Abstract: Described herein are compounds and related compositions for the treatment of viral infection, including RNA viral infection, and compounds that can modulate the RIG-I pathway in vertebrate cells, including compounds that can activate the RIG-I pathway.
Declarations under Rule 4.17:

— as to applicant’s entitlement to apply for and be granted a patent (Rule 4.17(A))

— as to the applicant’s entitlement to claim the priority of the earlier application (Rule 4.17(B))

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))
ANTI-VIRAL COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of U.S. Provisional Patent Application No. 61/752,846 filed January 15, 2013, the entire contents of which application is incorporated by reference herein.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with U. S. Government support under Grant No. AI90035 awarded by the National Institutes of Health. The U.S. Government has certain rights in this invention.

FIELD OF THE DISCLOSURE

[0003] Compounds and methods disclosed herein are useful for treating viral infection in vertebrates, including RNA viral infections.

BACKGROUND OF THE DISCLOSURE

[0004] As a group, RNA viruses represent an enormous public health problem. The U.S. and worldwide. Well-known RNA viruses include influenza virus (including the avian and swine isolates), hepatitis C virus (HCV), West Nile virus, severe acute respiratory syndrome (SARS)-coronavirus, respiratory syncytial virus (RSV), and human immunodeficiency virus (HIV).

[0005] More than 170 million people worldwide are infected by HCV, and 130 million of those are chronic carriers at risk of developing chronic liver diseases (cirrhosis, carcinoma, and liver failure). As such, HCV is responsible for two thirds of all liver transplants in the developed world. Recent studies show that the death rate from HCV infection is rising due to the increasing age of chronically infected patients. Likewise seasonal flu infects 5 - 20% of the population resulting in 200,000 hospitalizations and 36,000 deaths each year.

[0006] Compared to influenza and HCV, West Nile virus causes the lowest number of infections, 981 in the United States in 2010. Twenty percent of infected patients develop a severe form of the disease, resulting in a 4.5% mortality rate. Unlike influenza and HCV, there are no approved therapies for the treatment of West Nile virus infection, and it is a high-priority pathogen for drug development due to its potential as a bioterrorist agent.

[0007] Among the RNA viruses listed, vaccines exist only for influenza virus. Accordingly, drug therapy is essential to mitigate the significant morbidity and mortality associated with these viruses. Unfortunately, the number of antiviral drugs is limited, many are poorly effective, and
nearly all are plagued by the rapid evolution of viral resistance and a limited spectrum of action. Moreover, treatments for acute influenza and HCV infections are only moderately effective. The standard of care for HCV infection, PEGylated interferon and ribavirin, is effective in only 50% of patients, and there are a number of dose-limiting side effects associated with the combined therapy. Both classes of acute influenza antivirals, adamantanes and neuraminidase inhibitors, are only effective within the first 48 hours after infection, thereby limiting the window of opportunity for treatment. High resistance to adamantanes already restricts their use, and massive stockpiling of neuraminidase inhibitors will eventually lead to overuse and the emergence of resistant strains of influenza.

[0008] Most drug development efforts against these viruses target viral proteins. This is a large part of the reason that current drugs are narrow in spectrum and subject to the emergence of viral resistance. Most RNA viruses have small genomes and many encode less than a dozen proteins. Viral targets are therefore limited. Based on the foregoing, there is an immense and unmet need for effective treatments against viral infections.

SUMMARY OF THE DISCLOSURE

[0009] The compounds and methods disclosed herein shift the focus of viral drug development away from the targeting of viral proteins to the development of drugs that target and enhance the host’s innate antiviral response. Such compounds and methods are likely to be more effective, less susceptible to the emergence of viral resistance, cause fewer side effects and be effective against a range of different viruses.

[0010] The retinoic acid-inducible gene 1 (RIG-I) pathway is intimately involved in regulating the innate immune response to RNA virus infections. RIG-I agonists are expected to be useful for the treatment of many viruses including, without limitation, HCV, influenza, and West Nile virus. Accordingly, the present disclosure relates to compounds and methods for treating viral infection, including infection by RNA viruses, wherein the compounds can modulate the RIG-I pathway.

[0011] One embodiment of the present disclosure includes a compound represented by the formula

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Formula I
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![Formula I](attachment://image.png)
wherein a dashed line indicates the presence or absence of a pi bond; A and B are each independently a covalent single bond or covalent double bond linking the L group to the ring and R¹, respectively, A-L-B is a linker group having a structure A-C(=R²)-NR³-B, A-SO₂-NR³-B, A-NR³-SO₂-B, A-CH(CF₃)-NR³-B, A-NR³-CH(CF₃)-B,
m and n may independently be an integer from 0-5 such that \( m+n \geq 1 \); \( R^1 \) may be \( R^a, \) OR\(^2 \) or \( NR^2R^3 \); each \( R^a \) may independently be \( H, \) optionally substituted hydrocarbyl, optionally substituted aryl, or optionally substituted heteroaryl; \( R^2 \) and \( R^3 \) may each independently be \( R^a, \) COR\(^a, \) C(=0)OR\(^a, \) or S0\(^2R^a; \) \( Y^1, \) \( Y^2, \) \( Y^3, \) and \( Y^4, \) may each independently be CR\(^4 \) or N; \( Y^5, \) \( Y^6, \) \( Y^7, \) and \( Y^8 \) may each independently be CR\(^4 \) or \( R^x; \) each \( R^4 \) may independently be \( R^2, \) OR\(^a, \) NR\(^2R^3 \) SR\(^a, \) SOR\(^a, \) S0\(^2R^a, \) S0\(^2NHR^a, \) N(R\(^5\))COR\(^a, \) halogen, trihalomethyl, CN, S=O, or nitro; \( R^5 \) may be \( R^a, \) COR\(^a, \) S0\(^2R^a, \) or is not present; \( W \) and \( X \) may each independently be \( N, \) NR\(^a, \) O, S, CR\(^2R^4 \) or CR\(^4; \) each \( R^x \) may independently be \( O, \) S, CR\(^2R^3, \) or NR\(^5; \) \( R^y \) may be \( S, \) N-CN, or \( CHR^4; \) and \( Z^1 \) and \( Z^2 \) may each independently be \( C, \) CR\(^2, \) or N.

[0012] Additional embodiments include a compound represented by the formula

![Formula II](image)

[0013] \( \) wherein \( R^{10,} \) \( R^{11,} \) \( R^{14,} \) \( R^{16,} \) \( R^{17,} \) \( R^{18,} \) \( R^{19,} \) \( R^{20,} \) \( R^{21,} \) \( R^{22,} \) \( R^b, \) \( OR^b, \) SR\(^b, \) COR\(^b, \) C0\(_2R^b, \) OCOR\(^b, \) NR\(^bR^c, \) CONR\(^bR^c, \) NR\(^bCOR^c, \) S0\(^2NR^bR^c, \) CF\(_3, \) CN, N0\(_2, \) F, Cl, Br, I, or \( C_{2,5} \) heterocycl; each \( R^b \) is independently \( H \) or \( C_{1,3} \) hydrocarbyl, and each \( R^c \) is independently \( H \) or \( C_{1,3} \) alkyl. Some embodiments of the present disclosure include compounds represented by the formula:

![Formula III](image)

[0014] \( \) Certain embodiments of the present disclosure include compounds represented by the formula:
wherein $R^0$, $R$, $R^2$, $R^3$, $R^4$, $R^6$, $R^7$, and $R^8$ are independently $R^b$, OR$^b$, COR$^b$, CO$_2$R$^b$, OCOR$^b$, NR$^b$R$^c$, CF$_3$, CN, NO$_2$, F, Cl, Br, or I. wherein $R^b$ and $R^c$ are independently H or C$_{1-3}$ alkyl; and, $R^5$ is H or C$_{1-3}$ alkyl.

Further embodiments of the present disclosure include a compound represented by the formula:

![Formula IV](image)

Some embodiments of the present disclosure include a pharmaceutical composition comprising any of the compounds as described herein.

Some embodiments of the present disclosure include methods of treating or preventing a viral infection in a vertebrate comprising administering to the vertebrate a pharmaceutical composition as described herein. In some embodiments, the viral infection is caused by a virus from one or more of the following families: Arenaviridae, Astroviridae, Birnaviridae, Bromoviridae, Bunyaviridae, Caliciviridae, Closteroviridae, Comoviridae, Cystoviridae, Flaviviridae, Flexiviridae, Hepevirus, Leviviridae, Luteoviridae, Mononegavirales, Mosaic Viruses, Nidovirales, Nodaviridae, Orthomyxoviridae, Picobirnavirus, Picornaviridae, Potyviridae, Reoviridae, Retroviridae, Sequiviridae, Tenuivirus, Togaviridae, Tombusviridae, Tetraviridae, Tydiviridae, Hepadnaviridae, Herpesviridae, Paramyxoviridae or Papillomaviridae. In some embodiments, the viral infection is influenza virus, Hepatitis C virus, West Nile virus, SARS-coronavirus, poliovirus, measles virus, Dengue virus, yellow fever virus, tick-borne encephalitis virus, Japanese encephalitis virus, St. Louis encephalitis virus, Murray Valley virus, Powassan virus, Rocio virus, louping-ill virus, Banzi virus, Ilheus virus, Kokobera virus, Kunjin...
virus, Alfuy virus, bovine diarrhea virus, Kyasanur forest disease virus, respiratory syncytial virus or HIV.

[0018] Some embodiments of the methods of the present disclosure include administering any of the pharmaceutical compositions described herein as an adjuvant for a prophylactic or therapeutic vaccine. In some embodiments, the method includes immunizing a vertebrate by administering the composition with a vaccine against influenza virus, Hepatitis C virus, West Nile virus, SARS-coronavirus, poliovirus, measles virus, Dengue virus, yellow fever virus, tick-borne encephalitis virus, Japanese encephalitis virus, St. Louis encephalitis virus, Murray Valley virus, Powassan virus, Rocio virus, louping-ill virus, Banzi virus, Ilheus virus, Kokobera virus, Kunjin virus, Alfuy virus, bovine diarrhea virus, Kyasanur forest disease virus or HIV.

[0019] Some embodiments of the present disclosure include methods of modulating the innate immune response in a eukaryotic cell, comprising administering to the cell any of the compounds as described herein. In some embodiments the cell is in vivo. In other embodiments the cell is in vitro.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The various embodiments of the present disclosure may be better understood when read in conjunction with the following figures, wherein:

[0021] Figure 1 shows validation and characterization of compound KIN1000 ("RLU" = relative luciferase units). In Figure 1A, initial "hit" compounds were validated by demonstrating dose-dependent induction of the IFN3-luciferase (IFN3-LUC, left), ISG56-luciferase (ISG56-LUC, center), and the ISG54-luciferase (ISG54-LUC, right) reporter genes. Figure 1B confirms the specificity of KIN1000, which does not induce the non-specific β-actin promoter ("0.5% DMSO" = vehicle control; "10 µM KIN1000" = β-actin-luciferase reporter in presence of KIN1000; "10 µM Compound X" = positive control β-actin induction). In Figure 1C, the MTS assay demonstrated that KIN1000 did not show evident cytotoxicity to human cells treated for 48 hours with the compound. The OD value that represents 50% cell mortality is shown by a horizontal line, also demonstrating that the CC50 of KIN1000 is greater than 20 µM.

[0022] Figure 2 shows activation of transcription factors by KIN1000. In Figure 2A, HeLa cells treated with increasing amounts of KIN1000 showed dose-dependent increase in IRF-3 translocation to the nucleus, quantified by nuclear intensity minus cytoplasmic intensity ("normalized nuclear intensity"). In Figure 2B, HeLa cells treated with increasing amounts of KIN1000 showed dose-dependent increase in NFkB translocation, quantified by nuclear intensity minus cytoplasmic intensity. "SeV" refers to Sendai virus infection, the positive control.
Figure 3 shows anti-viral activity of KIN1000. MRC5 cells treated with increasing amounts of KIN1000 showed dose-dependent decrease in infection by influenza virus.

