monocyclic heterocyclyl (for example, tetrahydrofuran and tetrahydropyran), a bicyclic heteroaryl (for example, benzothiazole, benzoimidazole and benzooxazole), a bicyclic heterocyclyl, a monocyclic C_{3-6} cycloalkyl(alkyl), aryl(alkyl) (such as benzyl), heteroaryl(alkyl) (for example, a monocyclic heteroaryl- $(\text{CH}_2)-$, such as pyridinyl- $(\text{CH}_2)-$ and heterocyclyl(alkyl) (for example, a monocyclic heterocyclyl- $(\text{CH}_2)-$), wherein each of the aforementioned R^{y1} , R^{y2} and R^{z1} groups can be unsubstituted or substituted.

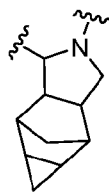
[0079] In some embodiments, R^1 can be $-\text{C}(=\text{O})\text{R}^{\text{y2}}$, wherein R^{y2} can be $-\text{C}_{1-4}$ alkyl(OH) (such as $-\text{CH}_2\text{OH}$). In some embodiments, R^1 can be $-\text{C}(=\text{O})-\text{C}(=\text{O})\text{NR}^{\text{y1}}\text{R}^{\text{z1}}$; wherein R^{y1} can be H; and R^{z1} can be any of the moieties listed for R^{z1} in the previous paragraph. In some embodiments, R^1 can be $-\text{C}(=\text{O})-\text{C}(=\text{O})\text{NR}^{\text{y1}}\text{R}^{\text{z1}}$; wherein R^{y1} can be H; and R^{z1} can be a monocyclic C_{3-8} cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl).

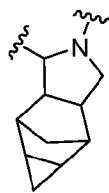
[0080] Prodrug-type and phosphate-containing moieties can be present at R^1 . In some embodiments, R^1 can be $-\text{CH}(\text{OH})-(\text{S}(=\text{O})_2-\text{O}^-)$. In other embodiments, R^1 can be $-\text{CH}(\text{OH})((\text{P}=\text{O})(\text{OR}^6)_2)$, wherein each R^6 can be independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C_{1-4} alkyl). In still other embodiments, R^1 can be $-\text{C}(=\text{O})\text{CH}_2-\text{O}-((\text{P}=\text{O})(\text{OR}^7)_2)$, wherein each R^7 can be independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an

unsubstituted C₁₋₆ haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C₁₋₄ alkyl). Other examples of R⁶ and R⁷ groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl (straight-chained and branched), hexyl (straight-chained and branched), ethenyl, propenyl, butenyl, pentenyl, hexenyl, chloromethyl, fluoromethyl, difluoromethyl, dichloromethyl, trifluoromethyl, trichloromethyl, an unsubstituted or a substituted phenyl and an unsubstituted or a substituted benzyl.

[0081] In some embodiments, R¹ can be cyano. In other embodiments, R¹ can be an unsubstituted C₂₋₅ alkynyl. In still other embodiments, R¹ can be a substituted C₂₋₅ alkynyl. The C₂₋₅ alkynyl can have various structures. For example, the C₂₋₅ alkynyl can have the structure $-(CH_2)_1-C_{2-4}$ alkynyl or $-(CH_2)_2-C_{2-3}$ alkynyl.

[0082] As described herein, Ring A¹ can be , wherein Ring A¹ can be optionally substituted. In some embodiments, Ring A¹ can be an unsubstituted . In other embodiments, Ring A¹ can be a substituted . In still other embodiments, Ring A¹ can be an unsubstituted . In yet still other embodiments, Ring A¹ can be a substituted . In some embodiments, Ring A¹ can be an unsubstituted . In

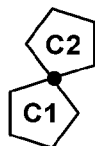


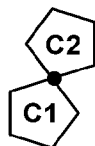
other embodiments, Ring A¹ can be a substituted . Example of suitable substituents that can be present in Ring A¹ include halogen (such as F or Cl), an unsubstituted C₁₋₄ alkyl (for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl), an unsubstituted C₁₋₄ haloalkyl (including -CF₃, -CCl₃, -CHF₂, -C(CH₃)F₂, -CHCl₂, -CH₂F, -CH(CH₃)F, -CH₂CF₃, -CH₂Cl, -CH₂CH₂F, -CH₂CH₂Cl, -CH₂CH₂CH₂F and -CH₂CH₂CH₂Cl), an unsubstituted C₂₋₄ alkenyl (such as ethenyl, propenyl and butenyl) and an unsubstituted or a substituted C₃₋₆ monocyclic cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl).

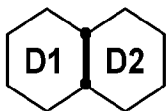
[0083] In some embodiments, R⁴ can be hydrogen. In other embodiments, R⁴ can be deuterium. In still other embodiments, R⁴ can be halogen (such as fluoro or chloro).

[0084] As provided herein R³ can be a non-hydrogen substituent selected from an unsubstituted or a substituted monocyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl) and an unsubstituted or a substituted bicyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl). In some embodiments, R³ can be an unsubstituted monocyclic nitrogen-containing heteroaryl(C₁₋₄ alkyl). In other embodiments, R³ can be a substituted monocyclic nitrogen-containing heteroaryl(C₁₋₄ alkyl). In still other embodiments, R³ can be an unsubstituted bicyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl). In yet still other embodiments, R³ can be a substituted bicyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl). When R³ is a bicyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl), the two rings of the bicyclic heterocyclyl can be connected in a fused-fashion (including bridged-fashion) or a spiro-fashion.

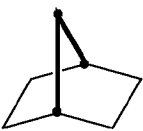
[0085] Those skilled in the art understand that when two rings are connected in a spiro-fashion, the two rings are connected by a single ring atom. For example, in the



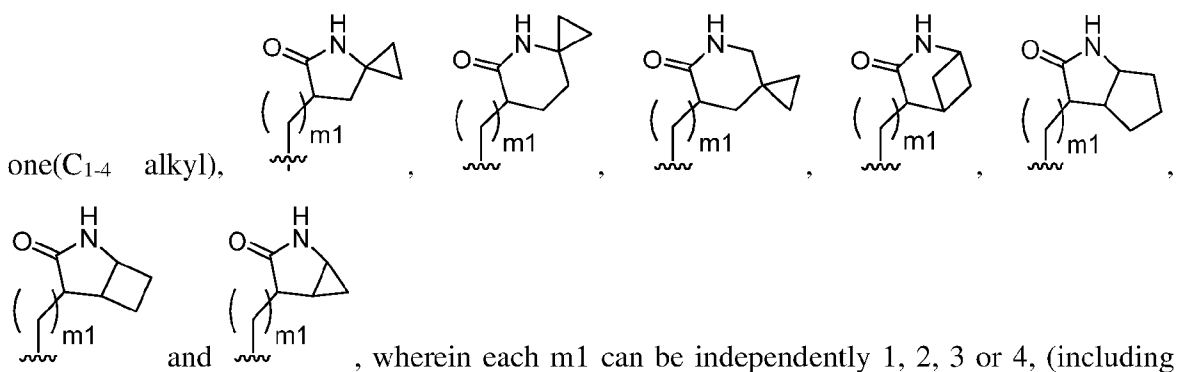
structure  rings C1 and C2 are joined in a spiro-fashion. When two rings described herein are connected in a fused-fashion, the two rings are connected by two or more ring atoms. . In some instances, the two rings can be connected by two adjacent ring atoms. As an example, rings D1 and D1 are connected in a fused-fashion by two adjacent ring atoms



. In some instances, two rings described herein can be connected by three or

more atoms are shared between the two rings. The following structure:  is an example of two rings being connected by three or more ring atoms. When two rings are connected by three or more ring atoms, the three or more ring atoms connecting the two rings would be referred to by those skilled in the art as “bridging” atoms. Further, those skilled in the art would understand based on the disclosure provided herein that two rings connected in a “bridged” fashion is an example of two rings connected in a fused-fashion.

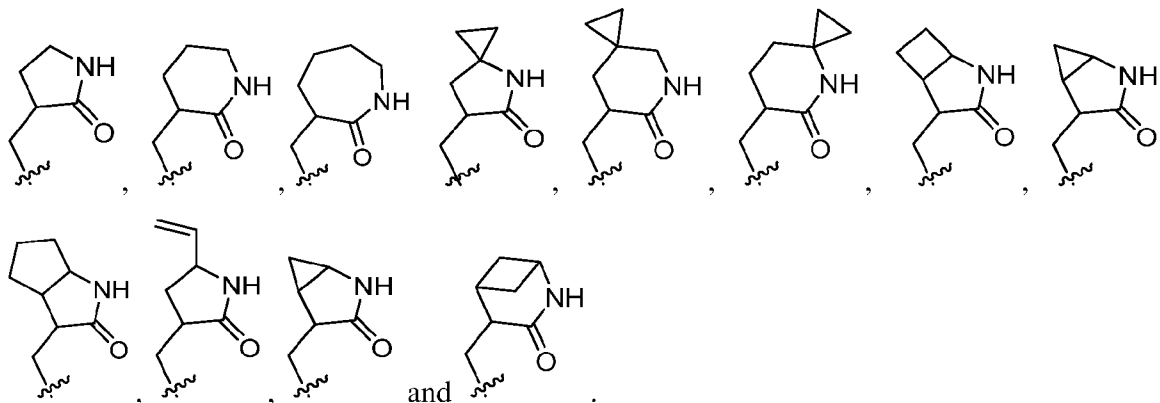
[0086] The number of ring atoms for a monocyclic and a bicyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl) can vary. Non-limiting examples include an unsubstituted or a substituted 5-membered monocyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl), 6-membered monocyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl), an unsubstituted or a substituted 9-membered bicyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl) and 10-membered bicyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl). Examples of suitable R³ groups include the following: azepan-2-one(C₁₋₄ alkyl), imidazolidin-2-one(C₁₋₄ alkyl), tetrahydropyrimidin-2-one(C₁₋₄ alkyl), pyrrolidin-2-one(C₁₋₄ alkyl), piperidin-2-



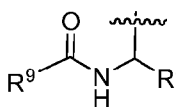
The R³ groups provided herein can be substituted with one or more moieties independently selected from those listed for “optionally substituted.” In some embodiments, a R³ group provided herein can be substituted with one or more moieties selected from halogen, hydroxy, an unsubstituted C₁₋₄ alkyl, an unsubstituted C₂₋₄ alkenyl an unsubstituted C₁₋₄ alkoxy, amino, –(an unsubstituted

C₁₋₄ alkyl)-O-P-(OH)₂ (such as -CH₂-O-P-(OH)₂) and -(an unsubstituted C₁₋₄ alkyl)-O-P-(O(an unsubstituted C₁₋₄ alkyl))₂ (such as -CH₂-O-P-(OCH₃)₂).

[0087] Non-limiting examples of R³ moieties include the following:



[0088] In some embodiments, R² can be hydrogen. In other embodiments, R² can be deuterium. In still other embodiments, R² can be halogen (for example, fluoro or chloro).

[0089] As provided herein, R⁵ can be . In some embodiments, R⁹ can be an unsubstituted C₁₋₆ haloalkyl. For example, R⁹ can be -CF₃, -CCl₃, -CHF₂, -C(CH₃)F₂, -CHCl₂, -CH₂F, -CH(CH₃)F, -CH₂CF₃, -CH₂Cl, -CH₂CH₂F, -CH₂CH₂Cl, -CH₂CH₂CH₂F and -CH₂CH₂CH₂Cl. In some embodiments, R⁹ can be -CF₃. In other embodiments, R⁹ can be an unsubstituted C₁₋₆ alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl (straight-chained or branched) and hexyl (straight-chained or branched). In still other embodiments, R⁹ can be halogen-substituted monocyclic C₃₋₆ cycloalkyl. In yet still other embodiments, R⁹ can be a monocyclic C₃₋₆ cycloalkyl substituted with an unsubstituted C₁₋₄ alkyl. In some embodiments, R⁹ can be a monocyclic C₃₋₆ cycloalkyl substituted with an unsubstituted C₁₋₄ haloalkyl. Suitable halogen-substituted monocyclic C₃₋₆ cycloalkyls include halogen-substituted cyclopropyl, halogen-substituted cyclobutyl, halogen-substituted cyclopentyl and halogen-substituted cyclohexyl. Additional monocyclic C₃₋₆ cycloalkyls include cyclopropyl substituted with an unsubstituted C₁₋₄ alkyl and/or an unsubstituted C₁₋₄ haloalkyl, cyclobutyl substituted with an unsubstituted C₁₋₄ alkyl and/or an unsubstituted C₁₋₄ haloalkyl, cyclopentyl substituted with an unsubstituted C₁₋₄ alkyl and/or an unsubstituted C₁₋₄ haloalkyl and cyclohexyl substituted with an unsubstituted C₁₋₄ alkyl and/or an unsubstituted C₁₋₄

haloalkyl. The number halogens on a halogen-substituted monocyclic C₃₋₆ cycloalkyl, the number of unsubstituted C₁₋₄ alkyls on a monocyclic C₃₋₆ cycloalkyl and the number of unsubstituted C₁₋₄ haloalkyls on a monocyclic C₃₋₆ cycloalkyl can vary. For example, 1, 2, 3 or 4 halogen can be present on a halogen-substituted monocyclic C₃₋₆ cycloalkyl, 1, 2, 3 or 4 unsubstituted C₁₋₄ alkyls can be present on a monocyclic C₃₋₆ cycloalkyl substituted with an unsubstituted C₁₋₄ alkyl, and 1, 2, 3 or 4 unsubstituted C₁₋₄ haloalkyls can be present on a monocyclic C₃₋₆ cycloalkyl substituted with an unsubstituted C₁₋₄ haloalkyl. In some embodiments, a monocyclic C₃₋₆ cycloalkyl substituted with 1 or more substituents (such as 1, 2, 3 or 4 substituents) selected from halogen, an unsubstituted C₁₋₄ alkyl and an unsubstituted C₁₋₄ haloalkyl. Suitable halogens that can be present on a substituted monocyclic C₃₋₆ cycloalkyl include, but are not limited to, fluoro (F) and chloro (Cl). Examples of unsubstituted C₁₋₄ haloalkyls include, but are not limited to, -CF₃, -CCl₃, -CHF₂, -C(CH₃)F₂, -CHCl₂, -CH₂F, -CH(CH₃)F, -CH₂CF₃, -CH₂Cl, -CH₂CH₂F, -CH₂CH₂Cl, -CH₂CH₂CH₂F and -CH₂CH₂CH₂Cl.

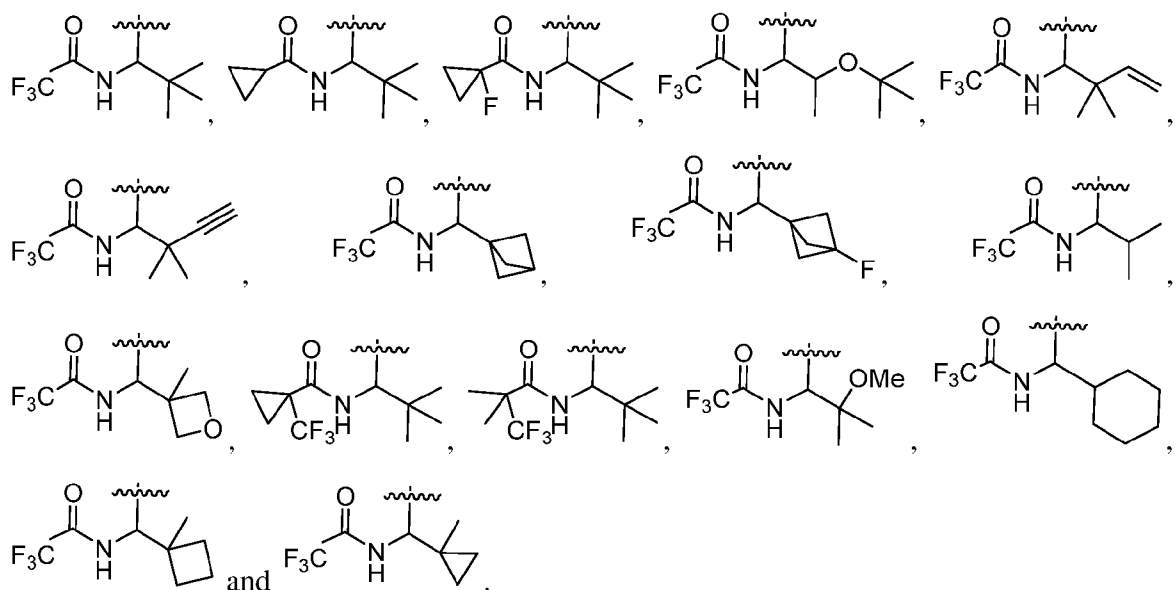
[0090] The R⁸ moiety can be a substituted or an unsubstituted version of a C₂₋₆ alkyl, a C₂₋₆ alkenyl, a C₂₋₆ alkynyl, a monocyclic C₃₋₆ cycloalkyl, a bicyclic C₅₋₈ cycloalkyl or a monocyclic 4- to 6-membered heterocyclyl. In some embodiments, R⁸ can be an unsubstituted C₂₋₆ alkyl. In other embodiments, R⁸ can be a substituted C₂₋₆ alkyl. Exemplary C₂₋₆ alkyls include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl (straight-chained and branched) and hexyl (straight-chained and branched). In some embodiments, R⁸ can be an unsubstituted C₂₋₆ alkenyl. In other embodiments, R⁸ can be a substituted C₂₋₆ alkenyl. In still other embodiments, R⁸ can be an unsubstituted C₂₋₆ alkynyl. In yet still other embodiments, R⁸ can be a substituted C₂₋₆ alkynyl.

[0091] Cyclic moieties, including monocyclic and bicyclic moieties, can also be present for R⁸. In some embodiments, R⁸ can be an unsubstituted monocyclic C₃₋₆ cycloalkyl. In some embodiments, R⁸ can be a substituted monocyclic C₃₋₆ cycloalkyl. For example, R⁸ can be a substituted or an unsubstituted cyclopropyl, a substituted or an unsubstituted cyclobutyl, a substituted or an unsubstituted cyclopentyl or a substituted or an unsubstituted cyclohexyl. In some embodiments, R⁸ can be an unsubstituted bicyclic C₅₋₈ cycloalkyl. In other embodiments, R⁸ can be an unsubstituted bicyclic C₅₋₈ cycloalkyl. The two rings of the bicyclic C₅₋₈ cycloalkyl can be joined in a fused or a spiro-fashion. Examples

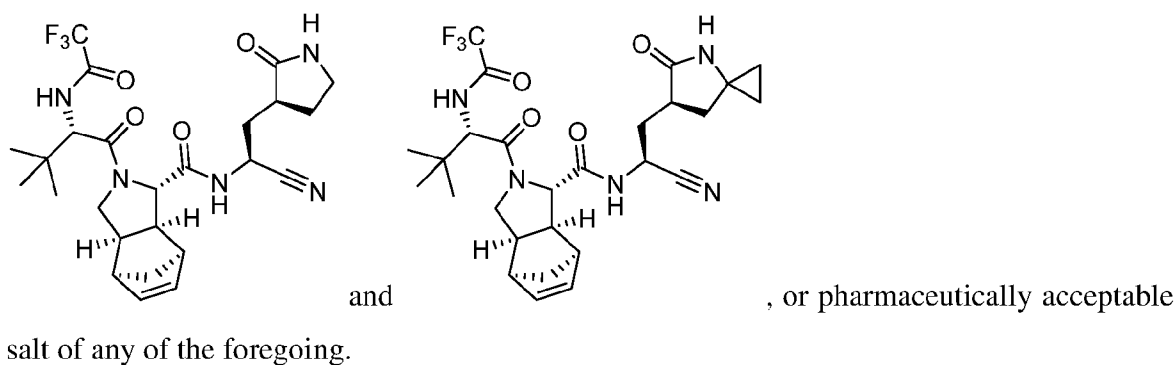
of rings connected in a fused and a spiro-fashion are provided herein. In some embodiments, R^8 can be an unsubstituted or a substituted bicyclo[1.1.1]pentyl. In still other embodiments, R^8 can be an unsubstituted monocyclic 4- to 6-membered heterocyclyl. In yet still other embodiments, R^8 can be an unsubstituted monocyclic 4- to 6-membered heterocyclyl. The number of heteroatoms present in a monocyclic 4- to 6-membered heterocyclyl for R^8 can vary. Suitable heteroatoms include, but are not limited to, O (oxygen), S (sulfur) and N (nitrogen). Examples of monocyclic 4- to 6-membered heterocyclyls are oxetane, thietane, azetidine, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, tetrahydropyran, tetrahydrothiopyran and piperidine (including unsubstituted or substituted versions of each of the aforementioned).

[0092] As described herein, R^8 can be substituted. In some embodiments, when R^8 is a C_{2-6} alkyl that is substituted, the C_{2-6} alkyl can be substituted 1, 2, 3 or 4 times with a substituents independently selected from halogen and an unsubstituted C_{1-4} alkoxy. Each halogen can be independently F (fluoro) or Cl (chloro). Suitable unsubstituted C_{1-4} alkoxy that can be substituted on a C_{2-6} alkyl of R^8 include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy. In some embodiments, when R^8 is a substituted C_{2-6} alkenyl, a substituted C_{2-6} alkynyl, a substituted monocyclic C_{3-6} cycloalkyl, a substituted bicyclic C_{5-8} cycloalkyl or a substituted monocyclic 4- to 6-membered heterocyclyl, each of the aforementioned can be substituted 1, 2, 3 or 4 times with a substituents independently selected from halogen, an unsubstituted C_{1-4} alkyl and an unsubstituted C_{1-4} alkoxy. Examples of unsubstituted C_{1-4} alkyls that can be substituted on a substituted C_{2-6} alkenyl, a substituted C_{2-6} alkynyl, a substituted monocyclic C_{3-6} cycloalkyl, a substituted bicyclic C_{5-8} cycloalkyl or a substituted monocyclic 4- to 6-membered heterocyclyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl and tert-butyl. Suitable halogens and unsubstituted C_{1-4} alkoxy that can be present on a substituted C_{2-6} alkenyl, a substituted C_{2-6} alkynyl, a substituted monocyclic C_{3-6} cycloalkyl, a substituted bicyclic C_{5-8} cycloalkyl or a substituted monocyclic 4- to 6-membered heterocyclyl are described herein, such as in this paragraph.

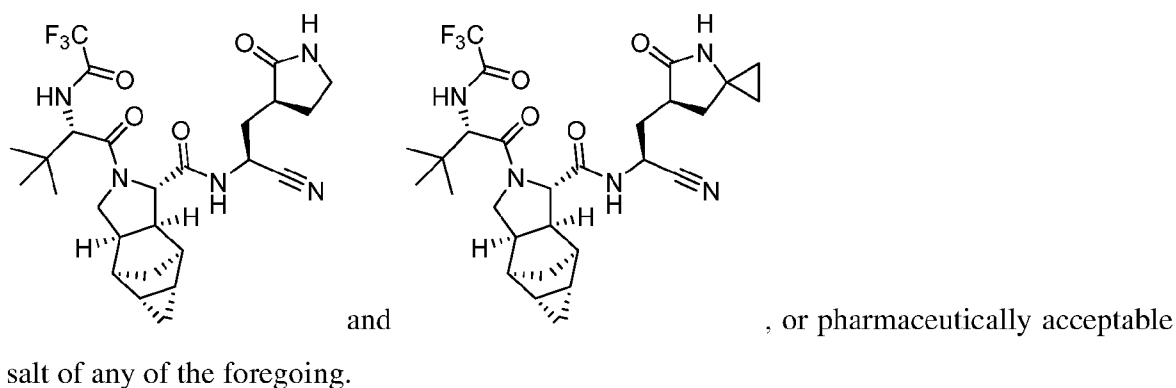
[0093] Exemplary R⁵ groups include the following:



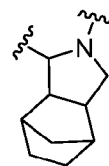
[0094] Examples of compounds of Formula (I), include the following:



[0095] Additional examples of compounds of Formula (I), include the following:



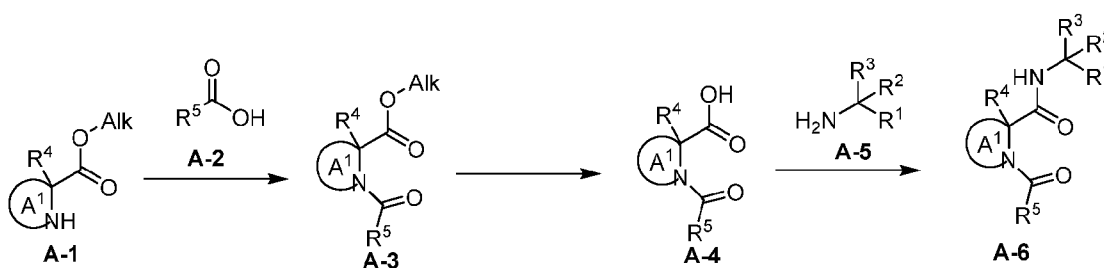
[0096] In some embodiments, Ring A¹ cannot be



Synthesis

[0097] Compounds of Formula (I) along with those described herein may be prepared in various ways. General synthetic routes for preparing compounds of Formula (I) are shown and described herein along with some examples of starting materials used to synthesize compounds described herein. Additionally, for the purpose of the general synthetic routes, the structures depicted are appropriately protected, as known by one skilled in the art and the generic structures are meant to include these protecting groups. The routes shown and described herein are illustrative only and are not intended, nor are they to be construed, to limit the scope of the claims in any manner whatsoever. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

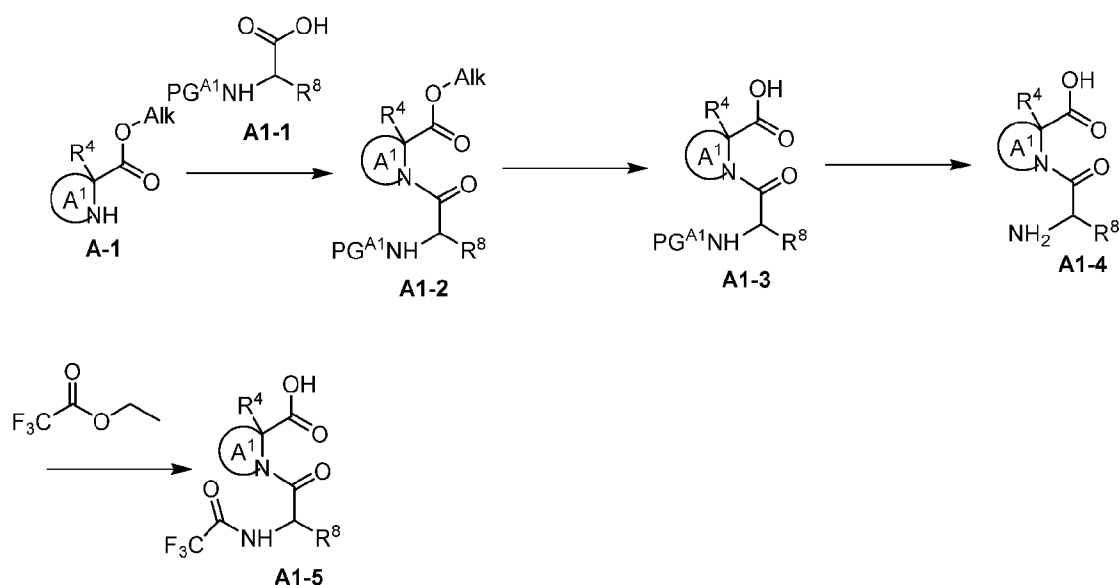
Scheme A



[0098] Scheme A describes the synthesis of compounds of general Formula (A-6). An amino ester of general Formula (A-1) (Alk represents alkyl) with an acid of general Formula (A-2), either by activating the carboxylic acid by converting it to an acid chloride, followed by reaction with the amino acid in the presence of a base, or by activation of the acid with a coupling reagent (such as HATU) followed by coupling with the amino ester in the presence of a base (such as DIPEA), resulting in a compound of general Formula (A-3). The ester functionality of general Formula (A-3) can be hydrolyzed, for example, under basic

conditions of -OAlk is -OMe, using LiOH in MeOH, providing in a compound of general Formula (A-4). Further coupling of the carboxylic acid of general Formula (A-4) with an amine of general Formula (A-5) can provide a compound of general Formula (A-6). For the purpose of the generic synthesis, R¹ may be a latent functionality, converted to a functionality as described herein for R¹.

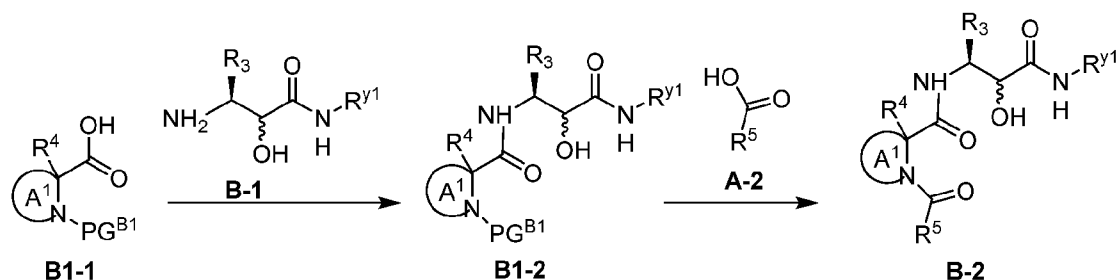
Scheme A1



[0099] Alternatively, as described in Scheme A1, a sub-group of amino acids of general Formula (A1-5) can be prepared as described in Scheme A1. A protected (PG^{A1}) amino acid of general Formula (A1-1) can be coupled with an aminoester of general Formula (A-1) under known amide formation conditions, for example, HATU and iPr₂NEt. The ester of a compound of Formula (A1-2) can be deprotected, for example, by using LiOH in THF/H₂O, resulting in the acid of general Formula (A1-3). The protecting group PG^{A1} can be removed, for example, by treatment with TFA in case PG^{A1} being Boc, resulting in a compound of general Formula (A1-4). This compound can be converted to a compound of general Formula (A1-5), for example, by treatment with trifluoroethyl acetate in the presence of triethylamine.