Figure 4 shows LUMINEX® (Luminex Corp.) quantified levels of cytokine expression induced by KIN1000. Human dendritic cells treated with increasing amounts of KIN1000 showed dose-dependent expression of cytokines including IL-8 (Fig. 4A), MCP-1/CCL2 (Fig. 4B), and MIP-1α/CCL3 (Fig. 4C) and MIP-1β/CCL4 (Fig. 4D).

Figure 5 shows induction of gene expression by KIN1000 and its derivative compound KIN1148. Figure 5A shows gene expression levels of IFIT2 (left) and OAS1 (right) in HeLa cells over time from 4-24 hours post treatment with 10uM KIN1000 (grey) or KIN1148 (black). Figure 5B shows gene expression levels of IFIT2 in PH5CH8 cells (left) treated with KIN1000 (solid grey bars) or KIN1148 (solid black bars), and in HeLa cells (right) treated with KIN1000 (grey striped bars) or KIN1148 (black checked bars). In each test group, the three vertical bars represent 5, 10, and 20 µM compound (KIN1000 or KIN1148), respectively. Figure 5C shows gene expression levels of IFIT2 (left), OAS1 (center), and MxA (right) in primary HUVEC cells that were treated with 1µM KIN1000 (grey) or 1µM KIN1148 (black).

Figure 6 shows antiviral activity of KIN1000 and KIN1148 against respiratory syncytial virus. Figure 6A shows that HeLa cells treated with increasing amount of KIN1000 and KIN1148 showed dose-dependent decrease in infection by RSV. Figure 6B shows that KIN1148 showed antiviral activity against RSV when drug is added up to 24 hours prior to infection.

Figure 7 shows antiviral activity of KIN1148 against Influenza A virus Udorn/72. H292 cells (left) and HEK293 cells (right) treated with 2µM (H292) or 10µM (HEK293) of KIN1148 showed decrease in infection by virus.

Figure 8 shows antiviral activity of KIN1148 against Dengue virus type 2. Huh 7 cells treated with increasing amounts of KIN1148 showed dose-dependent decrease in infection by virus.

Figure 9 shows antiviral activity of KIN1311 and KIN1054 against Dengue virus type 2. Huh 7 cells treated with increasing amounts of KIN1311 (left, checked bars) or KIN1054 (right, striped bars) showed dose-dependent decrease in infection by virus.

Figure 10 shows antiviral activity of KIN1148 and KIN1160 against Dengue virus type 2 when compound is administered 24 hours post-infection. Cultured THP-1 cells were infected with Dengue virus type 2 and treated with increasing amounts of compound 24 hours post-infection. Figure 10A demonstrates that KIN1148 and KIN1160 showed decrease in infection by virus. Figure 10B demonstrates that KIN1148 and KIN1160 showed induction of antiviral genes IFIT2 and OASL in THP-1 cells.
[0031] Figure 11 shows antiviral activity of KIN148 against Hepatitis B virus. HepAD38 cells treated with increasing amounts of KIN148 showed dose-dependent decrease in supernatant levels of virus. The OD value that represents no HBV in the supernatant is shown by a horizontal line labeled "NO HBV CELLS."

[0032] Figure 12 shows antiviral activity of KIN160 against human coronavirus OC43. Cultured MRC5 cells were infected with human coronavirus OC43 and treated with increasing amounts of KIN160. Treated cells showed a dose-dependent decrease in infection by virus.

[0033] Figure 13 shows antiviral activity of KIN160 in an in vivo model of SARS coronavirus infection. Mice infected with MHV-1 virus and treated with KIN160 (solid line) showed lower levels of weight loss compared to vehicle only treated mice (dashed line with squares). Weights of treated animals were comparable with those of uninfected animals (dashed line with circles).

[0034] Figure 14 shows IgG antibody production induced by KIN1000 and KIN148 in vivo. Animals (Lewis female rats, 10-12 weeks old) were vaccinated with suspensions of OVA in PBS, OVA+poly:C, OVA+KIN1000 or OVA+KIN148 subcutaneously in the footpad and base of tail (0.025 mL injection volume per site). Animals were boosted identically at 2 and 8 weeks post priming. Animals were bled at the indicated time points, sera was prepared and antibody levels were detected by ELISA. OD450 values for vaccine preparations containing KIN1000 (large checked bars) and KIN148 (horizontal striped bars) were normalized to values obtained from animals that received OVA in PBS alone as vaccines. Poly I:C (small checked bars) was used as a control adjuvant.

[0035] Figure 15 shows cellular response elicited by KIN compound vaccination under the same immunization scheme as Figure 14. Delayed type hypersensitivity responses elicited 2 weeks after the first boost (4 weeks post prime) were measured. Animals were challenged by injection of 0.02 mL of PBS (left ear pinna) or 0.02 mL of OVA (1 mg/mL) in PBS (right ear pinna) at indicated time point. 24 hours later ear thickness was measured with calipers. The calculated difference between right ear and left ear is shown. "OVA+K1 148" (vertical striped bar) = difference in ear thickness in animal injected with vaccine containing KIN1 148. Poly I:C ("OVA+pl:C;" horizontal striped bar) was used as a control adjuvant.

[0036] Figure 16 shows KIN148 adjuvant provides immune protection against a lethal influenza challenge following a single priming vaccination. Mice were vaccinated with a single subcutaneous dose of 1 µg of inactivated PR8 virus (gray squares) or PR8 plus 100 µg KIN1 148 (black squares) and challenged 3 weeks later with live mouse-adapted PR8 virus at 10X LD50. Figure 16A shows the percent survival after challenge. Figure 16B shows the weight
loss during infection. Figures 16C and 16D show neutralizing antibodies to homologous and heterologous virus. Sera collected 3 weeks post vaccination with PR8 alone (PR8; triangles) or PR8 + KIN1 148 (PR8+1 148; circles) was heat-inactivated and tested for its ability to neutralize infection of MDCK cells in vitro by PR8 virus (Figure 16C) or A/Brisbane/59/2007 (Figure 16D). N=5 mice per group.

[0037] Figure 17 shows KIN1 148 adjuvant causes significant IgG responses and protective serum antibodies in a prime/boost vaccination strategy. Mice were vaccinated subcutaneously at 0 and 3 weeks with 1 µg of inactivated PR8 virus (gray squares) or PR8 plus KIN1 148 (100 µg/mouse prime, 25 µg/mouse boost) in PBS (black squares) and challenged 2 weeks post boost with live mouse-adapted PR8 virus at 75X LD50. Figure 17A shows weight loss during infection. Figure 17B shows the total antigen-binding IgG antibodies 2 weeks after boosting as determined by ELISA. Figures 17C and 17D depict serum samples that were collected 2 weeks post-prime (Figure 17C) or 2 weeks post-boost (Figure 17D) were heat-inactivated and their neutralizing antibody titers were determined by analyzing their ability to block infection of MDCK cells in vitro by the homologous PR8 strain. N=5 mice per group.

[0038] Figure 18 shows KIN1 148 adjuvant enhances protection against a lethal influenza challenge following a single priming vaccination. Mice were vaccinated with a single subcutaneous dose of 0.2 µg, 0.6 µg, 1.8 µg, or 5.4 µg of inactivated split CA09 virus or CA09 plus 100 µg KIN1 148 and challenged 3 weeks later with live mouse-adapted CA07 virus at 5X LD50. Figure 18A shows weight loss during infection in groups vaccinated with 1.8 µg CA09 (gray squares) or CA09 with KIN1 148 (black squares). Figure 18B shows survival after challenge in groups vaccinated with 1.8µg CA09 (gray squares) or CA09 with KIN1 148 (black squares). N=6 mice per group.

[0039] Figure 19 shows KIN1 148 adjuvant enhances protection against a lethal influenza challenge following a single priming vaccination. Mice were vaccinated with a single intramuscular dose of 0.26 µg, 0.78 µg, or 2.35 µg of inactivated split CA09 virus or CA09 plus 50 µg KIN1 148 and challenged 3 weeks later with live mouse-adapted CA07 virus at 5X LD50. Figure 19A shows weight loss during infection in groups vaccinated with 2.35µg CA09 (gray squares) or CA09 with KIN1 148 (black squares). Figure 19B shows survival after challenge in groups vaccinated with 2.35µg CA09 (gray squares) or CA09 with KIN1 148 (black squares). Figure 19C shows serum IgG levels in samples from naïve (white), unadjuvanted (solid grey), and KIN1 148 adjuvanted (black/white hatched) groups. N=6 mice per group.
Figure 20 shows that KIN1148 adjuvant (black squares) enhances secretion of chemokines MIP-1α (Fig. 20A), MIP-1β (Fig. 20B), MIP-2 (Fig. 20C), MCP-1 (Fig. 20D), and MDC (Fig. 20E) at the site of injection. Levels were assayed up to 48 hours post injection.

**DETAILED DESCRIPTION**

The present disclosure provides compounds and methods that shift the focus of viral treatments away from the targeting of viral proteins to the development of drugs that target and enhance the host (patient's) innate antiviral response. Such compounds and methods are likely to be more effective, less susceptible to the emergence of viral resistance, cause fewer side effects and be effective against a range of different viruses.

The RIG-I pathway is intimately involved in regulating the innate immune response to RNA virus infections. RIG-I is a cytosolic pathogen recognition receptor that is essential for triggering immunity to a wide range of RNA viruses. RIG-I is a double-stranded RNA helicase that binds to motifs within the RNA virus genome characterized by homopolymeric stretches of uridine or polymeric U/A motifs. Binding to RNA induces a conformation change that relieves RIG-I signaling repression by an autologous repressor domain, thus allowing RIG-I to signal downstream through its tandem caspase activation and recruitment domains (CARDs). RIG-I signaling is dependent upon its NTPase activity, but does not require the helicase domain. RIG-I signaling is silent in resting cells, and the repressor domain serves as the on-off switch that governs signaling in response to virus infection.

RIG-I signaling is transduced through interferon-beta promoter stimulator 1 (IPS-1, also known as Cardif, MAVs, and VISA), an essential adaptor protein that resides in the outer mitochondrial membrane. IPS-1 recruits a macromolecular signaling complex that stimulates the downstream activation of interferon regulatory factor-3 (IRF-3), a transcription factor that induces the expression of type I interferons (IFNs) and virus-responsive genes that control infection. Compounds that trigger RIG-I signaling directly or through modulation of RIG-I pathway components, including IRF-3, present attractive therapeutic applications as antivirals or immune modulators.

A high-throughput screening approach was used to identify compounds that modulate the RIG-I pathway, a key regulator of the cellular innate immune response to RNA virus infection. In particular embodiments, validated RIG-I agonist lead compounds were demonstrated to specifically activate IRF-3. In additional embodiments they exhibit one or more of the following: they induce the expression of interferon-stimulated genes (ISGs), have low cytotoxicity in cell-based assays, are suitable for analog development and structure activity
relationship (SAR) studies, have drug-like physiochemical properties, and have antiviral activity against a variety of viruses.

[0045] As discussed below, these compounds represent a new class of potential antiviral therapeutics. Although the disclosure is not bound by a specific mechanism of action of the compounds in vivo, the compounds are selected for their modulation of the RIG-I pathway. In certain embodiments, the modulation is activation of the RIG-I pathway. Compounds and methods disclosed herein function to decrease one or more of: viral protein, viral RNA, and infectious virus in cell culture and/or in vivo models of infection by viruses including influenza, Dengue virus, and/or HCV.

[0046] Examples of antiviral compounds and pharmaceutical formulations prepared therefrom are described in detail in U.S. Provisional Application Serial No. 61/542,049, filed September 30, 2011 and PCT International Application No. PCT/US20 12/057646, filed September 27, 2012, the disclosures of each of which are incorporated herein in their entirety by this reference.