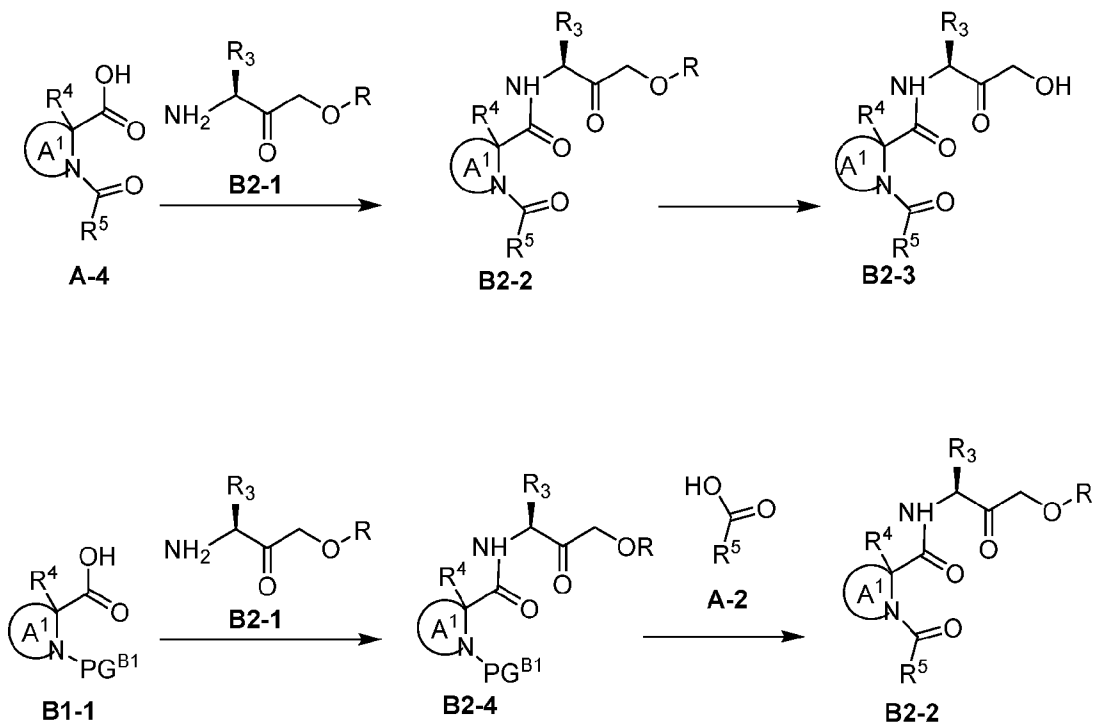
[0100] General methodology for the synthesis of amino acids of general Formula (A1-1), or precursors that could be converted to an amino acid of general Formula (A1-1) by one skilled in the art, are described in the literature, and include the following examples:

Scheme B1



[0102] Alternatively, as depicted in Scheme B1, an amino acid of general Formula (B1-1) (with PG^{B1} a protecting group of the nitrogen, for example, -Boc) can be coupled with a compound of general Formula (B-1), similar as described for the conversion of a compound of general Formula (A-4) to a compound of general Formula (B-2). The protecting group can be removed, for example, by treatment with an acid in case of PG^{B1} being Boc, followed by coupling with a compound of general Formula (A-2), resulting in the formation of a compound of general formula (B-2).

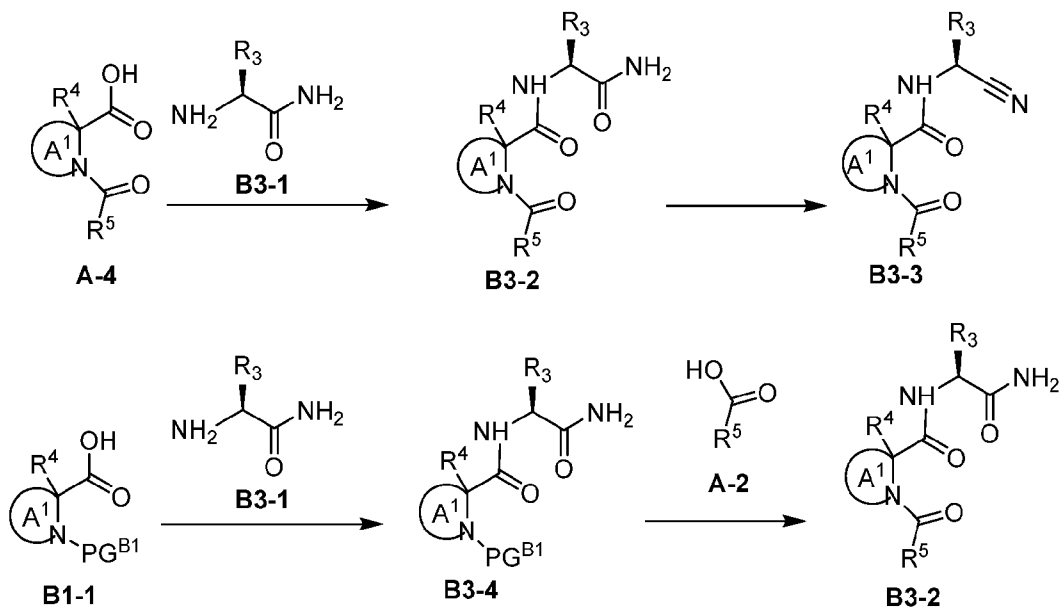
Scheme B2



[0103] As described herein, R¹ can be a substituted acyl, where the possible groups that can be present on the acyl include hydroxy, a substituted or an unsubstituted

alkoxy (for example, $-\text{O}-$ (an unsubstituted C_{1-4} alkyl) and $-\text{O}-$ (an unsubstituted C_{3-6} cycloalkyl)), an unsubstituted C_{1-4} alkyl (such as a heteroaryl substituted with an unsubstituted C_{1-4} alkyl), a substituted or an unsubstituted phenoxy or a substituted or an unsubstituted benzyloxy). In Scheme B2, R can represent any of the aforementioned moieties that can be present on a substituted acyl for R^1 . Compounds of general Formulae (B2-2) and (B2-3) can be prepared as described in Scheme B2. An amino-ketone compound of general Formula (B2-1) can be coupled to a carboxylic acid of general Formula (A-4) or (B1-1) under typical amide coupling conditions. A compound of general Formula (B2-2) can be optionally further converted in a hydroxyketone of general Formula (B2-3), for example, in case where R represents a benzyl group, by catalytic hydrogenolysis. The PG^{B1} of a compound of general Formula (B2-4) can be deprotected (for example in the case wherein PG^{B1} is a Boc-group, by treatment with HCl in Et_2O). The amine can then be coupled with a carboxylic acid of general Formula (A-2) under typical amide bond formation conditions, to provide a compound of general Formula (B2-2).

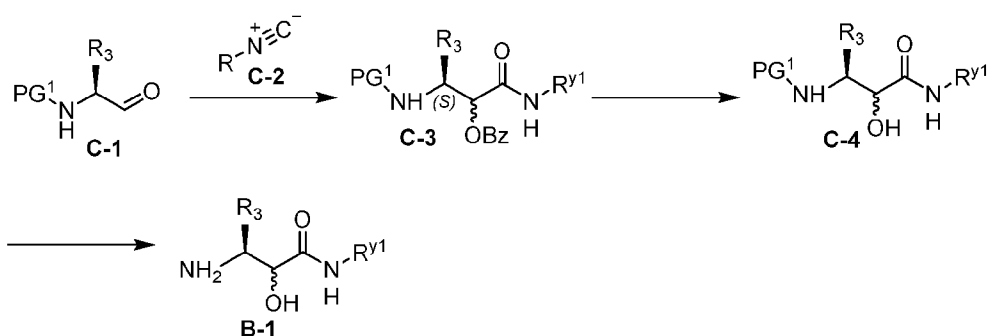
Scheme B3



[0104] Similar as described in Scheme B2 for a compound of Formula (B2-2), using an amide of general Formula (B3-1) in place of a compound of general Formula (B2-1), a compound of general Formula (B3-2) can be obtained. Conversion of a compound of

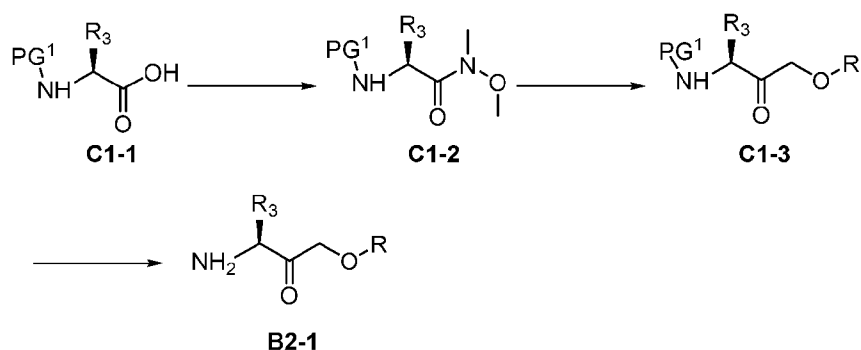
general Formula (B3-2) to a compound of general Formula B3-3 can, for example, occur under the influence of trifluoroacetic anhydride (TFAA) and pyridine in CH₂Cl₂, or by application of the Burgess reagent.

Scheme C



[0105] A compound of general Formula (B-1) can be prepared as outlined in Scheme C. An aldehyde of general Formula (C-1) (PG¹ can be a nitrogen protecting group, for example -Boc) and an isonitrile of general Formula (C-2), in the presence of a carboxylic acid (for example, benzoic acid), can be condensed in a Passerini-like reaction towards a compound of general Formula (C-3). After hydrolysis, a compound of general Formula (C-4) can be obtained. The PG¹ can be removed, for example, by treatment with HCl when PG¹ can be Boc.

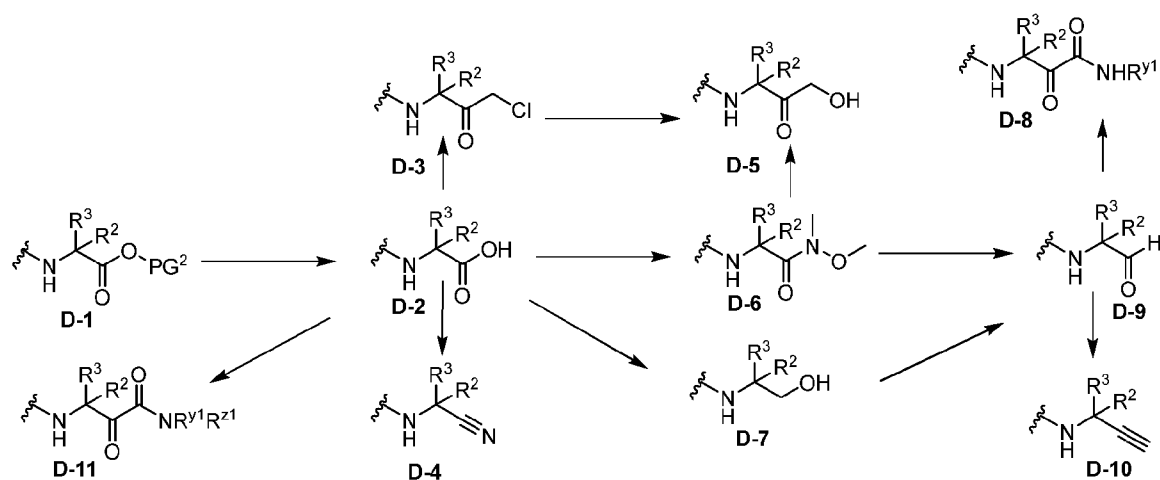
Scheme C1



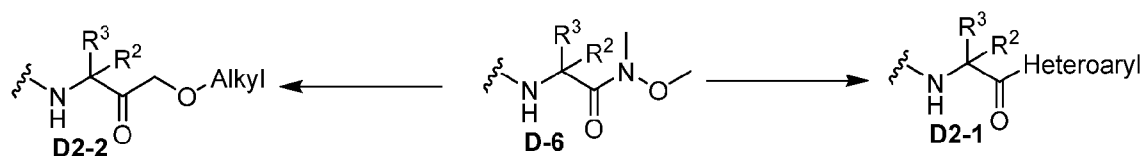
[0106] An amino ketone of general Formula (B2-1), can be prepared as outline in Scheme C1. A protected amino acid of general Formula (C1-1) can be converted to its corresponding Weinreb amide under typical amide coupling conditions. Addition of an organometallic reagent to the Weinreb amide, followed by work-up, can result in a ketone of

general Formula (C1-3). An example, wherein R can be benzyl, is the formation of an organometallic reagent by mixing Mg, HgCl₂ and benzylchloromethyl ether, followed by addition to a Weinreb amide of general Formula (C1-2), followed by work-up with saturated ammonium chloride. The protecting group (PG¹) can be removed (for example, when PG¹ is Boc, the protecting group can be removed using HCl) resulting in the formation of an amino ketone of general Formula (B2-1). When HCl is used for the deprotection, a compound of general Formula (B2-1) can be obtained as a HCl salt. Examples of a compound of general Formula (C1-1) are (S)-2-((tert-butoxycarbonyl)amino)-3-((S)-2-oxopiperidin-3-yl)propanoic acid and (S)-2-((tert-butoxycarbonyl)amino)-3-((S)-2-oxopyrrolidin-3-yl)propanoic acid.

Scheme D1

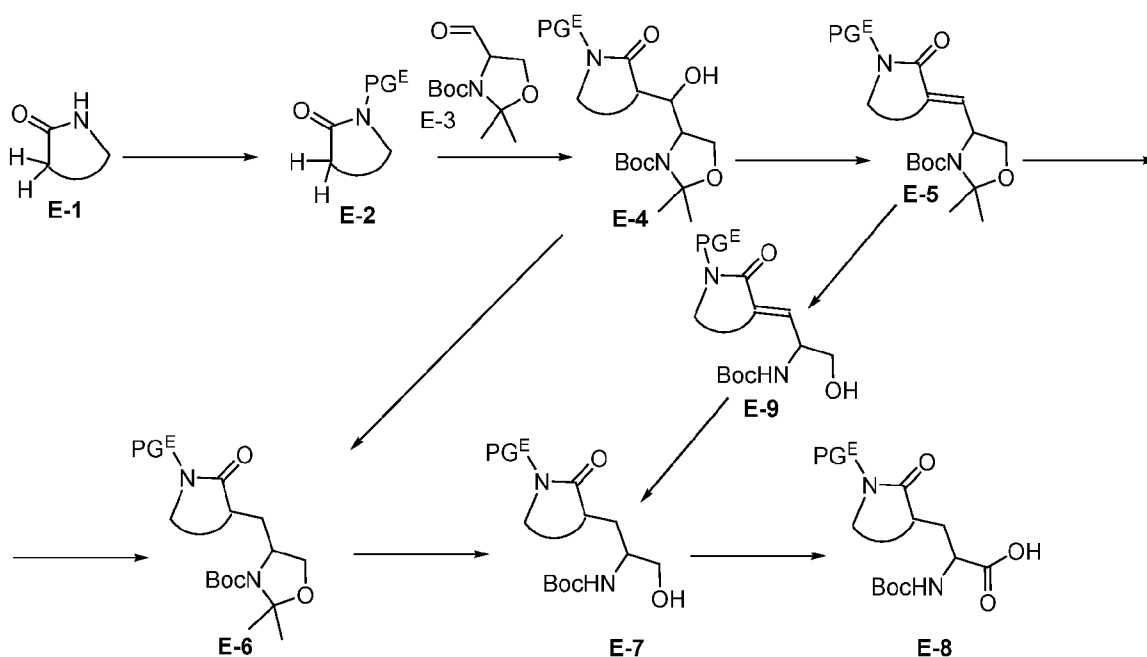


Scheme D2



[0107] Other conversions for R¹ described herein are shown in Schemes D1 and D2. In Schemes D1 and D2, PG² represents an appropriate protecting group, and R^{z1} and R^{y1} are part of the ketoamide described herein with respect to R¹.

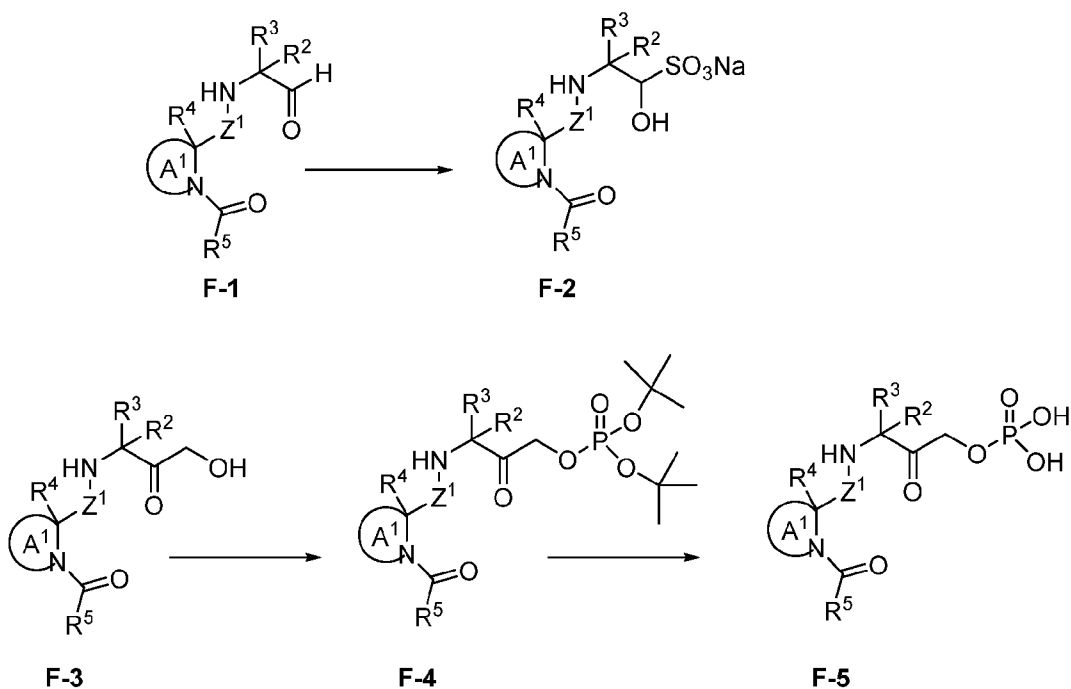
Scheme E



[0108] A method for preparing a sub-group of amino acids of general Formula (E-8) are provided in Scheme E. A lactam of general Formula (E-1) can be protected with a suitable protecting group, PG^E. An example of such a PG^E group is a Boc-group. For the purpose of the Scheme E, this protecting group can be removed at any relevant stage; and therefore, PG^E present hydrogen for any of compounds of general Formulae (E-4), (E-5), (E-6), (E-7), (E-8) and (E-9). The lactam of general Formula (E-2) can be reacted with an aldehyde of general Formula (E-3) (S or R-garner's aldehyde). The alcohol of general Formula (E-4) can be eliminated to provide an alkene compound of general Formula (E-5) (for example, by sequential conversion of the hydroxy to a corresponding mesylate, followed by elimination under basic conditions). The double bond can be reduced (for example, by hydrogenation, under influence of a homogeneous or a heterogenous catalyst, optionally diastereoselective) to provide a compound of general Formula (E-6). Removal of the acetonide in a compound of general Formula (E-6) to the Boc-protected amino alcohol of general Formula (E-7) can be followed by the oxidation to the carboxylic acid of general Formula (E-8). Alternatively, the acetonide can be deprotected in a compound of general Formula (E-5) to obtain a compound of general Formula (E-9). Reduction of the double bond of a compound of general Formula (E-9) (for example, by hydrogenation under

influence of a homogeneous or a heterogenous catalyst, optionally diastereoselective) can be used to obtain a compound of general Formula (E-7). A compound of general Formula (E-4) can be deoxygenated, for example, by a Barton-type deoxygenation, to provide a compound of general Formula (E-6).

Scheme F

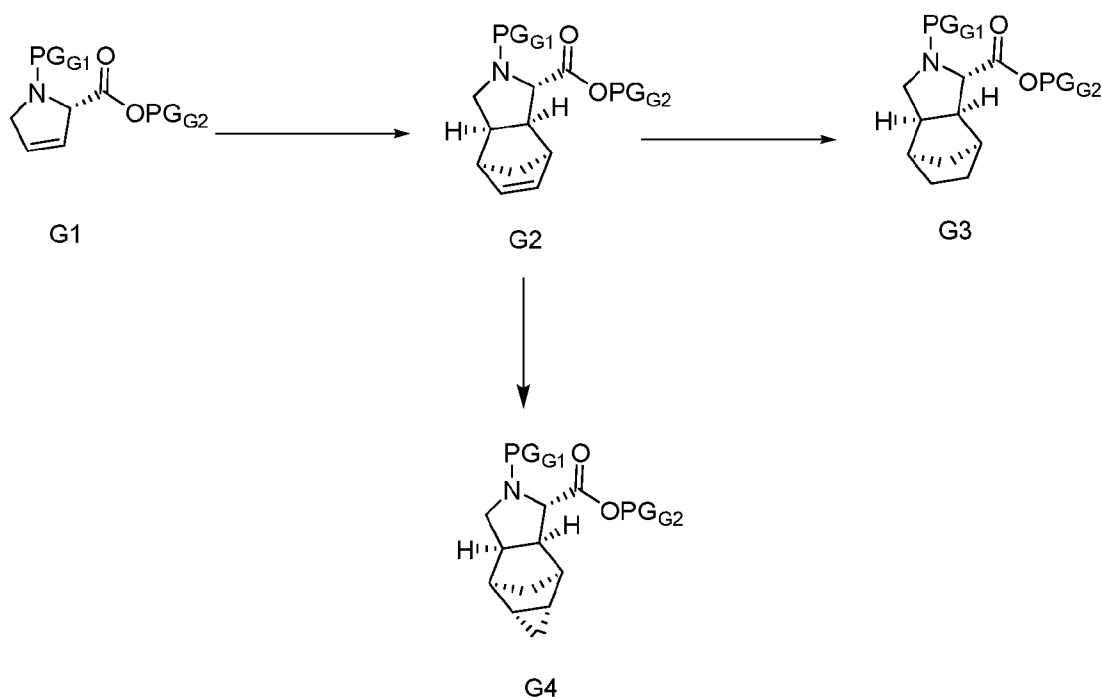


[0109] Compounds of Formula (I) can include a prodrug moieties. A method for including a prodrug moiety is depicted in Scheme F. For example an aldehyde of general Formula (F-1) can be transformed into the corresponding bisulfite adduct of general Formula (F-2), by treatment with NaHSO_3 . A hydroxyketone of general Formula (F-3), can be transformed to the corresponding phosphate of general Formula (F-5), for example, by treatment with di-tert-butyl N,N-dipropylphosphoramidite and tetrazole followed by oxidation with H_2O_2 , that can provide a compound of general Formula (F-4). A compound of general Formula (F-4) can be deprotected (for example by treatment with TFA) to provide a compound of general Formula (F-5).

[0110] As shown in Scheme G, the synthesis of an amino ester of general Formula (G2) can be accomplished via a Diels-Alder reaction, such as described in Arakawa et al., Chemical & Pharmaceutical Bulletin (2003) 51(8), 1015-1020 ($-\text{PG}_{\text{GI}}$ can be $-\text{Bz}$ and

–PG_{G2} can be –CH₃). Also described herein in the synthesis of intermediates, is the use of –PG_{G1} is –Boc and –PG_{G2} is –t-Butyl. A compound of general Formula (G2) can be deprotected using methods known to those skilled in the art and depending on the protecting group used for PG_{G1} and PG_{G2}. Alternatively, a compound of general Formula (G2) can be converted to a compound of general Formula (G3), by hydrogenation of the double bond, or to a compound of general Formula (G4), by cyclopropanation of the double bond. The cyclopropanation can, for example, be performed by application of a Simmons-smith cyclopropanation, by treatment with CH₂N₂ in the presence of Pd(OAc)₂, or other methods described known to those skilled in the art.

Scheme G



Pharmaceutical Compositions

[0111] Some embodiments described herein relate to a pharmaceutical composition, that can include an effective amount of a compound described herein (e.g., a compound, or a pharmaceutically acceptable salt thereof, as described herein) and a pharmaceutically acceptable carrier, excipient or combination thereof. A pharmaceutical composition described herein is suitable for human and/or veterinary applications.

[0112] As used herein, a “carrier” refers to a compound that facilitates the incorporation of a compound into cells or tissues. For example, without limitation, dimethyl sulfoxide (DMSO) is a commonly utilized carrier that facilitates the uptake of many organic compounds into cells or tissues of a subject.

[0113] As used herein, a “diluent” refers to an ingredient in a pharmaceutical composition that lacks pharmacological activity but may be pharmaceutically necessary or desirable. For example, a diluent may be used to increase the bulk of a potent drug whose mass is too small for manufacture and/or administration. It may also be a liquid for the dissolution of a drug to be administered by injection, ingestion or inhalation. A common form of diluent in the art is a buffered aqueous solution such as, without limitation, phosphate buffered saline that mimics the composition of human blood.

[0114] As used herein, an “excipient” refers to an inert substance that is added to a pharmaceutical composition to provide, without limitation, bulk, consistency, stability, binding ability, lubrication, disintegrating ability etc., to the composition. A “diluent” is a type of excipient.

[0115] Proper formulation is dependent upon the route of administration chosen. Techniques for formulation and administration of the compounds described herein are known to those skilled in the art. Multiple techniques of administering a compound exist in the art including, but not limited to, oral, rectal, topical, aerosol, injection, inhalation and parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intranasal and intraocular injections. Pharmaceutical compositions will generally be tailored to the specific intended route of administration.

[0116] One may also administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into the infected area, often in a depot or sustained release formulation. Furthermore, one may administer the compound in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes may be targeted to and taken up selectively by the organ.

[0117] The pharmaceutical compositions disclosed herein may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting

processes. As described herein, compounds used in a pharmaceutical composition may be provided as salts with pharmaceutically compatible counterions.

Methods of Use

[0118] Some embodiments described herein relate to a method of treating a coronavirus infection that can include administering to a subject identified as suffering from the coronavirus infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating a coronavirus infection. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein or a pharmaceutical composition that includes a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating a coronavirus infection.

[0119] Some embodiments disclosed herein relate to a method of treating a coronavirus infection that can include contacting a cell infected with the coronavirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating a coronavirus infection. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating a coronavirus infection.

[0120] Some embodiments disclosed herein relate to a method of inhibiting replication of a coronavirus that can include contacting a cell infected with the coronavirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a

compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for inhibiting replication of a coronavirus. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, for inhibiting replication of a coronavirus.

[0121] In some embodiments, the coronavirus can be an α -coronavirus or a β -coronavirus. A compound described herein may be effective against one or more variants of a coronavirus. Examples of variants include, but are not limited, to alpha-variant (B.1.1.7), beta-variant (B.1.351), gamma variant (P.1) and delta-variant (B.1.617.2). In some embodiments, the coronavirus can be selected from CoV 229E, CoV NL63, CoV OC43, CoV HKU1, Middle East Respiratory Syndrome (MERS)-CoV, Severe Acute Respiratory Syndrome (SARS)-CoV, and SARS-CoV-2.

[0122] Some embodiments described herein relate to a method of treating a picornavirus infection that can include administering to a subject identified as suffering from the picornavirus infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating a picornavirus infection. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein or a pharmaceutical composition that includes a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating a picornavirus infection.

[0123] Some embodiments disclosed herein relate to a method of treating a picornavirus infection that can include contacting a cell infected with the picornavirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable

salt thereof, as described herein in the manufacture of a medicament for treating a picornavirus infection. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating a picornavirus infection.

[0124] Some embodiments disclosed herein relate to a method of inhibiting replication of a picornavirus that can include contacting a cell infected with the picornavirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for inhibiting replication of a picornavirus. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, for inhibiting replication of a picornavirus.

[0125] In some embodiments, the picornavirus can be a rhinovirus, including rhinovirus A, B and/or C. In some embodiments, a compound described herein, including a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used to treat one or scrotypes of a rhinovirus.

[0126] Some embodiments described herein relate to a method of treating a norovirus infection that can include administering to a subject identified as suffering from the norovirus infection an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating a norovirus infection. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein or a

pharmaceutical composition that includes a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating a norovirus infection.

[0127] Some embodiments disclosed herein relate to a method of treating a norovirus infection that can include contacting a cell infected with the norovirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating a norovirus infection. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating a norovirus infection.

[0128] Some embodiments disclosed herein relate to a method of inhibiting replication of a norovirus that can include contacting a cell infected with the norovirus with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for inhibiting replication of a norovirus. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, for inhibiting replication of a norovirus.

[0129] Some embodiments disclosed herein relate to a method of treating a respiratory condition that is developed because of a coronavirus and/or a picornavirus infection that can include administering to a subject suffering from the respiratory condition and/or contacting a cell infected with the coronavirus and/or the picornavirus in a subject suffering from the respiratory condition with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically

acceptable salt thereof, as described herein. Other embodiments described herein relate to using a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating a respiratory condition due to a coronavirus infection and/or a picornavirus infection with an effective amount of the compound, or a pharmaceutically acceptable salt thereof. Still other embodiments described herein relate to the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein, or a pharmaceutical composition that includes an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as described herein for treating a respiratory condition due to a coronavirus infection and/or a picornavirus infection.

[0130] A subject infected with a coronavirus can be asymptotic. A coronavirus infection can manifest itself via one or more symptoms. Examples of symptoms include, but are not limited to, coughing, sore throat, runny nose, sneezing, headache, fever, shortness of breath, myalgia, abdominal pain, fatigue, difficulty breathing, persistent chest pain or pressure, difficulty waking, loss of smell and taste, muscle or joint pain, chills, nausea or vomiting, nasal congestion, diarrhea, haemoptysis, conjunctival congestion, sputum production, chest tightness and/or palpitations. A coronavirus infection can cause complications. A non-limiting list of complications include, but are not limited to, sinusitis, otitis media, pneumonia, acute respiratory distress syndrome, disseminated intravascular coagulation, pericarditis and/or kidney failure.

[0131] As with a coronavirus, a subject infected with a picornavirus can be asymptotic. Alternatively, a subject can exhibit one or more of symptoms. Examples of symptoms of a picornavirus infection include, but are not limited to, aseptic meningitis, rash, conjunctivitis, runny nose a headache a cough a fever a sore throat, chest and/or abdominal pain and paralysis. As provided herein, subjects infected with a norovirus can exhibit one or more the symptoms including, but not limited to, nausea, non-bloody diarrhea, vomiting and abdominal pain. An example of a complication that can be attributed to a norovirus infection is dehydration, including severe dehydration.

[0132] Various indicators for determining the effectiveness of a method for treating a coronavirus, picornavirus and/or norovirus infection are also known to those skilled in the art. Examples of suitable indicators include, but are not limited to, a reduction in viral load indicated by reduction in coronavirus (or load) (e.g., reduction $<10^5$ copies/mL

in serum), a reduction in plasma viral load, a reduction in viral replication, a reduction in time to seroconversion (virus undetectable in patient serum), an increase in the rate of sustained viral response to therapy a reduction of morbidity or mortality in clinical outcomes, reduction in the need for a ventilator and/or total time on a ventilator, reduction in hospitalization rates and/or reduction in time in an ICU (intensive care unit) and/or hospital.

[0133] As used herein, the terms “treat,” “treating,” “treatment,” “therapeutic,” and “therapy” do not necessarily mean total cure or abolition of the disease or condition. Any alleviation of any undesired signs or symptoms of a disease or condition, to any extent can be considered treatment and/or therapy. Furthermore, treatment may include acts that may worsen the subject’s overall feeling of well-being or appearance.

[0134] As used herein, a “subject” refers to an animal that is the object of treatment, observation or experiment. “Animal” includes cold- and warm-blooded vertebrates and invertebrates such as fish, shellfish, reptiles and, in particular, mammals. “Mammal” includes, without limitation, mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, horses, camels, non-human primates, such as monkeys, chimpanzees, and apes, and, in particular, humans. In some embodiments, the subject can be human, for example a human subject that is 60 years old or older.