[0047] According to certain embodiments, the present disclosure is directed to compounds having a structure represented by the formula:

![Formula 1](image)

wherein a dashed line indicates the presence or absence of a pi bond; \( R^1 \) may be \( R^a \), \( OR^2 \) or \( NR^2R^3 \); \( R^2 \) and \( R^3 \) each independently may be \( R^a \), COR \( a \), C(=0)OR \( a \), or S0 \( 2R^a \); \( Y^1, Y^2, Y^3 \) and \( Y^4 \) may each independently be \( CR^4 \) or \( N \); each \( R^4 \) may independently be \( R^2, OR^3, NR^2R^3, SR^5, SOR^a, S0_2R^a, S0_2NHR^a, N(R^5)COR^a \), halogen, trihalomethyl, \( CN, S=0 \), or nitro; \( R^5 \) may be \( R^a \), COR \( a \), S0 \( 2R^a \), or is not present; \( V \) may be \( CR^2, CR^2R^3, C=0, COCR^2R^3 \), or \( C=NR^2 \); and, \( W \) and \( X \) may each independently be \( N, NR^a, O, S, CR^2R^4 \) or \( CR^4 \). Each \( R^a \) can independently be \( H \); optionally substituted hydrocarbyl; optionally substituted aryl, such as optionally substituted phenyl or optionally substituted aryl; optionally substituted heteroaryl, such as optionally substituted pyridinyl, optionally substituted furyl, optionally substituted thieryl, etc. In some embodiments, each \( R^a \) can independently be \( H \), or \( C_{1-12} \) alkyl, including: linear or branched alkyl having the formula \( C_{a+b}H_{a+b+1} \); or cycloalkyl having the formula \( C_{a+b}H_{a+b} \), wherein \( a \) is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, such as linear or branched alkyl of the formula: \( CH_2, C_2H_5, C_3H_7, C_4H_9, C_5H_{11}, C_6H_{13}, C_7H_{15}, C_8H_{17}, C_9H_{19}, C_{10}H_{21} \), etc., or cycloalkyl of the formula: \( C_3H_5, C_4H_7, C_5H_9, C_6H_{11}, C_7H_{13}, C_8H_{15}, C_9H_{17}, C_{10}QH_{19} \), etc.
According to certain embodiments, effective compounds having Formula I may have an amide linker between the ring structure of Formula I and the group \( R^1 \). According to these embodiments, \( V \) may comprise \( C=0 \) and \( R^5 \) may be \( H \). However, the central amide linker present in these types of structures may be susceptible to protease hydrolysis, which might diminish the efficacy of the compound. Alternative linking groups, such as but not limited to amide isosteres or other small stable linking structures, may display lower levels of hydrolysis and in certain embodiments be less susceptible to hydrolysis by proteases. For example, in certain embodiments of the present disclosure, compounds having a structure according to Formula I, except where the amide is replaced with an amide isostere linkers such as methylene ethers (-CH\(_2\)O-) and methylene amines (-CH\(_2\)NH-) may retain the IRF-3 activity of the molecule while being more stable to hydrolysis. In addition, embodiments of the antiviral compounds represented by Formula I possess scaffold structures of a modular nature which should be amenable to preparation of analogs having different linking structures.

According to any of the structural formulas herein, a dashed line indicates the presence or absence of a \( \pi\pi \) bond between the indicated atoms in the structure. That is, when two atoms in the structure are connected by a solid line and a dashed line, the atoms may be connected by a covalent single bond (i.e., a sigma bond, when the dashed line represents the absence of a \( \pi\pi \) bond), a covalent double bond (i.e., a sigma and \( \pi\pi \) bond, when the dashed line represents the presence of a \( \pi\pi \) bond and the bonds are not part of an aromatic structure), or a delocalized "double bond" (i.e., a sigma bond and a \( \pi\pi \) bond that is part of a delocalized aromatic structure or other delocalized system). The number of bonds on any atom in any structural formula will be limited by the maximum valence of the atom; and may include the valence of an atom as determined by ionic charge. According to various formulas represented herein, A and B may each independently represent a single bond or double covalent bond between the two structural features connected by A or B. For example, a substructure shown as C\(^1\)-A-C\(^2\) or C\(^1\)-B-C\(^2\) may indicate either C\(^1\)-C\(^2\) (i.e., a covalent single bond between the atoms C\(^1\) and C\(^2\)) or C\(^1\)=C\(^2\) (i.e., a covalent double between the atoms C\(^1\) and C\(^2\)). Likewise, when two (or more) structural elements are indicated as separate elements, for example, C\(^1\)-A and A-C\(^2\) or C\(^1\)-B and B-C\(^2\), the A or B indicates the presence of a bond between the two structural elements, such that the over all structure may be represented by C\(^1\)-C\(^2\), where A or B indicated the covalent bond between the two elements. For example, structural elements represented by R\(^a\)-A, A-L-B and B-R\(^b\) may be taken to indicate the overall structure R\(^a\)-L-R\(^b\), where the three structural elements are connected by covalent bonds A and B (as indicated by the dash). In certain embodiments, A or B may represent a delocalized double bond. In embodiments where
A or B are between an atom of a structure and a linking group (i.e., a grouping of two or more atoms that link two or more substructures within a compound), such as C-A-L, or L-B-R\(^1\), where L has a generic structure shown as A-LINKER-B (where "LINKER" represents the atom structure of the linking group "L"), the A or B group indicates a single or double covalent bond (or delocalized double bond) as represented by C-LINKER-B, C=LINKER-B, C-LINKER=B, or C=LINKER=B, where the single or double bond is attached to the atoms in LINKER that has the A and/or B attached thereto.

According to various embodiments of the antiviral compounds described herein, the group L may be a linker having a structure represented by: A-C(=R\(^X\))-N\(^R\)-B, A-SO\(^2\)-N\(^R\)-B, A-NR\(^2\)-SO\(^2\)-B, A-CH(CF\(_3\))-N\(^R\)-B, A-N\(^R\)-CH(CF\(_3\))-B, A-N\(^R\)-C(=R\(^y\))-N\(^R\)-B, A-CR\(^2\)R\(^3\)-R\(^X\)-B, A-0-CR\(^2\)R\(^3\)-B, A-S-CR\(^2\)R\(^3\)-B, A-C(R\(^2\))=C(R\(^3\))-B,
where \( m \) and \( n \) may each independently be an integer from 0 to 5 and are selected such that \( m+n \geq 1 \). \( Y^5, Y^6, Y^7 \) and \( Y^8 \) may each independently be \( CR^4, N, \) or \( R^x \); each \( R^x \) may independently be \( O, S, CR^2R^3, \) or \( NR^5; R^y \) may be \( S, N-CN, \) or \( CHR^4; \) and \( Z^1 \) and \( Z^2 \) may each independently be \( C, CR^2, \) or \( N \).

According to one embodiment, the group \( L \) may have a structure of an amide, thioamide, enamine, or amidine where the sp\(^2\) carbon forms a bond with the ring carbon of Formula I (via A) and the nitrogen atom forms a bond with the \( R^1 \) group (via B). According to these embodiments, \( L \) may be a linker having a structure \( A-C(=R^3)-NR^5-B \), where \( R^x \) may be \( O \) (amide), \( S \) (thioamide), \( CR^2R^3 \) (enamine), or \( NR^5 \) (amidine); and \( R^2, R^3, \) and \( R^5 \) are as defined herein.

According to other embodiments, the group \( L \) may have a structure of a sulfonamide where the sulfur atom forms a bond with the ring carbon of Formula I (via A) and the nitrogen atom forms a bond with the \( R^1 \) group (via B) or alternatively, the nitrogen atom forms a bond with the ring carbon of Formula I (via A) and the sulfur atom forms a bond with the \( R^1 \) group (via B). According to these embodiments, \( L \) may be a sulfonamide linker having a structure \( A-SO_2-NR^5-B \) or \( A-NR^5-SO_2-B \), where \( R^5 \) is as defined herein.

According to other embodiments, the group \( L \) may have a structure of a 2,2,2-trifluoroethylamine where the \( C^1 \) carbon atom of the 2,2,2-trifluoroethyl group forms a bond with the ring carbon of Formula I (via A) and the nitrogen atom forms a bond with the \( R^1 \) group (via B) or alternatively, the nitrogen atom forms a bond with the ring carbon of Formula I (via A) and the \( C^1 \) carbon atom of the 2,2,2-trifluoroethyl group forms a bond with the \( R^1 \) group (via B). According to these embodiments, \( L \) may be a 2,2,2-trifluoroethylamine linker having a structure \( A-CH(CF_3)-NR^5-B \) or \( A-NR^5-CH(CF_3)-B \), where \( R^5 \) is as defined herein.

According to other embodiments, the group \( L \) may have a structure of a 3,3-oxetanylamine where the \( C^2 \) carbon atom of the oxetane forms a bond with the ring carbon of Formula I (via A) and the nitrogen atom forms a bond with the \( R^1 \) group (via B) or alternatively, the nitrogen atom forms a bond with the ring carbon of Formula I (via A) and the \( C^2 \) carbon atom...
of the oxetane forms a bond with the R¹ group (via B). According to these embodiments, L may be a 3,3-oxetanylamine linker having a structure:

where R⁵ is as defined herein.

According to other embodiments, the group L may have a structure of a 1,1-cyclopropylamine where the C¹ carbon atom of the cyclopropane forms a bond with the ring carbon of Formula I (via A) and the nitrogen atom forms a bond with the R¹ group (via B) or alternatively, the nitrogen atom forms a bond with the ring carbon of Formula I (via A) and the C¹ carbon atom of the cyclopropane forms a bond with the R¹ group (via B). According to these embodiments, L may be a 1,1-cyclopropylamine linker having a structure:

where R⁵ is as defined herein.

According to other embodiments, the group L may have a structure of a 1-fluoro-2-aminoethylene where the C¹ carbon atom of the ethylene forms a bond with the ring carbon of Formula I (via A) and the C² carbon atom of the ethylene forms a bond with the R¹ group (via B) or alternatively, the C¹ carbon atom of the ethylene forms a bond with the ring carbon of Formula I (via A) and the C¹ carbon atom of the ethylene forms a bond with the R¹ group (via B). According to these embodiments, L may be a 1-fluoro-2-aminoethylene linker having a structure:

According to other embodiments, the group L may have a structure of a saturated, unsaturated, or aromatic 5-membered 1,3-carbocyclyl or 1,3-heterocyclyl ring where the C¹ carbon atom or N¹ nitrogen atom of the 5-membered carbocyclic or heterocyclic ring forms a bond with the ring carbon of Formula I (via A) and the C³ carbon atom or N³ nitrogen atom of the 5-membered carbocyclic or heterocyclic ring forms a bond with the R¹ group (via B) or alternatively, the C³ carbon atom or N³ nitrogen atom of the 5-membered carbocyclic or heterocyclic ring forms a bond with the ring carbon of Formula I (via A) and the C¹ carbon atom
or N¹ nitrogen atom of the 5-membered carbocyclic or heterocyclic ring forms a bond with the R¹ group (via B). In another embodiment, the group L may be a saturated, unsaturated or aromatic 5-membered 1,2-carbocyclyl or 1,2-heterocyclyl ring where the C¹ carbon atom or N¹ nitrogen atom of the 5-membered carbocyclic or heterocyclic ring forms a bond with the ring carbon of Formula I (via A) and the C² carbon atom or N² nitrogen atom of the 5-membered carbocyclic or heterocyclic ring forms a bond with the ring carbon of Formula I (via A) and the C¹ carbon atom or N¹ nitrogen atom of the 5-membered carbocyclic or heterocyclic ring forms a bond with the R¹ group (via B) or alternatively, the C² carbon atom or N² nitrogen atom of the 5-membered carbocyclic or heterocyclic ring forms a bond with the ring carbon of Formula I (via A) and the C¹ carbon atom or N¹ nitrogen atom of the 5-membered carbocyclic or heterocyclic ring forms a bond with the R¹ group (via B). The 5-membered ring may contain carbon, nitrogen, oxygen and/or sulfur atoms as ring atoms. The 5-membered ring may be saturated (i.e., all single bonds), have one double bond, have two double bonds, or be aromatic (i.e., a delocalized pi system containing 6 pi electrons). According to these embodiments, L may be a 5-membered carbocyclic or heterocyclic ring linker having a structure:

![Diagram](image)

where Z¹, Z², Y⁵, Y⁶ and Y⁷ are as defined herein. In specific embodiments, the linker may be a carbocyclic ring comprising a cyclopentane ring or a cyclopentene ring. In other embodiments, the linker may be a five membered ring with one or more heteroatoms such as N, O and/or S. In embodiments where the linker is an aromatic 5-membered ring, at least one ring atom is a heteroatom. Non-limiting examples of aromatic ring structures may include a furan, a thiophuran, a pyrrole, an imidazole, a pyrazole, an oxazole, an isoxazole, a thiazole, a isothiazole, an azaoxazole, a triazole, a tetrazole, etc., where the heteroatom(s) may be located at the various positions of the 5-membered ring. Other non-limiting examples of five membered rings may include a dihydro- and tetrahydrofurans, dihydro- and tetrahydrothiofurans, pyrrolines, pyrrolidines, imidazolidine, imidazolines, pyrazolidines, pyrazolines, etc., where the heteroatom(s) may be located at the various positions of the 5-membered ring. In certain embodiments, where Z¹ and Z² each represent sp³ hybridized carbon atoms, the bonds A and B may be on the same face of the ring (i.e., cis) or on opposite faces of the ring (i.e., trans).