[0135] The term “effective amount” is used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. For example, an effective amount of compound can be the amount needed to alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. This response may occur in a tissue, system, animal or human and includes alleviation of the signs or symptoms of the disease being treated. Determination of an effective amount is well within the capability of those skilled in the art, in view of the disclosure provided herein. The effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated, and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

[0136] In some embodiments, the subject can be asymptomatic, for example, the subject can be infected with coronavirus but does not exhibit any symptoms of the viral infection. In some embodiments, the subject can be have a pre-existing condition, such as asthma, hypertension, immunocomprised subjects (such as subjects with cancer, HIV and/or genetic immune deficiencies, bone marrow transplant subjects, solid organ transplant subjects, subjects who have had stem cells for cancer treatment and/or subjects who use oral or intravenous corticosteroids or other medicines called immunosuppressants), liver disease, subjects at risk for severe illness, chronic kidney disease being treated with dialysis, chronic lung disease, diabetes, hemoglobin disorders, serious heart conditions (for example, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension), severe obesity (such as subjects with a body mass index (BMI) of 40 or above) and people who live in a nursing home or long-term care facility . Additional examples and/or further information is provided by the CDC (<https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html>).

[0137] A compound described herein, including a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered after a subject is infected with a coronavirus. In addition and/or alternatively, a compound described herein, including a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered prophylactically.

[0138] Examples of agents that have been used to treat a coronavirus infection include Remdesivir. However, there can be drawbacks associated with compounds being used to treat a coronavirus including, but not limited to, one or more adverse side effects, the need for subcutaneous administration and/or high cost. Potential advantages of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be less adverse side effects, delay in the onset of an adverse side effect and/or reduction in the severity of an adverse side effect.

[0139] A coronavirus infection can be treated by inhibiting certain mechanisms. In some embodiments, a compound described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can be selective for a coronavirus protease. For example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be

selective for a coronavirus protease compared to a host protease, for example, one or more host proteases selected from Cathepsin L, Cathepsin B, Cathepsin D, Cathepsin K, Leukocyte Elastase, Chymotrypsin, Trypsin, Thrombin, Pepsin, Caspase 2, Elastase and Calpain. In some embodiments, the selectivity for a coronavirus protease over a host protease (such as those described herein) can be > 2-fold. In some embodiments, the selectivity for a coronavirus protease over a host protease (such as those described herein) can be > 10-fold. In some embodiments, the selectivity for a coronavirus protease over a host protease (such as those described herein) can be > 100-fold.

[0140] Studies have shown that the entry of SARS-CoV-2 into the target cells is a process that can be mediated by multiple proteases including cysteine cathepsins L and/or transmembrane protease serine 2 (TMPRSS2) (Shang et al., PNAS (2020) 117:11727, and Hoffmann et al., Cell (2020) 181:271-280). The cathepsin L inhibitor K117777, which lacks an inhibitory effect on the 3CLpro, can result in potent inhibition of SARS-CoV-2 in VeroE6, A549-ACE2 and/or HeLa-ACE2 (Mellott et al., bioRxiv (2020) 2020.2010.2023.347534). It has also been shown that the potent antiviral effect of K117777 is abolished when TMPRSS2 was expressed in A549-ACE2 (Steuten et al., bioRxiv (2020) 2020.2011.2021.392753). Off target activity of 3CLpro inhibitors, for example, on cathepsin L, may lead to an inaccurate assessment of the 3CLpro component of a compound's cellular potency. As an example, a compound described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof) can have greater selectivity for a coronavirus protease over a host protease, such as cathepsin L. The selectivity can be determined by those skilled in the art, for example, using IC_{50} and/or K_i values. In some embodiments, a compound described herein does not significantly inhibit cathepsin L (for example, $IC_{50} \geq 10000$ nM or >3.3 μ M), but inhibits a coronavirus protease (for example, SARS-Cov-2 3CLpro).

[0141] A drawback with anti-viral treatment can be the development of resistance, including cross-resistance. Resistance can be a cause for treatment failure. The term "resistance" as used herein refers to a viral strain displaying a delayed, lessened and/or null response to an anti-viral agent. In some embodiments, a compound, or a pharmaceutically acceptable salt thereof, as described herein can be provided to a subject infected with a coronavirus strain that is resistant to one or more other anti-viral agents. In

some embodiments, development of coronavirus resistant strains is delayed when a subject is treated with a compound, or a pharmaceutically acceptable salt thereof, as described herein compared to the development of a coronavirus resistant strain when treated with one or more other anti-viral agents.

Combination Therapies

[0142] In some embodiments, a compound, or a pharmaceutically acceptable salt thereof, as described herein can be used in combination with one or more additional agent(s) for treating and/or inhibiting replication a coronavirus. Additional agents include, but are not limited to, an ACE inhibitor, an anticoagulant, an anti-inflammatory, an ARB, an ASO, a Covid-19 convalescent plasma, an entry inhibitor, an H₂ pump antagonist, an H-conducting channel, an HIV protease inhibitor, an HMG-CoA reductase inhibitor, an immune globulin, an immunosuppressant, an immunotherapeutic agent, a monoclonal antibody, a neuraminidase inhibitor, a nucleoside inhibitor, a nucleoside analog inhibitor, a polymerase inhibitor, a protease inhibitor, an siRNA, a statin, a tissue plasminogen activator, an antibiotic, an antimicrobial and a vaccine. Examples of additional agents include Ascorbic acid, Anakin, Azithromycin, Baloxavir, Baricitinib, Chloroquine Phosphate, Colchicine, a corticosteroid, Epoprostenol, Famotidine, Favipiravir, an IGIV, an interferon (for example, recombinant interferon alpha 2b, IFN- α and/or PEG-IFN- α -2a), an IVIG, Ivermectin, γ -globulin, lopinavir, Methylprednisolone, Molnupiravir (MK-4482 or EIDD-2801), Niclosamide, Nitazoxanide, Nitric oxide, Oseltamivir, Peramivir, RANTES, ribavirin, Remdesivir, Ruxolitinib, Sarilumab, Siltuximab, Sirolimus, a statin, Tacrolimus, Tocilizumab, Umifenovir, Zanamivir, Casirivimab, imdevimab, bamlanivimab, etesevimab and Molnupiravir.

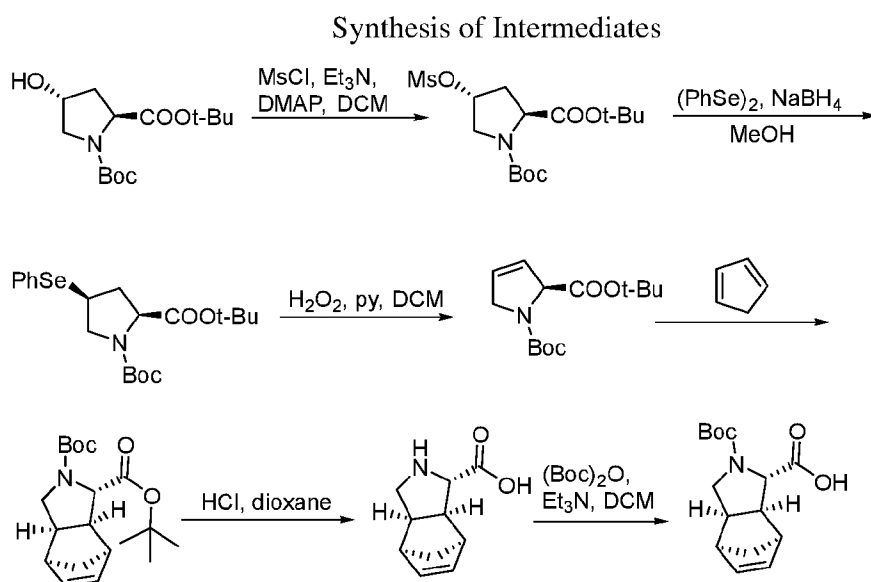
[0143] In some embodiments, a compound, or a pharmaceutically acceptable salt thereof, as described herein can be administered with one or more additional agent(s) together in a single pharmaceutical composition. In some embodiments, a compound, or a pharmaceutically acceptable salt thereof, can be administered with one or more additional agent(s) as two or more separate pharmaceutical compositions. Further, the order of administration of a compound, or a pharmaceutically acceptable salt thereof, as described herein with one or more additional agent(s) can vary.

EXAMPLES

[0144] Additional embodiments are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the claims.

COMPOUNDS

[0145] Compounds of Formula (I), along with pharmaceutically acceptable salts thereof, can be prepared in various ways, including those synthetic schemes shown and described herein, are provided below. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.



[0146] To a solution of 1,2-di-tert-butyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate (15 g, 52.2 mmol, 1.0 eq.) in DCM (250 mL) was added triethylamine (9.51 g, 93.9 mmol, 1.8 eq.) and DMAP (1.91 g, 15.7 mmol, 0.3 eq.). MsCl (8.97 g, 78.3 mmol, 1.5 eq.) was added dropwise at 0°C . The mixture was stirred at room temperature (rt) for 2 h, and the reaction was quenched with water (100 mL). The solution was extracted with DCM (3 x 150 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with EA:PE (1:10) to provide 1,2-di-tert-butyl

(2S,4R)-4-(methanesulfonyloxy)pyrrolidine-1,2-dicarboxylate (17.8 g, 89%) as a colorless oil. LC-MS (ESI, m/z): 366 $[M+H]^+$.

[0147] To a solution of 1,2-di-tert-butyl (2S,4R)-4-(methanesulfonyloxy)pyrrolidine-1,2-dicarboxylate (17.8 g, 48.7 mmol, 1.0 eq.) in MeOH (400 mL) was added (phenyldiselanyl)benzene (9.12 g, 29.2 mmol, 0.6 eq.). Sodium borohydride (2.4 g, 63.3 mmol, 1.3 eq.) was added at 0 °C in several portions. The mixture was refluxed overnight and then concentrated under reduced pressure. Water (100 mL) was added, and the mixture was extracted with EA (3 x 150 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with EA:PE (1:5) to provide 1,2-di-tert-butyl (2S,4S)-4-(phenylselanyl)pyrrolidine-1,2-dicarboxylate (7.5 g, 32%) as a colorless oil. LC-MS (ESI, m/z): 428 $[M+H]^+$.

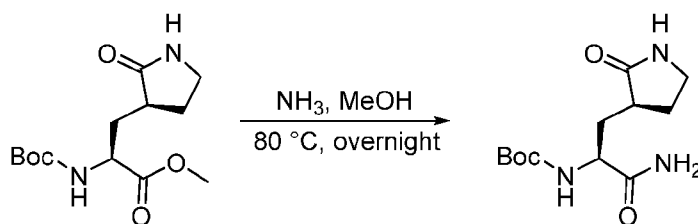
[0148] To a solution of 1,2-di-tert-butyl (2S,4S)-4-(phenylselanyl)pyrrolidine-1,2-dicarboxylate (7.5 g, 17.6 mmol, 1.0 eq.) in DCM (100 mL) was added pyridine (2.4 mL, 30.5 mmol, 1.7 eq.) and 30% aqueous H₂O₂ (5.6 mL, 71.6 mmol, 4.0 eq.). The mixture was stirred at rt for 12 h, and the reaction was quenched with water (20 mL). The solution was extracted with DCM (3 x 150 mL). The organic layers were combined, washed with 1 M citric acid (80 mL), sat. aq. Na₂SO₃ (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with EA:PE (1:9) to provide 1,2-di-tert-butyl (2S)-2,5-dihydropyrrole-1,2-dicarboxylate (2.8 g, 53%) as a colorless oil. ¹H NMR (300 MHz, DMSO-*d*₆) δ 6.02-6.09 (m, 1H), 5.76-5.83 (m, 1H), 4.72-4.78 (m, 1H), 4.05-4.09 (m, 2H), 1.17-1.42 (m, 18H). LC-MS (ESI, m/z): 270 $[M+H]^+$.

[0149] A solution of 1,2-di-tert-butyl (2S)-2,5-dihydropyrrole-1,2-dicarboxylate (2.8 g, 10.4 mmol, 1.0 eq.) in cyclopenta-1,3-diene (60 mL) was stirred at 170 °C for 48 h under nitrogen and then resolved with DCM (200 mL). After removal of the solvent, the residue was chromatographed on a silica gel column with EA:PE (1:9) to provide the product (2.5 g, crude) as a yellow oil. The crude oil was chromatographed on a C18 column with H₂O:MeCN (2:1) to provide di-tert-butyl (1S,3aR,4S,7R,7aS)-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisindole-1,2-dicarboxylate (690 mg, 19%) as a white solid. ¹H NMR (300

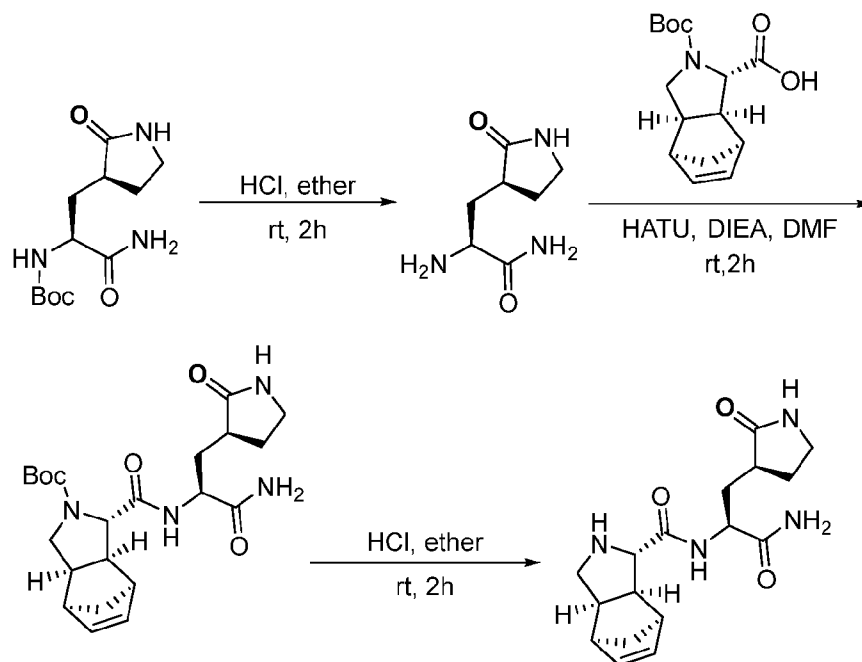
MHz, DMSO-*d*₆) δ 6.14-6.21 (m, 2H), 3.55-3.60 (m, 1H), 3.23-3.27 (m, 1H), 2.95-3.02 (m, 2H), 2.74-2.87 (m, 3H), 1.24-1.48 (m, 20H). LC-MS (ESI, *m/z*): 270 [M+H]⁺.

[0150] To a solution of i-tert-butyl (1S,3aR,4S,7R,7aS)-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisindole-1,2-dicarboxylate (690 mg, 2.1 mmol, 1.0 eq.) in dioxane (10 mL) was added hydrochloric acid (10 mL, 9M). The mixture was stirred at rt overnight and then concentrated under reduced pressure to provide (1S,3aR,4S,7R,7aS)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisindole-1-carboxylic acid (320 mg, crude) as a black solid. LC-MS (ESI, *m/z*): 180 [M+H]⁺.

[0151] To a solution of (1S,3aR,4S,7R,7aS)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisindole-1-carboxylic acid (320 mg, 1.79 mmol, 1.0 eq.) in DCM (8 mL) was added di-tert-butyl dicarbonate (429 mg, 1.97 mmol, 1.1 eq.) and triethylamine (542 mg, 5.34 mmol, 3.0 eq.). The mixture was stirred at rt for 3 h and then concentrated under reduced pressure to provide (1S,3aR,4S,7R,7aS)-2-(tert-butoxycarbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisindole-1-carboxylic acid (430 mg, crude) as a brown solid. LC-MS (ESI, *m/z*): 280 [M+H]⁺.