[0058] In other embodiments, the linker L may have a structure of a saturated, unsaturated or aromatic 5-membered 1,3-carbocyclyl or 1,3-heterocyclyl ring, as described herein, with an amine substituent bonded to the 1 or 3 position of the ring, where the C¹ carbon atom or N¹ nitrogen atom of the 5-membered carbocyclic or heterocyclic ring forms a bond with the ring
carbon of Formula I (via A) and the nitrogen atom of the amine substituent forms a bond with the R\textsuperscript{1} group (via B) or alternatively, the nitrogen atom of the amine substituent forms a bond with the ring carbon of Formula I (via A) and the C\textsuperscript{1} carbon atom or N\textsuperscript{1} nitrogen atom of the 5-membered carbocyclic or heterocyclic ring forms a bond with the R\textsuperscript{1} group (via B). According to these embodiments, L may be an amine substituted 5-membered carbocyclic or heterocyclic ring linker having a structure:

$$\text{A} - Z^1 - Z^2 - B$$

where R\textsuperscript{5}, Z\textsuperscript{1}, Z\textsuperscript{2}, Y\textsuperscript{5}, Y\textsuperscript{6} and Y\textsuperscript{7} are as defined herein. In certain embodiments, where Z\textsuperscript{1} and Z\textsuperscript{2} each represent sp\textsuperscript{3} hybridized carbon atoms, the substituent bonds to A and B or the NR\textsuperscript{5} group may be on the same face of the ring (i.e., cis) or on opposite faces of the ring (i.e., trans).

[0059] In further embodiments, the linker L may have a structure of a saturated, unsaturated or aromatic 5-membered 1,2-carbocyclyl or 1,2-heterocyclyl ring, as described herein, with an amine substituent bonded to the 1 or 2 position of the ring, where the C\textsuperscript{1} carbon atom or N\textsuperscript{1} nitrogen atom of the 5-membered carbocyclic or heterocyclic ring forms a bond with the ring carbon of Formula I (via A) and the nitrogen atom of the amine substituent forms a bond with the R\textsuperscript{1} group (via B) or alternatively, the nitrogen atom of the amine substituent forms a bond with the ring carbon of Formula I (via A) and the C\textsuperscript{1} carbon atom or N\textsuperscript{1} nitrogen atom of the 5-membered carbocyclic or heterocyclic ring forms a bond with the R\textsuperscript{1} group (via B). According to these embodiments, L may be an amine substituted 5-membered carbocyclic or heterocyclic ring linker having a structure:

$$\text{A} - Z^1 - Z^2 - B$$

where R\textsuperscript{5}, Z\textsuperscript{1}, Z\textsuperscript{2}, Y\textsuperscript{5}, Y\textsuperscript{6} and Y\textsuperscript{7} are as defined herein. In certain embodiments, where Z\textsuperscript{1} and Z\textsuperscript{2} each represent sp\textsuperscript{3} hybridized carbon atoms, the substituent bonds to A and B or the NR\textsuperscript{5} group may be on the same face of the ring (i.e., cis) or on opposite faces of the ring (i.e., trans).

[0060] According to other embodiments, the group L may have a structure of a saturated, unsaturated or aromatic 6-membered 1,3-carbocyclyl or 1,3-heterocyclyl ring where the C\textsuperscript{1} carbon atom or N\textsuperscript{1} nitrogen atom of the 6-membered carbocyclic or heterocyclic ring forms a bond with the ring carbon of Formula I (via A) and the C\textsuperscript{3} carbon atom or N\textsuperscript{3} nitrogen atom of the
6-membered carbocyclic or heterocyclic ring forms a bond with the R¹ group (via B) or alternatively, the C³ carbon atom or N³ nitrogen atom of the 6-membered carbocyclic or heterocyclic ring forms a bond with the ring carbon of Formula I (via A) and the C¹ carbon atom or N¹ nitrogen atom of the 6-membered carbocyclic or heterocyclic ring forms a bond with the R¹ group (via B). In another embodiment, the group L may be a saturated, unsaturated or aromatic 6-membered 1,2-carbocyclyl or 1,2-heterocyclyl ring where the C¹ carbon atom or N¹ nitrogen atom of the 6-membered carbocyclic or heterocyclic ring forms a bond with the ring carbon of Formula I (via A) and the C² carbon atom or N² nitrogen atom of the 6-membered carbocyclic or heterocyclic ring forms a bond with the ring carbon of Formula I (via A) and the C¹ carbon atom or N¹ nitrogen atom of the 6-membered carbocyclic or heterocyclic ring forms a bond with the R¹ group (via B). In another embodiment, the group L may be a saturated, unsaturated or aromatic 6-membered 1,4-carbocyclyl or 1,4-heterocyclyl ring where the C¹ carbon atom or N¹ nitrogen atom of the 6-membered carbocyclic or heterocyclic ring forms a bond with the ring carbon of Formula I (via A) and the C⁴ carbon atom or N⁴ nitrogen atom of the 6-membered carbocyclic or heterocyclic ring forms a bond with the R¹ group (via B) or alternatively, the C⁴ carbon atom or N⁴ nitrogen atom of the 6-membered carbocyclic or heterocyclic ring forms a bond with the ring carbon of Formula I (via A) and the C¹ carbon atom or N¹ nitrogen atom of the 6-membered carbocyclic or heterocyclic ring forms a bond with the R¹ group (via B). The 6-membered ring may contain carbon, nitrogen, oxygen and/or sulfur atoms as ring atoms. The 6-membered ring may be saturated (i.e., all single bonds), have one double bond, have two double bonds, or be aromatic (i.e., a delocalized pi system containing 6 pi electrons). According to these embodiments, L may be a 6-membered carbocyclic or heterocyclic ring linker having a structure:

![Structure](image)

where Z¹, Z², Y⁵, Y⁶, Y⁷ and Y⁸ are as defined herein. The atoms in the six membered ring may be substituted or unsubstituted. In specific embodiments, the linker may be a carbocyclic ring comprising a cyclohexane ring, a cyclohexene ring or cyclohexadiene ring. In other embodiments, the linker may be a six membered ring with one or more heteroatoms such as N, O and/or S. In embodiments where the linker is an aromatic 6-membered ring, the ring may be a phenyl ring (i.e., all ring atoms are carbon) or at least one ring atom may be a heteroatom. Non-
limiting examples of aromatic ring structures may include a phenyl, a pyridine, a pyridazine, a pyrimidine, a pyrazine, a triazine, a tetraazine, etc., where the heteroatom(s) may be located at the various positions of the 6-membered ring. Other non-limiting examples of six membered rings may include pyran, dihydro- and tetrahydropyrans, thiopyrans, dihydro- and tetrahydrothiopyrans, piperidines, piperazines, hexahydropyridine, tetrahydro-, and dihydropyrimidines, morpholines, thiomorpholines, dioxanes, oxathianes, thianes, dithianes, etc., where the heteroatom(s) may be located at the various positions of the 6-membered ring. In certain embodiments, where \( Z^1 \) and \( Z^2 \) each represent \( \text{sp}^3 \) hybridized carbon atoms, the bonds A and B may be on the same face of the ring (i.e., cis) or on opposite faces of the ring (i.e., trans).

[0061] In other embodiments, the linker L may have a structure of a saturated, unsaturated or aromatic 6-membered 1,3-carbocyclyl or 1,3-heterocyclyl ring, as described herein, with an amine substituent bonded to the 1 or 3 position of the ring, where the \( C^1 \) carbon atom or \( N^1 \) nitrogen atom of the 6-membered carbocyclic or heterocyclic ring forms a bond with the ring carbon of Formula I (via A) and the nitrogen atom of the amine substituent forms a bond with the \( R^1 \) group (via B) or alternatively, the nitrogen atom of the amine substituent forms a bond with the ring carbon of Formula I (via A) and the \( C^1 \) carbon atom or \( N^1 \) nitrogen atom of the 6-membered carbocyclic or heterocyclic ring forms a bond with the \( R^1 \) group (via B). According to these embodiments, L may be an amine substituted 6-membered carbocyclic or heterocyclic ring linker having a structure:

\[
\begin{align*}
&\text{or} \hspace{1cm}
\end{align*}
\]

where \( R^5, Z^1, Z^2, Y^5, Y^6, Y^7 \) and \( Y^8 \) are as defined herein. In certain embodiments, where \( Z^1 \) and \( Z^2 \) each represent \( \text{sp}^3 \) hybridized carbon atoms, the substituent bonds to A and B or the \( NR^5 \) group may be on the same face of the ring (i.e., cis) or on opposite faces of the ring (i.e., trans).

[0062] In further embodiments, the linker L may have a structure of a saturated, unsaturated or aromatic 6-membered 1,2-carbocyclyl or 1,2-heterocyclyl ring, as described herein, with an amine substituent bonded to the 1 or 2 position of the ring, where the \( C^1 \) carbon atom or \( N^1 \) nitrogen atom of the 6-membered carbocyclic or heterocyclic ring forms a bond with the ring carbon of Formula I (via A) and the nitrogen atom of the amine substituent forms a bond with the \( R^1 \) group (via B) or alternatively, the nitrogen atom of the amine substituent forms a bond with the ring carbon of Formula I (via A) and the \( C^1 \) carbon atom or \( N^1 \) nitrogen atom of the 6-membered carbocyclic or heterocyclic ring forms a bond with the \( R^1 \) group (via B). According to
these embodiments, L may be an amine substituted 6-membered carbocyclic or heterocyclic ring linker having a structure:

\[ \begin{array}{c}
\text{A} \quad \text{NR}^5 \quad \text{B} \\
\text{Z}^1 \equiv \text{Z}^2
\end{array} \]

where \( R^5, Z^1, Z^2, Y^5, Y^6, Y^7 \) and \( Y^8 \) are as defined herein. In certain embodiments, where \( Z^1 \) and \( Z^2 \) each represent \( sp^3 \) hybridized carbon atoms, the substituent bonds to A and B or the NR\(^5\) group may be on the same face of the ring (i.e., cis) or on opposite faces of the ring (i.e., trans).

[0063] In further embodiments, the linker L may have a structure of a saturated, unsaturated or aromatic 6-membered 1,4-carbocycyl or 1,4-heterocyclyl ring, as described herein, with an amine substituent bonded to the 1 or 4 position of the ring, where the C\(^1\) carbon atom or N\(^1\) nitrogen atom of the 6-membered carbocyclic or heterocyclic ring forms a bond with the ring carbon of Formula I (via A) and the nitrogen atom of the amine substituent at the 4-position forms a bond with the R\(^1\) group (via B) or alternatively, the nitrogen atom of the amine substituent at the 4-position forms a bond with the ring carbon of Formula I (via A) and the C\(^1\) carbon atom or N\(^1\) nitrogen atom of the 6-membered carbocyclic or heterocyclic ring forms a bond with the R\(^1\) group (via B). According to these embodiments, L may be an amine substituted 6-membered carbocyclic or heterocyclic ring linker having a structure:

\[ \begin{array}{c}
\text{A} \quad \text{NR}^5 \quad \text{B} \\
\text{Z}^1 \equiv \text{Z}^2
\end{array} \]

where \( R^5, Z^1, Z^2, Y^5, Y^6, Y^7 \) and \( Y^8 \) are as defined herein. In certain embodiments, where \( Z^1 \) and \( Z^2 \) each represent \( sp^3 \) hybridized carbon atoms, the substituent bonds to A and B or the NR\(^5\) group may be on the same face of the ring (i.e., cis) or on opposite faces of the ring (i.e., trans).

[0064] In further embodiments, the linker L may have a structure of a 5-membered 3,4-diamino substituted 1,1-dioxo thio-2,5-imidazole ring, with amine substituents bonded to the 3 or 4 positions of the ring, where the nitrogen atom of the amine substituent at the 3 position of the ring forms a bond with the ring carbon of Formula I (via A) and the nitrogen atom of the amine substituent at the 4 position of the ring forms a bond with the R\(^1\) group (via B). According to these embodiments, L may be a 3,4-diamino substituted 1,1-dioxo thio-2,5-imidazole ring linker having a structure:
where \( R^5 \) is as defined herein.

[0065] In further embodiments, the linker \( L \) may have a structure of a thiourea, a N-cyanoguanidine, or a 1,1-diaminoalkene, where the nitrogen atom of one of the amino groups forms a bond with the ring carbon of Formula I (via A) and the nitrogen atom of the other amino group forms a bond with the \( R^1 \) group (via B). According to these embodiments, \( L \) may be a thiourea, a N-cyanoguanidine, or a 1,1-diaminoalkene linker having a structure: \( A-NR^5-C(=R^b)-NR^a-B \), where \( R^b \) may be \( S \), \( N-CN \), or \( CHR^4 \), and \( R^a \) and \( R^5 \) are as defined herein.

[0066] In other embodiments, the linker \( L \) may have a structure having a linking chain of two atoms between the ring carbon of Formula I and \( R^1 \), where one of the atoms is a substituted or unsubstituted carbon atom and the other atom may be a substituted or unsubstituted carbon or nitrogen atom or a sulfur or oxygen atom (i.e. a two carbon alkyl linker, an amine linker, an ether linker or a thioether linker), where the carbon atom forms a bond with the ring carbon of Formula I (via A) and the carbon atom, nitrogen atom, oxygen atom or sulfur atom of the linker forms a bond with the \( R^1 \) group (via B), or alternatively, the other carbon atom, nitrogen atom, oxygen atom or sulfur atom of the linker forms a bond with the ring carbon of Formula I (via A) and the carbon atom forms a bond with the \( R^1 \) group (via B). According to these embodiments, \( L \) may be a two carbon alkyl linker, an amine linker, an ether linker or a thioether linker having a structure: \( A-CR^2R^3-R^5B \), \( A-0-CR^2R^3-B \), or \( A-S-CR^2R^3-B \), where \( R^x \), \( R^2 \) and \( R^3 \) are as defined herein.

[0067] In other embodiments, the linker \( L \) may have a structure of a di-, mono- or unsubstituted ethylene unit (i.e., two carbon unit connected by a double bond), where one carbon atom of the ethylene group forms a bond with the ring carbon of Formula I (via A) and the other carbon atom of the ethylene group forms a bond with the \( R^1 \) group (via B). According to these embodiments, \( L \) may be a two carbon ethylene linker having a structure: \( A-C(R^2)=C(R^3)-B \), where \( R^2 \) and \( R^3 \) are as defined herein and the bonds A and B may be on the same side of the double bond (i.e., cis) or on opposite sides of the double bond (i.e., trans).

[0068] In other embodiments, the linker \( L \) may comprise a 1,2-cyclopropane, 1,2-epoxide, 1,2-thioepoxide, or 1,2-aziridine, where one carbon atom of the ring forms a bond with the ring carbon of Formula I (via A) and another carbon atom of the ring forms a bond with the \( R^1 \) group.
(via B). According to these embodiments, L may be a 1,2-cyclopropane, 1,2-epoxide, 1,2-thioepoxide, or 1,2-aziridine linker having a structure:

where \( R^x \) may be as defined herein and the bonds A and B may be on the same face of the ring (i.e., cis) or on opposite faces of the ring (i.e., trans).

In still other embodiments, the linker L may comprise a 1,2-cyclobutane, 1,2-oxetane, 1,2-thiooxetane, or 1,2-azetidine, where one carbon atom of the ring forms a bond with the ring carbon of Formula I (via A) and another carbon atom of the ring forms a bond with the \( R^1 \) group (via B). According to these embodiments, L may be a 1,2-cyclobutane, 1,2-oxetane, 1,2-thiooxetane, or 1,2-azetidine linker having a structure:

where each \( R^x \) may independently be O, S, CR\(^2 CR^3\), or NR\(^5\), and the bonds A and B may be on the same face of the ring (i.e., cis) or on opposite faces of the ring (i.e., trans).

In still other embodiments, the linker L may comprise an amino substituted-1,2-cyclobutane, amino substituted-1,2-oxetane, amino substituted-1,2-thiooxetane, or amino substituted-1,2-azetidine, where the amino substituent on the \( C^1 \) carbon atom of the ring forms a bond with the ring carbon of Formula I (via A) and \( C^2 \) carbon atom of the ring forms a bond with the \( R^1 \) group (via B), or alternatively \( C^1 \) carbon atom of the ring forms a bond with the ring carbon of Formula I (via A) and the amino substituent on the \( C^2 \) carbon atom of the ring forms a bond with the \( R^1 \) group (via B). According to these embodiments, L may be an amino substituted-1,2-cyclobutane, amino substituted-1,2-oxetane, amino substituted-1,2-thiooxetane, or amino substituted-1,2-azetidine linker having a structure:

where each \( R^x \) may independently be O, S, CR\(^2 CR^3\), or NR\(^5\), each \( R^5 \) are independently as defined herein, and the bonds A and B may be on the same face of the ring (i.e., cis) or on opposite faces of the ring (i.e., trans).

In still other embodiments, the linker L may comprise a 1,1-cycloalkyl or 1,1-heterocycle, where a carbon atom of the ring forms a bond with the ring carbon of Formula I (via
A) and the same carbon atom of the ring forms a bond with the $R^1$ group (via $B$). According to certain embodiments, the 1,1-cycloalkyl may be a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl ring which may be saturated or contain one or more double bonds. In other embodiments, the 1,1-heterocycloalkyl may be a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl ring which may be saturated or contain one or more double bond. According to these embodiments, $L$ may be a 1,1-cycloalkyl or 1,1-heterocycloalkyl linker having a structure:

$$\begin{array}{c}
A \xrightarrow{\text{m}} \bigg( \bigg\{ \bigg( R^x \bigg)_{n} \bigg\}_{A} \bigg) \xrightarrow{\text{n}} B,
\end{array}$$

where $m$ and $n$ may each independently be an integer from 0 to 5 such that $m+n \geq 1$ each $R^x$ may independently be O, S, CR$_2$CR$_3$, or NR$_5$. In those embodiments where the ring carbon with bonds $A$ and $B$ may be a stereoisomer, both stereoisomers may be considered part of the disclosure.

[0072] In still other embodiments, the linker $L$ may comprise an amino substituted-1,1-cycloalkyl or an amino substituted 1,1-heterocycle, where the amino substituent on the $C^1$ carbon atom of the ring forms a bond with the ring carbon of Formula I (via $A$) and $C^1$ carbon atom of the ring forms a bond with the $R^1$ group (via $B$), or alternatively $C^1$ carbon atom of the ring forms a bond with the ring carbon of Formula I (via $A$) and the amino substituent on the $C^1$ carbon atom of the ring forms a bond with the $R^1$ group (via $B$). According to these embodiments, $L$ may be an amino substituted 1,1-spirocycle or an amino substituted 1,1-spiroheterocycle linker having a structure:

$$\begin{array}{c}
A \xrightarrow{\text{m}} \bigg( \bigg\{ \bigg( R^x \bigg)_{n} \bigg\}_{A} \bigg) \xrightarrow{\text{n}} B \\
A \xrightarrow{\text{N}} R_{5} \xrightarrow{\text{m}} \bigg( \bigg\{ \bigg( R^x \bigg)_{n} \bigg\}_{A} \bigg) \xrightarrow{\text{n}} B,
\end{array}$$

where $m$ and $n$ may each independently be an integer from 0 to 5 such that $m+n \geq 1$ each $R^x$ may independently be O, S, CR$_2$CR$_3$, or NR$_5$. In those embodiments where the ring carbon with bonds $A$ and $B$ may be a stereoisomer, both stereoisomers may be considered part of the disclosure.

[0073] The listing of possible structures for group $L$ is not exhaustive and one having ordinary skill in the art, reading the present disclosure would understand that other possible linkers, including other possible amide isostere linkers, would also be within the scope of the structures described herein.

[0074] With respect to Formula I, $Y^1$ may be CR$_4$ or $N$. In some embodiments, $Y^1$ is CR$_4$. 

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With respect to Formula 1, $Y^2$ may be CR$^4$ or N. In some embodiments, $Y^2$ is CR$^4$.

In some embodiments of the compounds represented by Formula 1, $Y^1$ and $Y^2$ are both CR$^4$, and together form an additional heterocyclic ring optionally substituted by R$^4$ or R$^5$. In some embodiments, $Y^1$ and $Y^2$ may together form a heterocyclic ring, such as an aromatic or a heteroaromatic ring, including but not limited to a thiazole ring having a structure:

With respect to Formula 1, $Y^3$ may be CR$^4$ or N. In some embodiments, $Y^3$ is CR$^4$.

With respect to Formula 1, $Y^4$ may be CR$^4$ or N. In some embodiments, $Y^4$ is CR$^4$.

In some embodiments, $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are CR$^4$. In some embodiments, $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are CH. In some embodiments, $Y^1$ and $Y^2$ are and $Y^3$ and $Y^4$ are CH.

In certain embodiments of the compounds of the present disclosure, W may be S. In certain embodiments of the present disclosure, X may be N. In specific embodiments, W may be S and X may be N, such that the ring containing W and X may be a thiazol ring. In various embodiments of the compounds described herein, each R$^5$ may independently be H or C$_{1-3}$ alkyl.

In various embodiments of the compounds described herein, $Y^3$ is CR$^4$, wherein R$^4$ is R$^b$, OR$^b$, COR$^b$, C0$_2$R$^b$, OCOR$^b$, NR$^b$R$^c$, CF$_3$, CN, N0$_2$, F, Cl, Br, or i, wherein R$^b$ and R$^c$ are independently H or C$_{1-3}$ alkyl. In various embodiments of the compounds described herein, $Y^4$ is CR$^4$, wherein R$^4$ is R$^b$, OR$^b$, COR$^b$, C0$_2$R$^b$, OCOR$^b$, NR$^b$R$^c$, CF$_3$, CN, N0$_2$, F, Cl, Br, or i, wherein R$^b$ and R$^c$ are independently H or C$_{1-3}$ alkyl.