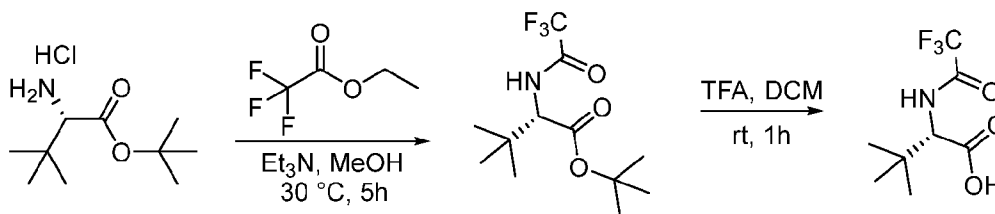
[0152] A mixture of methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[(3S)-2-oxopyrrolidin-3-yl]propanoate (10.0 g, 34.9 mmol, 1.00 eq.) in ammonia (150 mL, 7 M in MeOH) was stirred overnight at 80 °C and concentrated under reduced pressure to afford tert-butyl N-[(1S)-1-carbamoyl-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamate (10.0 g, crude) as a light brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.65 (s, 1H), 7.29 (s, 1H), 7.01 (s, 1H), 6.88-6.95 (m, 1H), 3.84-4.15 (m, 1H), 3.09-3.21 (m, 2H), 2.08-2.26 (m, 2H), 1.84-1.96 (m, 1H), 1.60-1.74 (m, 1H), 1.44-1.54 (m, 1H), 1.38 (s, 9H). LC-MS (ESI, *m/z*): 272[M+H]⁺.



[0153] A solution of tert-butyl ((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamate (710 mg, 2.62 mmol, 1.0 eq.) in hydrochloric acid in ether (12 mL, 2 mol/L) was stirred at rt for 2 h and concentrated under reduced pressure to provide (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanamide (500 mg, crude) as a white solid. LC-MS (ESI, m/z): 172 $[M+H]^+$.

[0154] To a solution of (1S,3aR,4S,7R,7aS)-2-(tert-butoxycarbonyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisindole-1-carboxylic acid (979 mg, 3.5 mmol, 1.2 eq.) in DMF (2 mL) was added N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (1.44 g, 3.8 mmol, 1.3 eq.) and N,N-diisopropylethylamine (2.64 g, 20.4 mmol, 7.0 eq.). The mixture was stirred at 0 °C for 30 min and then (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanamide (500 mg, 2.92 mmol, 1.0 eq.) was added. The mixture was stirred at rt for 2 h, and the reaction was quenched with water (5 mL). The mixture was extracted with EA (3 x 10 mL). The organic layers were combined, washed with brine (3 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a C18 column with water:MeCN (2:1) to provide tert-butyl (1S,3aR,4S,7R,7aS)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisindole-2-carboxylate (1.05 g, 75%) as a brown yellow solid. LC-MS (ESI, m/z): 433 $[M+H]^+$.

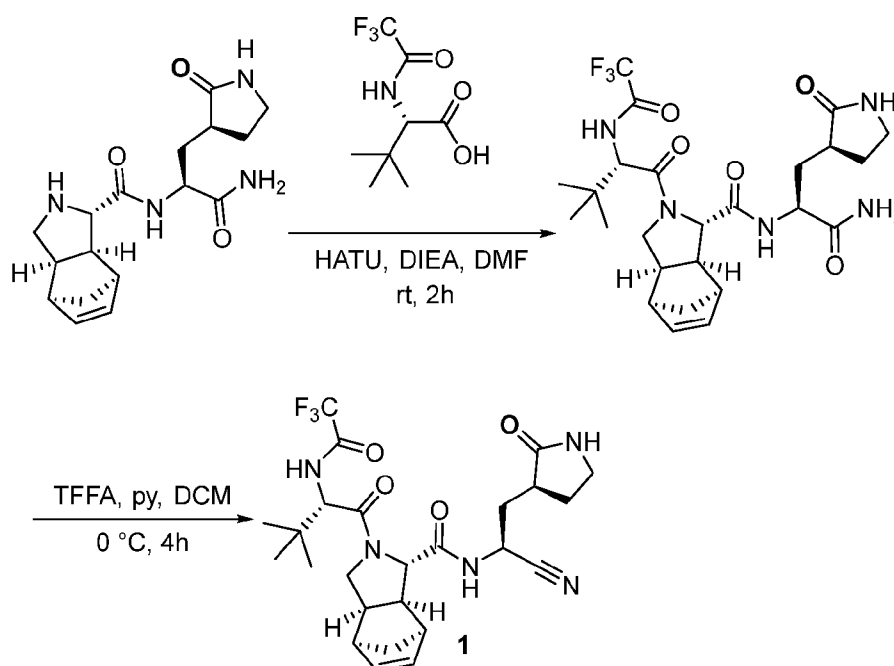
[0155] A solution of tert-butyl (1S,3aR,4S,7R,7aS)-1-(((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)carbamoyl)-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisindole-2-carboxylate (300 mg, 0.69 mmol, 1.0 eq.) in hydrochloric acid in ether (5 mL, 2 mol/L) was stirred at rt for 2 h and then concentrated under reduced pressure to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisindole-1-carboxamide (200 mg, crude) as a white solid. LC-MS (ESI, m/z): 333 $[M+H]^+$.



[0156] To a stirred mixture of tert-butyl (2S)-2-amino-3,3-dimethylbutanoate hydrochloride (6.00 g, 26.8 mmol, 1.0 eq.) and trifluoroethyl acetate (7.62 g, 53.6 mmol, 2.0 eq.) in MeOH (100 mL) was added triethylamine (5.43 g, 53.7 mmol, 2.0 eq.) at 0 °C. The mixture was stirred for 5 h at 30 °C and then concentrated under reduced pressure to afford the crude product. The crude product was diluted with DCM (150 mL) and made into a slurry with 100 ~ 200 silica gel mesh (15 g), and the slurry was loaded to a column chromatography after removing the DCM. The sample was purified by column chromatography (Column size 6 x 24 cm, column volume: 600 mL, silica gel size (100 ~ 200 mesh) quantity: 330 g) and eluted with MeOH:DCM (0% ~ 10% over 30 min). The collected fractions: 0% MeOH:DCM fractions were chosen as the pure fractions. and those fractions were combined and concentrated under reduced pressure to provide tert-butyl (2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoate (7.20 g, 90%) as a white solid. ^1H NMR (300 MHz, Chloroform- d) δ 6.78-6.90 (m, 1H), 4.32-4.38 (m, 1H), 1.50 (s, 9H), 1.01 (s, 9H). LC-MS (ESI, m/z): 282 $[M-H]^-$.

[0157] To a mixture of tert-butyl (2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoate (1.03 g, 3.64 mmol, 1.0 eq.) in DCM (5 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred for 1 h at rt and then concentrated under reduced pressure to (2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoic acid (826 mg, crude) as a yellow oil. LC-MS (ESI, m/z): 226 $[M-H]^-$.

EXAMPLE 1
Compound 1



[0158] To a solution of tert-butyl (2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoate (118 mg, 0.42 mmol, 1.2 eq.) in DMF (2 mL) was added N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (171 mg, 0.45 mmol, 1.3 eq.) and N,N-diisopropylethylamine (313 mg, 2.42 mmol, 7.0 eq.). The mixture was stirred at 0 °C for 30 min and then (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisindole-1-carboxamide (115 mg, 0.35 mmol, 1.0 eq.) was added. The mixture was stirred at rt for 2 h, and the reaction was quenched with water (3 mL). The mixture was extracted with EA (3 x 5 mL). The organic layers were combined, washed with brine (3 x 5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on a C18 column with water:MeCN (2:1) to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisindole-1-carboxamide (150 mg, yield 72%) as a brown yellow solid. LC-MS (ESI, m/z): 542 $[M+H]^+$.

[0159] To a solution of (1S,3aR,4S,7R,7aS)-N-((S)-1-amino-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisindole-1-carboxamide (120 mg, 0.22 mmol, 1.0

eq.) in DCM (3 mL) was added TFAA (88.4 mg, 0.42 mmol, 1.9 eq.) and pyridine (61.3mg, 0.78 mmol, 3.5 eq.). The mixture was stirred at 0 °C for 4 h, and the reaction was quenched with water (4 mL). The mixture was extracted with DCM (3 x 5 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 19*150 mm, 5µm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 30% B to 50% B in 7 min, 50% B; Wave Length: 254 nm; RT1(min): 5.55;) to provide (1S,3aR,4S,7R,7aS)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisindole-1-carboxamide (**1**) (53.2 mg, yield 45%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆, 80 °C) δ 8.66-8.95 (m, 2H), 7.28-7.37 (m, 1H), 5.96-6.23 (m, 2H), 4.87-4.93 (m, 1H), 4.41-4.68 (m, 1H), 3.86-4.17 (m, 1H), 3.58-3.71 (m, 1H), 3.20-3.51 (m, 2H), 2.83-3.06 (m, 4H), 2.59-2.79 (m, 1H), 2.29-2.38 (m, 1H), 2.03-2.28 (m, 2H), 1.61-1.84 (m, 2H), 1.31-1.42 (m, 2H), 0.79-0.90 (m, 9H). LC-MS (ESI, *m/z*): 524 [M+H]⁺.

EXAMPLE A SARS-Cov-2 3CLpro and HRV3C Duplex assay

[0160] Protease assays were performed in 384-well low volume polypropylene microtiter plates at ambient temperature. For the duplex assay, 3CLpro and HRV3C was added using a Multidrop Combi (Thermo Scientific; Waltham, MA) and preincubated for 30 mins with small molecules. The reactions were initiated by the addition of the two peptide substrates. The reactions were incubated for 30 mins and quenched by the addition of 0.5% formic acid (final) with subsequent neutralization using 1% sodium bicarbonate (final). Internal standard peptides were added in 20 mM Hepes pH 8.0 for quantitation of the protease products. For SAMDI-MS analysis, 2 µL of each reaction mixture was transferred using a 384-channel automated liquid handler to SAMDI biochip arrays functionalized with a neutravidin-presenting self-assembled monolayer. The SAMDI arrays were incubated for 1 h in a humidified chamber to allow the specific immobilization of the biotinylated peptide substrates, cleaved products and internal standards. The samples were purified by washing the SAMDI arrays with deionized ultrafiltered water and dried with compressed air. A matrix comprising alpha-cyano cinnamic acid in 80% acetonitrile:20% aqueous ammonium

citrate was applied in an automated format by dispensing 50 nL to each spot in the array. SAMDI-MS was performed using reflector-positive mode on an AB Sciex TOF-TOF 5800 System (AB Sciex, Framingham, MA) with 400 shots/spot analyzed in a random raster sampling. For data analysis, area under the curves (peaks) (AUCs) for the product and internal standard were calculated using the TOF/TOF Series Explorer (AB Sciex), and the amount of product formed was calculated using the equation (AUC product/AUC internal standard). The amount of product generated was calculated using the ratio of product area under the curve (AUC) divided by the AUC of the internal standard. Negative controls were pre-quenched with 0.5% formic acid final. Assay robustness was determined by Z-Factor. The IC₅₀s were determined by fitting the curves using a four-parameter equation in Graphpad Prism 8.

[0161] Table 1 indicates related IC₅₀ values for the tested compounds where ‘A’ indicates an EC₅₀ < 20 nM, ‘B’ indicates an IC₅₀ of ≥20 nM and < 200 nM, ‘C’ indicates an IC₅₀ ≥ 200 nM and < 2000 nM, ‘D’ indicates an IC₅₀ ≥ 2000 nM and < 20000 nM and ‘E’ indicates an IC₅₀ ≥ 20000 nM and < 100000 nM. As shown by the data in Table 1, compounds described herein (including pharmaceutically acceptable salts thereof) can effectively inhibit and be used to treat a coronavirus and rhinovirus.

Table 1

Compound	SARS-Cov-2	HRV
1	A	>10 μM

EXAMPLE B CORONAVIRUS ASSAY

OC43 Coronavirus Assay in HeLa cells

[0162] The human beta-coronavirus OC43 was purchased from ATCC (Manassas, VA) and propagated using HCT-8 human colorectal epithelial cells (ATCC). HeLa human cervical epithelial cells (ATCC) were used as susceptible host cell lines and were cultured using EMEM media, supplemented with 10% fetal bovine serum (FBS), 1% (v/v) penicillin/streptomycin (P/S), 1% (v/v) HEPES and 1% (v/v) cellgro glutagro™ supplement (all Corning, Manassas, VA) at 37 °C. For the OC43 antiviral assay, 1.5 x 10⁴ HeLa cells per well were plated in 100 μL complete media in white 96-well plates with clear

bottoms at 37 °C for up to 24 h to facilitate attachment and allow cells to recover from seeding stresses. Next day, the cell culture medium was removed. Serially diluted compounds in 100 µL assay media (EMEM, 2% FBS, 1% P/S, 1% cellgro glutagro™ supplement, 1% HEPES) were added to the cells and incubated for 4 h at 37 °C in a humidified 5% CO₂ incubator. 100 µL of OC43 virus stock was diluted to a concentration known to produce optimal cytopathic effect, inducing 80-90% reduction in cell viability. 96-well plates were incubated for 6 (HeLa) days at 33 °C; each plate contains uninfected control wells as well as virus-infected wells that were not treated with compound. Cytotoxicity plates without the addition of OC43 virus were carried out in parallel. At the end of the incubation period, 100 µL cell culture supernatant was replaced with 100 µL cell-titer-glo reagent (Promega, Madison, WI) and incubated for at least 10 min at rt prior to measuring luminescence. Luminescence was measured on a Perkin Elmer (Waltham, MA) Envision plate reader. Antiviral % inhibition was calculated as follows: [(Compound treated cells infected sample) – (no compound infected control)]/[(Uninfected control) – (no compound infected control)]*100; Using GraphPad (San Diego, CA) prism software version 8.3.1, the antiviral dose-response plot was generated as a sigmoidal fit, log(inhibitor) vs response-variable slope (four parameters) model and the EC₅₀ was calculated which is the predicted compound concentration corresponding to a 50% inhibition of the viral cytopathic effect.

[0163] Table 2 indicates related EC₅₀ and CC₅₀ values for the tested compounds ‘A’ indicates an EC₅₀ < 100 nM, ‘B’ indicates an EC₅₀ of ≥100 nM and < 1000 nM, ‘C’ indicates an EC₅₀ ≥ 1000 nM and < 10000 nM and ‘D’ indicates an EC₅₀ ≥ 10000 nM and < 100000 nM. For CC₅₀, ‘A’ indicates a CC₅₀ ≥ 10000 nM, ‘B’ indicates an CC₅₀ of ≥1000 nM and < 10000 nM and ‘C’ indicates an CC₅₀ < 1000 nM.

Table 2

Compound	EC ₅₀	CC ₅₀
1	A	A

SARS-CoV-2 infection model in VeroE6 cells

[0164] The SARS-CoV-2 antiviral assay is derived from the previously established SARS-CoV assay (PMID: 15961169). In this assay, fluorescence of Vero E6-eGFP cells declines after infection with SARS-CoV-2 due to the cytopathogenic effect of the

virus. In the presence of an antiviral compound, the cytopathogenicity is inhibited and the fluorescent signal rescued. On day -1, the test compounds were serially diluted in assay medium (DMEM supplemented with 2% v/v FCS). The plates were incubated (37 °C, 5% CO₂ and 95% relative humidity) overnight. On day 0, the diluted compounds were mixed with Vero E6-eGFP cells (25,000 cells/well), SARS-CoV-2-GHB-03021/2020 (20 TCID₅₀/well) and the MDR1-inhibitor CP-100356 (final concentration 0.5 µM) in 96-well blackview plates (Greiner Bio-One, Vilvoorde, Belgium). The plates were incubated in a humidified incubator at 37 °C and 5% CO₂. At 4 days p.i., the wells were examined for eGFP expression using an argon laser-scanning microscope. The microscope settings were excitation at 488 nm and emission at 510 nm and the fluorescence images of the wells were converted into signal values. The results were expressed as EC₅₀ values defined as the concentration of compound achieving 50% rescue from the virus-reduced eGFP signals as compared to the untreated virus-infected control cells. Toxicity of compounds in the absence of virus was evaluated in a standard MTS-assay as described previously (PMID: 22575574).