In specific embodiments, R$^1$ may be an optionally substituted naphthyl ring. In certain embodiments of the present disclosure, the antiviral compound may be a compound having a structure represented by the formula:
where A and B may independently represent a single covalent bond or double covalent bond, L
may be a linker group comprising a structure as described herein, \( R^{10}, R^{11}, R^{14}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, \) and \( R^{22} \) are independently \( R^b, OR^b, SR^b, COR^b, CO_2R^b, OCOR^b, NR^bR^c, CONR^bR^c, NR^bCOR^c, SOR_2NR^bR^c, CF_3, CN, NO_2, F, Cl, Br, I, C_{2-5} \) cyclyl or \( C_{2-5} \) heterocyclyl and \( C_{1-6} \) aryl or \( C_{1-6} \) heteroaryl, including where two adjacent R groups come together to form a fused cyclyl, heterocyclyl, aryl or heteroaryl ring structure; each \( R^b \) is independently \( H \) or \( C_{1-3} \) hydrocarbyl, and each \( R^c \) is independently \( H \) or \( C_{1-3} \) alkyl. In specific embodiments, \( R^{18} \) may be \( H \) or \( C_{1-3} \) alkyl and in particular embodiments, \( R^{18} \) may be \( H \).

[0083] In certain embodiments, \( R^1 \) may be a naphthyl where \( R^{19}, R^{20}, R^{21}, \) and \( R^{22} \) are each \( H \), \( Y^1 \) and \( Y^2 \) may form a thiazole ring as shown herein where \( R^{18} \) may be \( H \), and \( Y^3 \) and \( Y^4 \) may each be \( CH \). According to these embodiments, the antiviral compound may be represented by the structure:

![Formula III](image)

where A and B may independently represent a single covalent bond or double covalent bond, L
may be a linker group comprising a structure as described herein.

[0084] In specific embodiments, \( R^1 \) may be an optionally substituted phenyl ring. In certain
embodiments of the present disclosure, the antiviral compound may be a compound having a
structure represented by the formula:

![Formula IV](image)
where A and B independently represent a single covalent bond or double covalent bond, L is a linker group comprising a structure as described herein, \( R_1^{10}, R_1^{11}, R_1^{12}, R_1^{13}, R_1^{14}, R_1^{16}, R_1^{17}, \) and \( R_1^{18} \) are independently \( R^b, OR^b, COR^b, CO_2R^b, OCOR^b, NR^bR^c, CF_3, CN, NO_2, F, Cl, Br, \) or \( i \), wherein \( R^b \) and \( R^c \) are independently H or \( C_{13} \) alkyl; and, \( R^5 \) is H or \( C_{13} \) alkyl. In specific embodiments, \( R_1^{18} \) may be H or \( C_{13} \) alkyl and in particular embodiments, \( R_1^{16} \) may be \( CH_3 \). In specific embodiments, \( R_1^{15} \) may be halogen, and in particular embodiments, \( R_1^{15} \) may be \( Br \).

[0085] In certain embodiments, \( R_1^1 \) may be a phenyl where \( R_1^{10}, R_1^{11}, R_1^{12}, \) and \( R_1^{14} \) are each H, \( R_1^{13} \) is \( Br \), \( Y_1 \) and \( Y_2 \) may form a thiazole ring as shown herein where \( R_1^{18} \) may be \( CH_3 \), and \( Y_3 \) and \( Y_4 \) may each be CH. According to these embodiments, the antiviral compound may be represented by the structure:

![Formula V](image)

where A and B may independently represent a single covalent bond or double covalent bond, L may be a linker group comprising a structure as described herein.

[0086] Some embodiments include compounds represented by any of Formulas VI-XIII.

![Formula VI](image)

![Formula VII](image)

![Formula VIII](image)

![Formula IX](image)
With respect to any relevant structural feature herein, each R^3 may independently be H; optionally substituted hydrocarbyl, such as C1-12 or C1-6 hydrocarbyl; optionally substituted aryl, such as optionally substituted C6-12 aryl, including optionally substituted phenyl; optionally substituted heteroaryl, including optionally substituted C2-12 heteroaryl, such as optionally substituted furyl, optionally substituted thienyl, etc. In some embodiments, each R^3 can independently be H, or C1-12 alkyl, including: linear or branched alkyl having the formula C_a H_{a+1}, or cycloalkyl having the formula C_a H_{a+1}, wherein a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, such as linear or branched alkyl of the formula: CH₃, C₂H₅, C₃H₇, C₄H₉, C₅H₁₁, C₆H₁₃, C₇H₁₅, C₈H₁₇, C₉H₁₉, C₁₀H₂₁, etc., or cycloalkyl of the formula: C₃H₅, C₄H₇, C₅H₉, C₆H₁₁, C₇H₁₃, C₈H₁₅, C₉H₁₇, C₁₀H₁₉, etc.

With respect to R^3, in some embodiments, the aryl group is substituted with halogen, trihalomethyl, alkoxy, alkylamino, OH, CN, alkylthio, arylthio, sulfoxide, arylsulfonfonyl, alkylsulfonfonyl, carboxylic acid, nitro or acylamino.

With respect to R^3, in some embodiments, the heteroaryl group is single or fused. In some embodiments, the single heteroaryl group is imidazole. In some embodiments, the fused heteroaryl group is benzimidazole. In some embodiments, the heteroaryl group is substituted with halogen, trihalomethyl, alkoxy, alkylamino, OH, CN, alkylthio, arylthio, sulfoxide, arylsulfonfonyl, alkylsulfonfonyl, carboxylic acid, nitro or acylamino. In some embodiments, the alkyl group is branched, cyclic or polycyclic.

With respect to R^3, a hydrocarbyl may be alkyl, alkenyl, or alkynyl. In some embodiments, the alkyl group is substituted with halogen, trihalomethyl, alkoxy, alkylamino, OH,
CN, heteroaryl, alkylthio, arylthio, sulfoxide, arylsulfonyl, alkylsulfonyl, carboxylic acid, nitro, or acylamino. In some embodiments, the heteroaryl group is single or fused. In some embodiments, the single heteroaryl group is imidazole. In some embodiments, the fused heteroaryl group is benzimidazole. In some embodiments, the alkenyl group is branched, cyclic or polycyclic. In some embodiments, the alkenyl group is substituted with halogen, trihalomethyl, alkoxy, alkylamino, OH, CN, heteroaryl, alkylthio, arylthio, sulfoxide, arylsulfonyl, alkylsulfonyl, carboxylic acid, nitro, or acylamino.

With respect to any relevant structural feature herein, \( R^c \) may be \( H \), or \( C_{1,3} \) hydrocarbyl, such as \( \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_3\text{H}_7 \), cyclopropyl, \( \text{CH}=\text{CH}_2, \text{CH}_2\text{CH}=\text{CH}_2, \text{C}=\text{CH}, \text{CH}_2\text{C}=\text{CH} \), etc.

With respect to any relevant structural feature herein, \( R^c \) may be 1-) \( H \), or 2-) \( C_{1,3} \) alkyl, such as \( \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_3\text{H}_7 \), cyclopropyl, etc. In some embodiments, \( R^c \) is 1-) \( H \).

With respect to any relevant formula or structural depiction herein, \( R^1 \) may be \( R^a, \text{OR}^2 \text{OR}^3 \). In some embodiments, \( R^1 \) may be optionally substituted phenyl. In some embodiments, \( R^1 \) may be unsubstituted phenyl. In some embodiments, \( R^1 \) may be substituted or unsubstituted pyridyl or pyrimidyl. In some embodiments, \( R^1 \) may be optionally substituted naphthyl. In some embodiments, \( R^1 \) may be unsubstituted naphthyl. In some embodiments, \( R^1 \) may be substituted or unsubstituted quinolinyl, isoquinolinyl, or azoquinolinyl.

In some embodiments, \( R^1 \) may be

In some embodiments, \( R^1 \) may be

In some embodiments, \( R^1 \) may be
In some embodiments, $R^1$ may be:

In some embodiments, $R^2$ may be:

In some embodiments, $R^3$ may be:

In some embodiments, $R^4$ may be:

Generally $R^5$ and $R^6-R^{32}$ may be $H$ or any substituent, such as a substituent having from 0 to 6 carbon atoms and from 0 to 5 heteroatoms independently selected from: O, N, S, F, Cl, Br, and I, and/or having a molecular weight of 15 g/mol to 300 g/mol. Any of $R^5$ and $R^6-R^{32}$ may comprise: a) 1 or more alkyl moieties optionally substituted with, or optionally connected...
by, b) 1 or more functional groups, such as C=O, C=C, CO, CO₂, CON, NCO₂, OH, SH, O, S, N, N=O, F, Cl, Br, i. CN, N₂O₂, CO₂H, NH₂, etc.; or may be a substituent having no alkyl portion, such as F, Cl, Br, i. NO₂, CN, NH₂, OH, COH, CO₂H, etc.

[00105] With respect to any relevant structural feature herein, in some embodiments, R⁵ may be R₃, COR₃, Sₐ₂R₃, or may not be present. Some non-limiting examples of R⁵ may include H or C₁₋₃ alkyl, such as CH₃, C₂H₅, C₇, cyclopropyl, etc. In some embodiments, R⁵ may be CH₃. In some embodiments, R⁵ may be H.

[00106] With respect to any relevant formula or structural depiction above, some non-limiting examples of R₈ may include R₈, OR₈, SR₈, COR₈, CO₂R₈, OCOR₈, NR₈R₈, CONR₈R₈, NR₈COR₈, Sₐ₂NR₈R₈, CF₃, CN, N₂O₂, F, Cl, Br, i. or C₂₋₅ heterocycl. In some embodiments, R₈ may be H, CH₃, CH₂CH₃, Cl, Br, OH, OCH₃, SCH₃, NH₂, NHCH₃, N(CH₃)₂, S₀₂NH₂, morpholino, CH₂=CH, or N₂O₂. In some embodiments, R₈ may be H.

[00107] With respect to any relevant formula or structural depiction above, some non-limiting examples of R⁹ may include R⁹, COR⁹, CO₂R⁹, OCOR⁹, NR⁹R⁹, CONR⁹R⁹, Sₐ₂NR⁹R⁹, CF₃, CN, N₂O₂, F, Cl, Br, i. or C₂₋₅ heterocycl. In some embodiments, R⁹ may be H, CH₃, CH₂CH₃, S₀₂NH₂, or CH₂=CH. In some embodiments, R⁹ may be H, CH₃, CH₂CH₃, CH₂CH₂CH₃, CH₂CH=CH₂, or CH₂=CH. In some embodiments, R⁹ may be CH₂C≡CH. In some embodiments, R⁹ may be H.

[00108] With respect to any relevant formula or structural depiction above, some non-limiting examples of R¹₀ may include R¹₀, OR¹₀, SR¹₀, COR¹₀, CO₂R¹₀, OCOR¹₀, NR¹₀R¹₀, CONR¹₀R¹₀, NR¹₀COR¹₀, Sₐ₂NR¹₀R¹₀, CF₃, CN, N₂O₂, F, Cl, Br, i. or C₂₋₅ heterocycl. In some embodiments, R¹₀ may be H, CH₃, CH₂CH₃, Cl, Br, OH, OCH₃, SCH₃, NH₂, NHCH₃, N(CH₃)₂, S₀₂NH₂, morpholino, CH₂=CH, or N₂O₂. In some embodiments, R¹₀ may be H.

[00109] With respect to any relevant formula or structural depiction above, some non-limiting examples of R¹₁ may include R¹₁, OR¹₁, SR¹₁, COR¹₁, CO₂R¹₁, OCOR¹₁, NR¹₁R¹₁, CONR¹₁R¹₁, NR¹₁COR¹₁, Sₐ₂NR¹₁R¹₁, CF₃, CN, N₂O₂, F, Cl, Br, i. or C₂₋₅ heterocycl. In some embodiments, R¹₁ may be H, CH₃, CH₂CH₃, Cl, Br, OH, OCH₃, SCH₃, NH₂, NHCH₃, N(CH₃)₂, S₀₂NH₂, morpholino,
CH₂=C=CH, or N₂. In some embodiments, R¹¹ may be H, Cl or Br. In some embodiments, R¹¹ may be Cl. In some embodiments, R¹¹ may be Br. In some embodiments, R¹¹ may be H.