[0165] Table 3 indicates related EC₅₀ and CC₅₀ values for the tested compounds ‘A’ indicates an EC₅₀ < 100 nM, ‘B’ indicates an EC₅₀ of ≥100 nM and < 1000 nM, ‘C’ indicates an EC₅₀ ≥ 1000 nM and < 10000 nM. For CC₅₀, ‘A’ indicates a CC₅₀ ≥ 10000 nM, ‘B’ indicates an CC₅₀ of ≥1000 nM and < 10000 nM, ‘C’ indicates an CC₅₀ < 1000 nM. >100 refers to >100 µM, >50 refers to >50 µM and > 10 refers to > 10 µM.

Table 3

Compound	VeroE6+CP (EC ₅₀)	VeroE6+CP (CC ₅₀)
1	A	A

[0166] Tables 2 and 3 demonstrate that compounds described herein (including pharmaceutically acceptable salts thereof) can effectively inhibit and treat a coronavirus.

EXAMPLE C PICORNAVIRUS & NOROVIRUS ASSAYS

[0167] Compounds of Formula (I), including pharmaceutically acceptable salts thereof, are tested following a protocol similar to the protocol described in one of the

following articles: Kim et al., Journal of Virology (2012) 86(21):11754-11762, Zhang et al, JACS (2020) (<https://dx.doi.org/10.1021/acs.jmedchem.9b01828>), and U.S. Patent No. 9,603,864.

[0168] The protocols of Kim et al., and Zhang et al., can be used to test for activity against a coronavirus.

EXAMPLE D

[0169] For the cathepsin L assay, 10 pM of human cathepsin L (R&D Systems; Minneapolis, MN) was preincubated for 30 mins with test compounds. Reactions were initiated by the addition of a peptide substrate Z-FR-AMC (final concentration 2 μ M, Anaspec; Fremont, CA). Fluorescence was measured at 2-minute intervals for 30 mins using a 355/460 excitation/emission filter module on an Envision plate reader (Perkin Elmer; Waltham, MA). The IC₅₀ values were calculated for each assay by fitting the curves using a four-parameter equation in GraphPad Prism.

[0170] Table 4 indicates related IC₅₀ values for the tested compounds where ‘A’ indicates an IC₅₀ $\geq$ 10000 nM, ‘B’ indicates an IC₅₀ of $\geq$ 1000 nM and < 10000 nM, ‘C’ indicates an IC₅₀ $\geq$ 100 nM and < 1000 nM, ‘D’ indicates an IC₅₀ <100 nM.

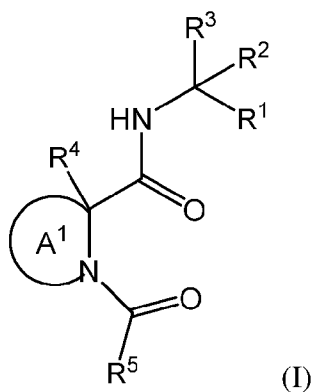
Table 4

Compound	Cathepsin L IC ₅₀
1	A

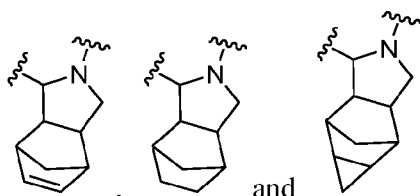
[0171] Although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. Therefore, it should be clearly understood that the forms disclosed herein are illustrative only and are not intended to limit the scope of the present disclosure, but rather to also cover all modification and alternatives coming with the true scope and spirit of the present disclosure.

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



wherein:



Ring A¹ is , and , and wherein Ring A¹ is optionally substituted with one or more moieties independently selected from the group consisting of halogen, an unsubstituted C₁₋₄ alkyl, an unsubstituted C₁₋₄ haloalkyl, an unsubstituted C₂₋₄ alkenyl and an unsubstituted or a substituted C₃₋₆ monocyclic cycloalkyl;

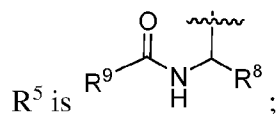
R¹ is selected from the group consisting of cyano, an unsubstituted or a substituted C₂₋₅ alkynyl, an unsubstituted or a substituted acyl, an unsubstituted or a substituted ketoamide, $-\text{CH}(\text{OH})-(\text{S}(=\text{O})_2-\text{O}^-)$, $-\text{CH}(\text{OH})((\text{P}=\text{O})(\text{OR}^6)_2)$ and $-\text{C}(=\text{O})\text{CH}_2-\text{O}-((\text{P}=\text{O})(\text{OR}^7)_2)$;

each R⁶ and each R⁷ are independently hydrogen, an unsubstituted C₁₋₆ alkyl, an unsubstituted C₂₋₆ alkenyl, an unsubstituted C₁₋₆ haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C₁₋₄ alkyl);

R² is hydrogen, deuterium or halogen;

R³ is an unsubstituted or a substituted monocyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl) or an unsubstituted or a substituted bicyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl);

R⁴ is hydrogen, deuterium or halogen; and



R^8 is selected from the group consisting of an unsubstituted or a substituted C_{2-6} alkyl, an unsubstituted or a substituted C_{2-6} alkenyl, an unsubstituted or a substituted C_{2-6} alkynyl, an unsubstituted or a substituted monocyclic C_{3-6} cycloalkyl, an unsubstituted or a substituted bicyclic C_{5-8} cycloalkyl and an unsubstituted or a substituted monocyclic 4- to 6-membered heterocyclyl,

wherein when the C_{2-6} alkyl is substituted, the C_{2-6} alkyl is substituted 1, 2, 3 or 4 times with a substituent independently selected from the group consisting of halogen and an unsubstituted C_{1-4} alkoxy;

wherein when the C_{2-6} alkenyl, the C_{2-6} alkynyl, the monocyclic C_{3-6} cycloalkyl, the bicyclic C_{5-8} cycloalkyl and the monocyclic 4- to 6-membered heterocyclyl are substituted, the C_{2-6} alkenyl, the C_{2-6} alkynyl, the monocyclic C_{3-6} cycloalkyl, the bicyclic C_{5-8} cycloalkyl and the monocyclic 4- to 6-membered heterocyclyl are substituted 1, 2, 3 or 4 times with a substituent independently selected from the group consisting of halogen, an unsubstituted C_{1-4} alkyl and an unsubstituted C_{1-4} alkoxy; and

R^9 is selected from the group consisting of an unsubstituted C_{1-6} alkyl, an unsubstituted C_{1-6} haloalkyl and a substituted monocyclic C_{3-6} cycloalkyl, wherein the substituted monocyclic C_{3-6} cycloalkyl is substituted 1, 2, 3 or 4 times with a substituent independently selected from the group consisting of halogen, an unsubstituted C_{1-4} alkyl and an unsubstituted C_{1-4} haloalkyl.

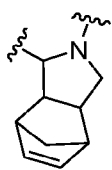
2. The compound of Claim 1, wherein R^1 is an unsubstituted or a substituted ketoamide.
3. The compound of Claim 1, wherein R^1 is an unsubstituted or a substituted acyl.
4. The compound of Claim 1, wherein R^1 is $-\text{CH}(\text{OH})-(\text{S}(=\text{O})_2-\text{O}^-)$.
5. The compound of Claim 1, wherein R^1 is $-\text{CH}(\text{OH})((\text{P}=\text{O})(\text{OR}^6)_2)$, wherein each R^6 are independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C_{1-4} alkyl).

6. The compound of Claim 1, wherein R^1 is $-C(=O)CH_2-O-(P=O)(OR^7)_2$, wherein each R^7 are independently hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{1-6} haloalkyl, an unsubstituted or a substituted aryl or an unsubstituted or a substituted aryl(C_{1-4} alkyl).

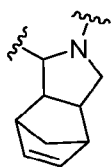
7. The compound of Claim 1, wherein R^1 is cyano.

8. The compound of Claim 1, wherein R^1 is an unsubstituted or a substituted C_{2-5} alkynyl.

9. The compound of any one of Claims 1-8, wherein Ring A^1 is an unsubstituted

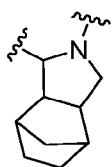


10. The compound of any one of Claims 1-8, wherein Ring A^1 is a substituted

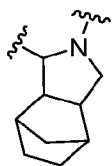


substituted with one or more moieties independently selected from the group consisting of halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl.

11. The compound of any one of Claims 1-8, wherein Ring A^1 is an unsubstituted

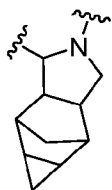


12. The compound of any one of Claims 1-8, wherein Ring A^1 is a substituted

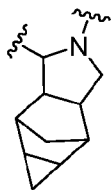


substituted with one or more moieties independently selected from the group consisting of halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} haloalkyl, an unsubstituted C_{2-4} alkenyl and an unsubstituted or a substituted C_{3-6} monocyclic cycloalkyl.

13. The compound of any one of Claims 1-8, wherein Ring A¹ is an unsubstituted



14. The compound of any one of Claims 1-8, wherein Ring A¹ is a substituted



substituted with one or more moieties independently selected from the group consisting of halogen, an unsubstituted C₁₋₄ alkyl, an unsubstituted C₁₋₄ haloalkyl, an unsubstituted C₂₋₄ alkenyl and an unsubstituted or a substituted C₃₋₆ monocyclic cycloalkyl.

15. The compound of any one of Claims 1-14, wherein R⁸ is an unsubstituted C₂₋₆ alkyl,
16. The compound of any one of Claims 1-14, wherein R⁸ is a substituted C₂₋₆ alkyl.
17. The compound of any one of Claims 1-14, wherein R⁸ is an unsubstituted C₂₋₆ alkenyl.
18. The compound of any one of Claims 1-14, wherein R⁸ is a substituted C₂₋₆ alkenyl.
19. The compound of any one of Claims 1-14, wherein R⁸ is an unsubstituted C₂₋₆ alkynyl.
20. The compound of any one of Claims 1-14, wherein R⁸ is a substituted C₂₋₆ alkynyl.
21. The compound of any one of Claims 1-14, wherein R⁸ is an unsubstituted monocyclic C₃₋₆ cycloalkyl.
22. The compound of any one of Claims 1-14, wherein R⁸ is a substituted monocyclic C₃₋₆ cycloalkyl.
23. The compound of any one of Claims 1-14, wherein R⁸ is an unsubstituted bicyclic C₅₋₈ cycloalkyl.

24. The compound of any one of Claims 1-14, wherein R⁸ is a substituted bicyclic C₅₋₈ cycloalkyl.

25. The compound of any one of Claims 1-14, wherein R⁸ is an unsubstituted monocyclic 4- to 6-membered heterocyclyl.

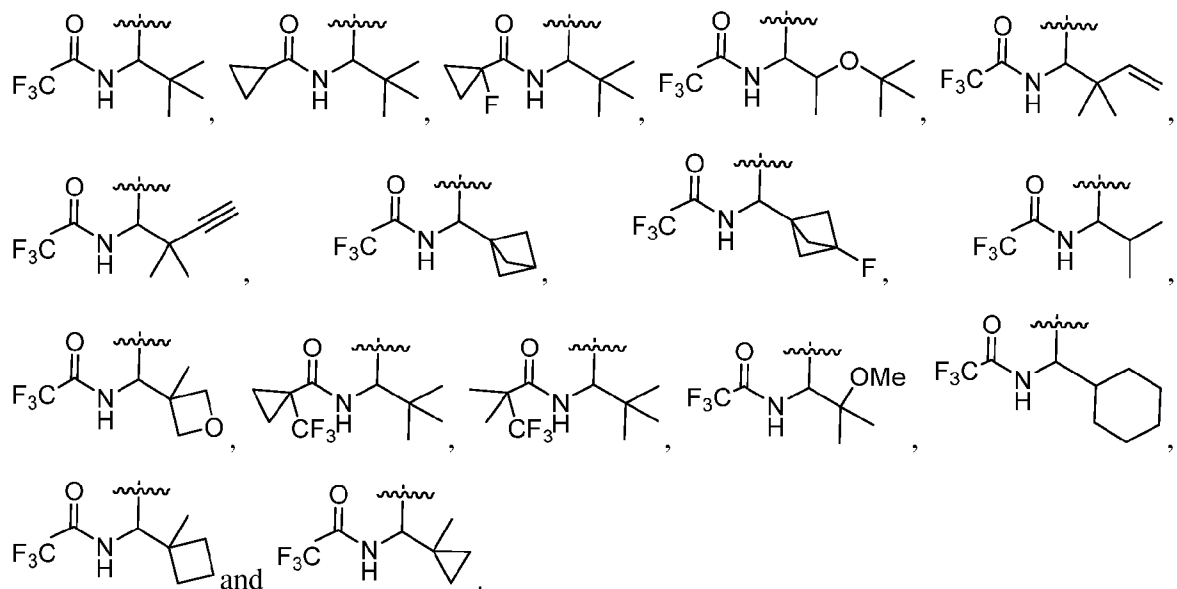
26. The compound of any one of Claims 1-14, wherein R⁸ is a substituted monocyclic 4- to 6-membered heterocyclyl.

27. The compound of any one of Claims 1-26, wherein R⁹ is an unsubstituted C₁₋₆ alkyl.

28. The compound of any one of Claims 1-26, wherein R⁹ is an unsubstituted C₁₋₆ haloalkyl.

29. The compound of any one of Claims 1-26, wherein R⁹ is a substituted monocyclic C₃₋₆ cycloalkyl, wherein the substituted monocyclic C₃₋₆ cycloalkyl is substituted 1, 2, 3 or 4 times with a substituent independently selected from the group consisting of halogen, an unsubstituted C₁₋₄ alkyl and an unsubstituted C₁₋₄ haloalkyl.

30. The compound of any one of Claims 1-4, wherein R⁵ is selected from the group consisting of:



31. The compound of any one of Claims 1-30, wherein R³ is an unsubstituted monocyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl).

32. The compound of any one of Claims 1-30, wherein R³ is a substituted monocyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl).

33. The compound of Claim 31 or 32, wherein the monocyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl) is a 5-membered monocyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl).

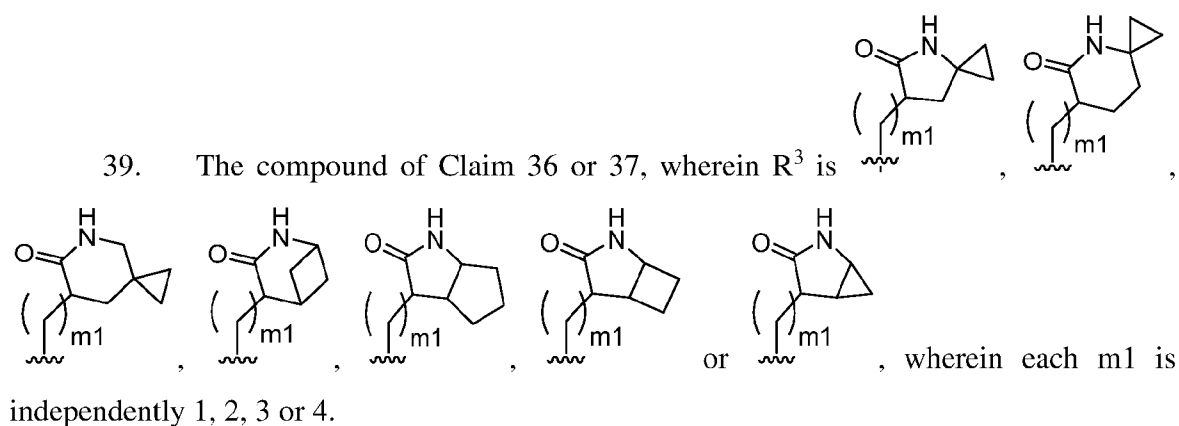
34. The compound of Claim 31 or 32, wherein the monocyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl) is a 6-membered monocyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl).