[0010] With respect to any relevant formula or structural depiction above, some non-limiting examples of R¹² may include R², OR², SR², COR², C⁰₂R², OCOR², NR²R², CONR²R², NR²COR², SO₂NR²R², CF₃, CN, N₂, F, Cl, Br, i, or C₆H₅ heterocycl. In some embodiments, R¹² may be H, CH₃, CH₂CH₃, CI, Br, OH, OCH₃, SCH₃, NH₂, NHCH₃, N(CH₃)₂, SΟ₂NH₂, morpholino, CH₂C≡CH, or N₂. In some embodiments, R¹² may be H. In some embodiments, R¹² may be Cl. In some embodiments, R¹² may be SΟ₂NH₂. In some embodiments, R¹² may be H.

[0011] In some embodiments, R¹¹ and R¹² may together form a fused cyclic, heterocyclic, aryl, or heteraryl structure, such as, but not limited to the structure:


[0012] With respect to any relevant formula or structural depiction above, some non-limiting examples of R¹³ may include R⁵, OR⁵, SR⁵, COR⁵, C⁰₂R⁵, OCOR⁵, NR⁵R⁵, CONR⁵R⁵, NR⁵COR⁵, SO₂NR⁵R⁵, CF₃, CN, N₂, F, Cl, Br, i, or C₆H₅ heterocycl. In some embodiments, R¹³ may be H, CH₃, CH₂CH₃, CI, Br, OH, OCH₃, SCH₃, NH₂, NHCH₃, N(CH₃)₂, SΟ₂NH₂, morpholino, CH₂C≡CH, or N₂. In some embodiments, R¹³ may be H or Cl. In some embodiments, R¹³ may be H. In some embodiments, R¹³ may be Cl. In some embodiments, R¹¹ and R¹³ may each be Cl.

[0013] With respect to any relevant formula or structural depiction above, some non-limiting examples of R¹⁴ may include R⁶, OR⁶, SR⁶, COR⁶, C⁰₂R⁶, OCOR⁶, NR⁶R⁶, CONR⁶R⁶, NR⁶COR⁶, CF₃, CN, N₂, F, Cl, Br, or i. In some embodiments, R¹⁴ may be H, CH₃, CH₂CH₃, CI, Br, OH, OCH₃, SCH₃, NH₂, NHCH₃, N(CH₃)₂, CH₂C≡CH, or N₂. In some embodiments, R¹⁴ may be H.

[0014] In some embodiments, R¹⁰ and R¹⁴ may be H. In some embodiments, R¹⁰, R¹², and R¹⁴ may be H. In some embodiments, R¹⁰, R¹¹, and R¹⁴ may be H. In some embodiments, R¹⁰, R¹¹, R¹³, and R¹⁴ may be H. In some embodiments, R¹⁰, R¹¹, R¹², and R¹⁴ may be H. In some embodiments, R¹⁰, R¹¹, R¹², R¹³, and R¹⁴ may be H.

[0015] With respect to any relevant formula or structural depiction above, some non-limiting examples of R¹⁶ may include R⁶, OR⁶, SR⁶, COR⁶, C⁰₂R⁶, OCOR⁶, NR⁶R⁶, CONR⁶R⁶, NR⁶COR⁶, SO₂NR⁶R⁶, CF₃, CN, N₂, F, Cl, Br, or C₆H₅ heterocycl. In some embodiments, R¹⁶ may be H, CH₃, CH₂CH₃, CI, Br, OH, OCH₃, SCH₃, NH₂, NHCH₃, N(CH₃)₂, SΟ₂NH₂, morpholino, CH₂C≡CH, or N₂. In some embodiments, R¹⁶ may be H.
With respect to any relevant formula or structural depiction above, some non-limiting examples of $R_7$ may include $R^b$, $OR^b$, $SR^b$, $COR^b$, $CO_2R^b$, $OCOR^b$, $NR^bR^c$, $CONR^bR^c$, $NR^bCOR^c$, $SO_2NR^bR^c$, $CF_3$, $CN$, $N_2$, $F$, $Cl$, $Br$, $i$, or $C_{2-5}$ heterocycl. In some embodiments, $R_7$ may be $H$, $CH_3$, $CH_2CH_3$, $Cl$, $Br$, $OH$, $OCH_3$, $SCH_3$, $NH_2$, $NHCH_3$, $N(CH_3)_2$, $SO_2NH_2$, morpholino, $CH_2C=CH$, or $N_2$. In some embodiments, $R_7$ may be $H$.

With respect to any relevant formula or structural depiction above, some non-limiting examples of $R_8$ may include $R^b$, $OR^b$, $SR^b$, $COR^b$, $CO_2R^b$, $OCOR^b$, $NR^bR^c$, $CONR^bR^c$, $NR^bCOR^c$, $SO_2NR^bR^c$, $CF_3$, $CN$, $N_2$, $F$, $Cl$, $Br$, $i$, or $C_{2-5}$ heterocycl. In some embodiments, $R_8$ may be $H$, $CH_3$, $CH_2CH_3$, $Cl$, $Br$, $OH$, $OCH_3$, $SCH_3$, $NH_2$, $NHCH_3$, $N(CH_3)_2$, $SO_2NH_2$, morpholino, $CH_2C=CH$, or $N_2$. In some embodiments, $R_8$ may be $H$ or $CH_3$. In some embodiments, $R_8$ may be $H$. In some embodiments, $R_8$ may be $CH_3$.

With respect to any relevant formula or structural depiction above, some non-limiting examples of $R_9$ may include $R^b$, $OR^b$, $SR^b$, $COR^b$, $CO_2R^b$, $OCOR^b$, $NR^bR^c$, $CONR^bR^c$, $NR^bCOR^c$, $SO_2NR^bR^c$, $CF_3$, $CN$, $N_2$, $F$, $Cl$, $Br$, $i$, or $C_{2-5}$ heterocycl. In some embodiments, $R_9$ may be $H$, $CH_3$, $CH_2CH_3$, $Cl$, $Br$, $OH$, $OCH_3$, $SCH_3$, $NH_2$, $NHCH_3$, $N(CH_3)_2$, $SO_2NH_2$, morpholino, $CH_2C=CH$, or $N_2$. In some embodiments, $R_9$ may be $H$.

With respect to any relevant formula or structural depiction above, some non-limiting examples of $R_{10}$ may include $R^b$, $OR^b$, $SR^b$, $COR^b$, $CO_2R^b$, $OCOR^b$, $NR^bR^c$, $CONR^bR^c$, $NR^bCOR^c$, $SO_2NR^bR^c$, $CF_3$, $CN$, $N_2$, $F$, $Cl$, $Br$, $i$, or $C_{2-5}$ heterocycl. In some embodiments, $R_{10}$ may be $H$, $CH_3$, $CH_2CH_3$, $Cl$, $Br$, $OH$, $OCH_3$, $SCH_3$, $NH_2$, $NHCH_3$, $N(CH_3)_2$, $SO_2NH_2$, $CH_2C=CH$, or $N_2$. In some embodiments, $R_{10}$ may be $H$.

With respect to any relevant formula or structural depiction above, some non-limiting examples of $R_{11}$ may include $R^b$, $OR^b$, $SR^b$, $COR^b$, $CO_2R^b$, $OCOR^b$, $NR^bR^c$, $CONR^bR^c$, $NR^bCOR^c$, $SO_2NR^bR^c$, $CF_3$, $CN$, $N_2$, $F$, $Cl$, $Br$, $i$, or $C_{2-5}$ heterocycl. In some embodiments, $R_{11}$ may be $H$, $CH_3$, $Cl$, $Br$, $OH$, $OCH_3$, $SCH_3$, $NH_2$, $NHCH_3$, $N(CH_3)_2$, $SO_2NH_2$, morpholino, $CH_2C=CH$, or $N_2$. In some embodiments, $R_{11}$ may be $H$.

With respect to any relevant formula or structural depiction above, some non-limiting examples of $R_{12}$ may include $R^b$, $OR^b$, $SR^b$, $COR^b$, $CO_2R^b$, $OCOR^b$, $NR^bR^c$, $CONR^bR^c$, $NR^bCOR^c$, $SO_2NR^bR^c$, $CF_3$, $CN$, $N_2$, $F$, $Cl$, $Br$, $i$, or $C_{2-5}$ heterocycl. In some embodiments, $R_{12}$ may be $H$, $CH_3$, $CH_2CH_3$, $Cl$, $Br$, $OH$, $OCH_3$, $SCH_3$, $NH_2$, $NHCH_3$, $N(CH_3)_2$, $SO_2NH_2$, morpholino, $CH_2C=CH$, or $N_2$. In some embodiments, $R_{12}$ may be $H$.

In some embodiments, $R_{19}$, $R_{20}$, $R_{11}$, and $R_{22}$ may be $H$.

With respect to any relevant formula or structural depiction above, some non-limiting examples of $R_{23}$ may include $R^b$, $OR^b$, $SR^b$, $COR^b$, $CO_2R^b$, $OCOR^b$, $NR^bR^c$, $CONR^bR^c$.
NR^bCOR^c, S_0^2NR^bR^c, CF_3, CN, N_0^2, F, Cl, Br, i, or C_{2-5} heterocyclyl. In some embodiments, R^{23} may be H, CH_3, CH_2CH_3, Cl, Br, OH, OCH_3, SCH_3, NH_2, NHCH_3, N(CH_3)_2, S_0^2NH_2, CH_2≡CH, or N_0^2. In some embodiments, R^{23} may be H or S_0^2NH_2. In some embodiments, R^{23} may be H. In some embodiments, R^{23} may be S_0^2NH_2.

[00124] With respect to any relevant formula or structural depiction above, some non-limiting examples of R^{24} may include R^b, OR^b, SR^b, COR^b, C_0^2R^b, OCOR^b, NR^bR^c, CONR^bR^c, NR^bCOR^c, S_0^2NR^bR^c, CF_3, CN, N_0^2, F, Cl, Br, i, or C_{2-5} heterocyclyl. In some embodiments, R^{24} may be H, CH_3, CH_2CH_3, Cl, Br, OH, OCH_3, SCH_3, NH_2, NHCH_3, N(CH_3)_2, S_0^2NH_2, morpholino, or N_0^2. In some embodiments, R^{24} may be H.

[00125] In some embodiments, R^{23} and R^{24} may be H.

[00126] With respect to any relevant formula or structural depiction above, some non-limiting examples of R^{25} may include R^b, OR^b, SR^b, COR^b, C_0^2R^b, OCOR^b, NR^bR^c, CONR^bR^c, NR^bCOR^c, S_0^2NR^bR^c, CF_3, CN, N_0^2, F, or C_{2-5} heterocyclyl. In some embodiments, R^{25} may be H, CH_3, CH_2CH_3, N(CH_3)_2, S_0^2NH_2, morpholino, CH_2≡CH, or N_0^2. In some embodiments, R^{25} may be H or CH_3. In some embodiments, R^{25} may be H.

[00127] With respect to any relevant formula or structural depiction above, some non-limiting examples of R^{26} may include R^b, CF_3, CN, or N_0^2. In some embodiments, R^{26} is H, CH_3, or CH_2CH_3. In some embodiments, R^{26} may be H.