35. The compound of Claim 31 or 32, wherein the monocyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl) is azepan-2-one(C₁₋₄ alkyl), imidazolidin-2-one(C₁₋₄ alkyl), tetrahydropyrimidin-2-one(C₁₋₄ alkyl), pyrrolidin-2-one(C₁₋₄ alkyl) or piperidin-2-one(C₁₋₄ alkyl).

36. The compound of any one of Claims 1-30, wherein R³ is an unsubstituted bicyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl).

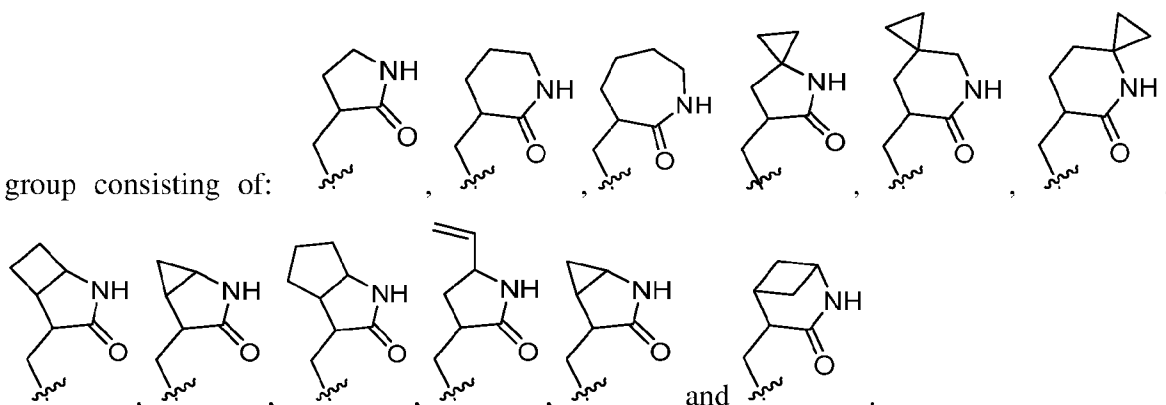
37. The compound of any one of Claims 1-30, wherein R³ is a substituted bicyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl).

38. The compound of Claim 36 or 37, wherein the bicyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl) is a 9-membered or 10-membered bicyclic nitrogen-containing heterocyclyl(C₁₋₄ alkyl).



40. The compound of any one of Claims 1-30, wherein R^3 is selected from the

group consisting of:



41. The compound of any one of Claims 1-40, wherein R² is hydrogen.

42. The compound of any one of Claims 1-40, wherein R² is deuterium.

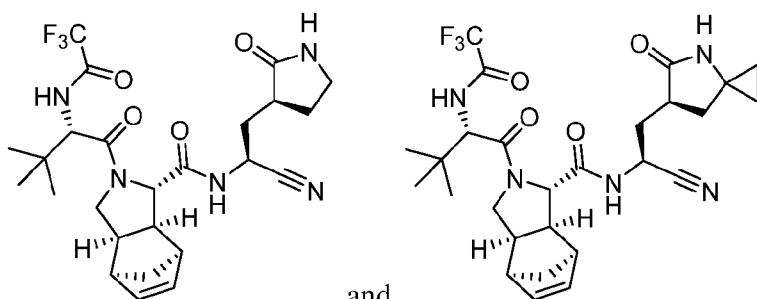
43. The compound of any one of Claims 1-40, wherein R² is halogen.

44. The compound of any one of Claims 1-43, wherein R⁴ is hydrogen.

45. The compound of any one of Claims 1-43, wherein R⁴ is deuterium.

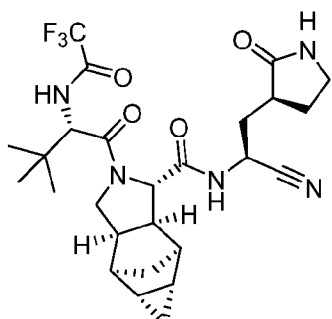
46. The compound of any one of Claims 1-43, wherein R⁴ is halogen.

47. The compound of Claim 1, wherein the compound is selected from the group consisting of:

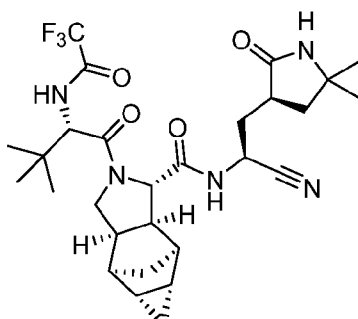


 and , or pharmaceutically acceptable salt of any of the foregoing.

48. The compound of Claim 1, wherein the compound is selected from the group consisting of:



and



, or pharmaceutically acceptable salt of any of the foregoing.

49. A pharmaceutical composition comprising an effective amount of a compound of any one of Claims 1-48, or a pharmaceutically acceptable salt thereof, and excipient.

50. Use of the compound of any one of Claims 1-48, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of a coronavirus infection.

51. The use of Claim 50, wherein the use further comprises the use of an additional agent selected from the group consisting of an ACE inhibitor, an anticoagulant, an anti-inflammatory, an ARB, an ASO, a Covid-19 convalescent plasma, an entry inhibitor, an H₂ pump antagonist, an H-conducting channel, an HIV protease inhibitor, an HMG-CoA reductase inhibitor, an immune globulin, an immunosuppressant, an immunotherapeutic agent, a neuraminidase inhibitor, a nucleoside inhibitor, a nucleoside analog inhibitor, a polymerase inhibitor, a protease inhibitor, an siRNA, a statin, a tissue plasminogen activator, an antibiotic, an antimicrobial and a vaccine.

52. The use of Claim 51, wherein the additional agent selected from the group consisting of Ascorbic acid, Anakinra, Azithromycin, Baloxavir, Baricitinib, Chloroquine Phosphate, Colchicine, a corticosteroid, Epoprostenol, Famotidine, Favipiravir, an IGIV, an interferon, an IVIG, Ivermectin, γ -globulin, lopinavir, Methylprednisolone, Niclosamide, Molnupiravir (MK-4482 or EIDD-2801), Nitazoxanide, Nitric oxide, Oseltamivir, Peramivir, RANTES, ribavirin, Remdesivir, Ruxolitinib, Sarilumab, Siltuximab, Sirolimus, a statin, Tacrolimus, Tocilizumab, Umifenovir and Zanamivir.

53. The use of any one of Claims 50-52, wherein the coronavirus is β -coronavirus.

54. The use of any one of Claims 50-52, wherein the coronavirus is coronavirus selected from the group consisting of CoV 229E, CoV NL63, CoV OC43, CoV HKU1, Middle East Respiratory Syndrome (MERS)-CoV, Severe Acute Respiratory Syndrome (SARS)-CoV, and SARS-CoV-2.

55. Use of the compound of any one of Claims 1-48, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of a picornavirus infection.

56. The use of Claim 55, wherein the picornavirus infection is a rhinovirus infection.

57. Use of the compound of any one of Claims 1-48, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of a norovirus infection.

58. A compound of any one of Claims 1-48, or a pharmaceutically acceptable salt thereof, for use in treating a coronavirus infection.

59. The compound of Claim 58, wherein the compound is used in combination with an additional agents selected from the group consisting of an ACE inhibitor, an anticoagulant, an anti-inflammatory, an ARB, an ASO, a Covid-19 convalescent plasma, an entry inhibitor, an H₂ pump antagonist, an H-conducting channel, an HIV protease inhibitor, an HMG-CoA reductase inhibitor, an immune globulin, an immunosuppressant, an immunotherapeutic agent, a neuraminidase inhibitor, a nucleoside inhibitor, a nucleoside analog inhibitor, a polymerase inhibitor, a protease inhibitor, an siRNA, a statin, a tissue plasminogen activator, an antibiotic, an antimicrobial and a vaccine.

60. The compound of Claim 59, wherein the additional agent is selected from the group consisting of Ascorbic acid, Anakinra, Azithromycin, Baloxavir, Baricitinib, Chloroquine Phosphate, Colchicine, a corticosteroid, Epoprostenol, Famotidine, Favipiravir, an IGIV, an interferon, an IVIG, Ivermectin, γ -globulin, lopinavir, Methylprednisolone, Molnupiravir (MK-4482 or EIDD-2801), Niclosamide, Nitazoxanide, Nitric oxide, Oseltamivir, Peramivir, RANTES, ribavirin, Remdesivir, Ruxolitinib, Sarilumab, Siltuximab, Sirolimus, a statin, Tacrolimus, Tocilizumab, Umifenovir and Zanamivir.

61. The compound of any one of Claims 58-60, wherein the coronavirus is β -coronavirus.

62. The compound of any one of Claims 58-60, wherein the coronavirus is coronavirus selected from the group consisting of CoV 229E, CoV NL63, CoV OC43, CoV HKU1, Middle East Respiratory Syndrome (MERS)-CoV, Severe Acute Respiratory Syndrome (SARS)-CoV, and SARS-CoV-2.

63. A compound of any one of Claims 1-48, or a pharmaceutically acceptable salt thereof, for use in treating a picornavirus infection.

64. The compound of Claim 63, wherein the picornavirus infection is a rhinovirus infection.

65. A compound of any one of Claims 1-48, or a pharmaceutically acceptable salt thereof, for use in treating a norovirus infection.

66. A method for treating a coronavirus infection in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of Claims 1-48, or a pharmaceutically acceptable salt thereof.

67. The method of Claim 66, further comprising administering an additional agent selected from the group consisting of an ACE inhibitor, an anticoagulant, an anti-inflammatory, an ARB, an ASO, a Covid-19 convalescent plasma, an entry inhibitor, an H₂ pump antagonist, an H-conducting channel, an HIV protease inhibitor, an HMG-CoA reductase inhibitor, an immune globulin, an immunosuppressant, an immunotherapeutic agent, a neuraminidase inhibitor, a nucleoside inhibitor, a nucleoside analog inhibitor, a polymerase inhibitor, a protease inhibitor, an siRNA, a statin, a tissue plasminogen activator, an antibiotic, an antimicrobial and a vaccine.

68. The method of Claim 67, wherein the additional agent selected from the group consisting of Ascorbic acid, Anakinra, Azithromycin, Baloxavir, Baricitinib, Chloroquine Phosphate, Colchicine, a corticosteroid, Epoprostenol, Famotidine, Favipiravir, an IGIV, an interferon, an IVIG, Ivermectin, γ -globulin, lopinavir, Methylprednisolone, Molnupiravir (MK-4482 or EIDD-2801), Niclosamide, Nitazoxanide, Nitric oxide, Oseltamivir, Peramivir, RANTES, ribavirin, Remdesivir, Ruxolitinib, Sarilumab, Siltuximab, Sirolimus, a statin, Tacrolimus, Tocilizumab, Umifenovir and Zanamivir.

69. The method of any one of Claims 66-68, wherein the coronavirus is β -coronavirus.

70. The method of any one of Claims 66-68, wherein the coronavirus is coronavirus selected from the group consisting of CoV 229E, CoV NL63, CoV OC43, CoV HKU1, Middle East Respiratory Syndrome (MERS)-CoV, Severe Acute Respiratory Syndrome (SARS)-CoV, and SARS-CoV-2.

71. A method for treating a picornavirus infection in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of Claims 1-48, or a pharmaceutically acceptable salt thereof.

72. The method of Claim 71, wherein the picornavirus infection is a rhinovirus infection.

73. A method for treating a norovirus infection in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of Claims 1-48, or a pharmaceutically acceptable salt thereof.

74. The use of any one of Claims 50-57, the compound of any one of Claims 58-65, or the method of any one of Claims 66-73, wherein the subject is a human.

75. The use, compound or method of Claim 74, wherein the subject is 60 years old or older.

76. The use, compound or method of Claim 74, wherein the subject is a non-human primate.

77. The use, compound or method of Claim 74, wherein the subject is a cat.

78. The use, compound or method of Claim 74, wherein the subject is a camel.

79. The use of any one of Claims 50-57, the compound of any one of Claims 58-65, or the method of any one of Claims 66-73, wherein the coronavirus causes one or more symptoms selected from the group consisting of coughing, sore throat, runny nose, sneezing, headache, fever, shortness of breath, myalgia, abdominal pain, fatigue, difficulty breathing, persistent chest pain or pressure, difficulty waking, loss of smell and taste, muscle or joint pain, chills, nausea or vomiting, nasal congestion, diarrhea, haemoptysis, conjunctival congestion, sputum production, chest tightness and palpitations.

80. The use of any one of Claims 50-57, the compound of any one of Claims 58-65, or the method of any one of Claims 66-73, wherein the coronavirus causes a complication selected from the group consisting of sinusitis, otitis media, pneumonia, acute respiratory distress syndrome, disseminated intravascular coagulation, pericarditis and kidney failure.

81. The use of any one of Claims 50-57, the compound of any one of Claims 58-65, or the method of any one of Claims 66-73, wherein the compound is administered intravenously, subcutaneously, orally or via inhalation.

82. The use of Claim 52, the compound of Claim 60, or the method of Claim 68, wherein the interferon is selected from the group consisting of recombinant interferon alpha 2b, IFN- α and PEG-IFN- α -2a.

83. A method for inhibiting a coronavirus protease comprising contacting a cell infected with a coronavirus with an effective amount of a compound of any one of Claims 1-48, or a pharmaceutically acceptable salt thereof, wherein the compound of any one of Claims 1-48, or a pharmaceutically acceptable salt thereof, selectively inhibits the coronavirus protease compared to a host protease.

84. The method of Claim 83, wherein the compound of formula (I) selectively inhibits the coronavirus protease over the host protease that is selected from the group consisting of Cathepsin L, Cathepsin B, Cathepsin D, Cathepsin K, Leukocyte Elastase, Chymotrypsin, Trypsin, Thrombin, Pepsin, Caspase 2, Elastase and Calpain.

85. The method of Claim 83 or 84, wherein the host protease is selected from Cathepsin L and Cathepsin B.

86. The method of any one of Claims 83-85, wherein the selectively is > 2-fold.

ABSTRACT

Provided herein are compounds of Formula (I), or pharmaceutically acceptable salts thereof, pharmaceutical compositions that include a compound described herein (including pharmaceutically acceptable salts of a compound described herein) and methods of synthesizing the same. Also provided herein are methods of treating diseases and/or conditions with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
63/203,135

RECEIPT DATE / TIME
07/09/2021 03:43:49 PM ET

ATTORNEY DOCKET #
ALIG.072PR

Title of Invention

ANTI-VIRAL COMPOUNDS

Application Information

APPLICATION TYPE Utility - Provisional Application under
35 USC 111(b)

PATENT # -

CONFIRMATION # 7753

FILED BY Kealani Aguon

PATENT CENTER # 60236464

FILING DATE -

CUSTOMER # 20995

FIRST NAMED INVENTOR Koen Vandyck

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Kimberly Miller

Documents

TOTAL DOCUMENTS: 4

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
alig072pr_ads.pdf	9	Application Data Sheet	1227 KB
alig072pr_application.pdf	69	-	591 KB
alig072pr_application-SPEC.pdf	(1-56) 56	Specification	495 KB
alig072pr_application-CLM.pdf	(57-68) 12	Claims	118 KB
alig072pr_application-ABST.pdf	(69-69) 1	Abstract	12 KB

Digest

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If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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