[00128] With respect to any relevant formula or structural depiction above, some non-limiting examples of R^{27} may include R^b, OR^b, SR^b, COR^b, C_0^2R^b, CONR^bR^c, S_0^2NR^bR^c, CF_3, CN, N_0^2, F, Cl, Br, i, or C_{2-5} heterocyclyl. In some embodiments, R^{27} may be H, CH_3, CH_2CH_3, Cl, Br, OH, OCH_3, SCH_3, S_0^2NH_2, CH_2≡CH, or N_0^2. In some embodiments, R^{27} may be H, (CH_2)_3CH_3, CH_2CH_2OCH_3, CH_2CH_2N(CH_3)_2, CH_2CH_2-morpholino, or CH_2CH_2SCH_3. In some embodiments, R^{27} may be H. In some embodiments, R^{27} may be (CH_2)_3CH_3. In some embodiments, R^{27} may be CH_2CH_2OCH_3. In some embodiments, R^{27} may be CH_2CH_2N(CH_3)_2. In some embodiments, R^{27} may be CH_2CH_2-morpholino. In some embodiments, R^{27} may be CH_2CH_2SCH_3.

[00129] With respect to any relevant formula or structural depiction above, some non-limiting examples of R^{28} may include R^b, OR^b, SR^b, COR^b, C_0^2R^b, OCOR^b, NR^bR^c, CONR^bR^c, NR^bCOR^c, S_0^2NR^bR^c, CF_3, CN, N_0^2, F, Cl, Br, i, or C_{2-5} heterocyclyl. In some embodiments, R^{28} may be H, CH_3, CH_2CH_3, Cl, Br, OH, OCH_3, SCH_3, NH_2, NHCH_3, N(CH_3)_2, S_0^2NH_2, morpholino, CH_2≡CH, or N_0^2. In some embodiments, R^{28} may be H, CH_2CH_3, OCH_3, N(CH_3)_2, morpholino, or SCH_3. In some embodiments, R^{28} may be H. In some embodiments, R^{28} may be CH_2CH_3. In some embodiments, R^{28} may be OCH_3. In some embodiments, R^{28} may be CH_2CH_3. In some embodiments, R^{28} may be morpholino. In some embodiments, R^{28} may be SCH_3.
With respect to any relevant formula or structural depiction above, some non-limiting examples of R²⁹ may include R⁵, OR⁵, SR⁵, CF₃, CN, NO₂, F, Cl, Br, i, or C₂₋₅ heterocycl. In some embodiments, R²⁹ may be H, CH₃, or CH₂CH₃. In some embodiments, R²⁹ may be H.

In some embodiments, R⁸ and R²⁹ may be H.

With respect to any relevant formula or structural depiction above, some non-limiting examples of R³⁰ may include R⁵, OR⁵, SR⁵, COR⁵, C⁰₂R⁵, OCOR⁵, NR⁵R⁶, CONR⁵R⁶, NR⁵COR⁵, SO₂NR²R⁵, CF₃, CN, N₂O, F, Cl, Br, or i. In some embodiments, R³⁰ may be H, CH₃, CH₂CH₃, Cl, Br, OH, OCH₃, SCH₃, NH₂, NHCH₃, N(CH₃)₂, SO₂NH₂, CH₂C≡CH, or N₂O. In some embodiments, R³⁰ may be H.

With respect to any relevant formula or structural depiction above, some non-limiting examples of R³¹ may include R⁵, OR⁵, SR⁵, COR⁵, C⁰₂R⁵, OCOR⁵, NR⁵R⁶, CONR⁵R⁶, NR⁵COR⁵, SO₂NR²R⁵, CF₃, CN, N₂O, F, Cl, Br, i, or C₂₋₅ heterocycl. In some embodiments, R³¹ may be H, CH₃, CH₂CH₃, Cl, Br, OH, OCH₃, SCH₃, NH₂, NHCH₃, N(CH₃)₂, SO₂NH₂, morpholino, CH₂C≡CH, or N₂O. In some embodiments, R³¹ may be H.

With respect to any relevant formula or structural depiction above, some non-limiting examples of R³² may include R⁵, OR⁵, SR⁵, COR⁵, C⁰₂R⁵, OCOR⁵, NR⁵R⁶, CONR⁵R⁶, NR⁵COR⁵, SO₂NR²R⁵, CF₃, CN, N₂O, F, Cl, Br, i, or C₂₋₅ heterocycl. In some embodiments, R³² may be H, CH₃, CH₂CH₃, Cl, Br, OH, OCH₃, SCH₃, NH₂, NHCH₃, N(CH₃)₂, SO₂NH₂, morpholino, CH₂C≡CH, or N₂O. In some embodiments, R³² may be H. In some embodiments, R³² may be H. In some embodiments, R³² may be H.

In some embodiments, R³⁰, R³¹, and R³² may be H. In some embodiments, R³¹ and R³² may be H.

With respect to any relevant formula or structural depiction above, some non-limiting examples of R³³ may include R⁵, OR⁵, SR⁵, COR⁵, C⁰₂R⁵, OCOR⁵, NR⁵R⁶, CONR⁵R⁶, NR⁵COR⁵, SO₂NR²R⁵, CF₃, CN, N₂O, F, Cl, Br, i, or C₂₋₅ heterocycl. In some embodiments, R³³ may be H, CH₃, CH₂CH₃, Cl, Br, OH, OCH₃, SCH₃, NH₂, NHCH₃, N(CH₃)₂, SO₂NH₂, morpholino, CH₂C≡CH, or N₂O. In some embodiments, R³³ may be H.

Unless otherwise indicated, any reference to a compound herein by structure, formula, name or any other means, includes pharmaceutically acceptable salts, such as sodium, potassium, and ammonium salts; prodrugs, such as ester prodrugs; alternate solid forms, such as polymorphs, solvates, hydrates, etc.; tautomers; or, any other chemical species that may rapidly convert to a compound described herein under conditions in which the compounds are used as described herein.
Unless stereochemistry is unambiguously depicted, any structure, formula or name for a compound can refer to any stereoisomer or any mixture of stereoisomers of the compound.

As used herein, the term "functional group" refers to an atom or a group of atoms that have similar chemical properties whenever they occur in different compounds, and as such the functional group defines the characteristic physical and chemical properties of families of organic compounds.

Unless otherwise indicated, when any compound or chemical structural feature (collectively referred to herein as a "compound"), such as for example alkyl, aryl, etc., is referred to as being "optionally substituted," that compound can have no substituents (in which case it is "unsubstituted"), or it can include one or more substituents (in which case it is "substituted"). The term "substituent" has the ordinary meaning known to one of ordinary skill in the art. In some embodiments, the substituent may be an ordinary organic moiety known in the art, which can have a molecular weight (e.g., the sum of the atomic masses of the atoms of the substituent) of 15 g/mol to 50 g/mol, 15 g/mol to 100 g/mol, 15 g/mol to 150 g/mol, 15 g/mol to 200 g/mol, 15 g/mol to 300 g/mol, or 15 g/mol to 500 g/mol. In some embodiments, the substituent comprises: 0-30, 0-20, 0-10, or 0-5 carbon (C) atoms; and/or 0-30, 0-20, 0-10, or 0-5 heteroatoms including N, O, S, Si, F, Cl, Br, or I; provided that the substituent comprises at least one atom including C, N, O, S, Si, F, Cl, Br, or I in a substituted compound. Examples of substituents include, but are not limited to, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, hydroxy, alkoxy, arloxy, acyl, acyloxy, alkylcarboxylate, thiol, alkylthio, cyano, halo, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, isocyano, thiocyano, isothiocyanato, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, etc. For convenience, the term "molecular weight" is used with respect to a moiety or part of a molecule to indicate the sum of the atomic masses of the atoms in the moiety or part of a molecule, even though it may not be a complete molecule.

As used herein, the term "hydrocarbyl" has the broadest meaning generally understood in the art, and can include a moiety composed of carbon and hydrogen. Some examples can include alkyl, alkenyl, alkynyl, aryl, etc., and combinations thereof, and can be linear, branched, cyclic, or a combination thereof. Hydrocarbyl can be bonded to any other number of moieties (for example, can be bonded to one other group, such as -CH₃, -CH=CH₂, etc.; two other groups, such as -phenyl-, -C≡C-, etc.; or any number of other groups) that the structure can bear, and in some embodiments, can contain from one to thirty-five carbon atoms. Examples of hydrocarbyl groups include but are not limited to C₁ alkyl, C₂ alkyl, C₂ alkenyl, C₂
alkynyl, C₃ alkyl, C₃ alkenyl, C₃ alkynyl, C₄ alkyl, C₄ alkenyl, C₄ alkynyl, C₅ alkyl, C₅ alkenyl, C₅ alkynyl, C₆ alkyl, C₆ alkenyl, C₆ alkynyl, phenyl, etc.

[001 42] As used herein the term "alkyl" has the broadest meaning generally understood in the art, and can include a moiety composed of carbon and hydrogen containing no double or triple bonds and not having any cyclic structure. Alkyl can be linear alkyl, branched alkyl, cycloalkyl, or a combination thereof, and in some embodiments, can contain from one to thirty-five carbon atoms. In some embodiments, alkyl can include C₁₀ linear alkyl, such as methyl (-CH₃), ethyl (-CH₂CH₃), n-propyl (-CH₂CH₂CH₃), n-butyl (-CH₂CH₂CH₂CH₃), n-pentyl (-CH₂CH₂CH₂CH₂CH₃), n-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), etc.; C₃-10 branched alkyl, such as C₃H₇ (e.g. iso-propyl), C₄H₉ (e.g., branched butyl isomers), C₅H₁₁ (e.g., branched pentyl isomers), C₆H₁₃ (e.g., branched hexyl isomers), C₇H₁₅ (e.g., branched heptyl isomers), etc.; C₅-10 cycloalkyl, such as C₅H₅ (e.g. cyclopropyl), C₆H₇ (e.g., cyclobutyl isomers such as cyclobutyl, methylcyclobutyl, etc.), C₇H₉ (e.g., cyclopentyl isomers such as cyclopentyl, methylcyclopentyl, dimethylcyclopentyl, etc.) C₆H₁₁ (e.g., cyclohexyl isomers), C₇H₁₃ (e.g., cycloheptyl isomers), etc.; and the like.

[001 43] The terms "alkyl," "alkenyl" and "alkynyl" refer to substituted and unsubstituted alkyls, alkenyls and alkynyls, respectively. An alkyl group can be optionally substituted as defined herein.

[001 44] Substituted alkyls, alkenyls and alkynyls refers to alkyls, alkenyls and alkynyls substituted with one to five substituents including H, lower alkyl, aryl, alkenyl, alkynyl, arylalkyl, alkoxy, aryloxy, aryalkoxy, alkoxyalkylaryl, alkylamino, arylamino, NH₂, OH, CN, NO₂, OCF₃, CF₃, F, 1-amidine, 2-amidine, alkylcarbonyl, morpholinyl, piperidinyl, dioxanyl, pyranyl, heteroaryl, furanyl, thiophenyl, tetrazolo, thiazolyl, isothiazolyl, imidazolyl, thiazolyl, thiaizole S-oxide, thiaizole S,S-dioxide, pyrazolo, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl, SR, SOR, S₀₂R, C₀₂R, COR, CONR′R″, CSN R′R″ and SO₉NR′R″.

[001 45] As used herein, either alone or in combination, the term "alkynyl" refers to a functional group comprising a straight-chain or branched-chain hydrocarbon containing from 2 to 20 carbon atoms and having one or more carbon-carbon triple bonds and not having any cyclic structure. An alkynyl group may be optionally substituted as defined herein. Examples of alkynyl groups include, without limitation, ethynyl, propynyl, hydroxypropynyl, butynyl, butyn-1-yl, butyn-2-yl, 3-methylbutyn-1-yl, pentynyl, pentyn-1-yl, hexynyl, hexyn-2-yl, heptynyl, octynyl, nonynyl, decynyl, undecynyl, dodecynyl, tridecynyl, tetradecynyl, pentadecynyl, hexadecynyl, heptadecynyl, octadecynyl, nonadecynyl, eicosynyl, and the like.
The term "alkylene" as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene (\(-\text{CH}_2\)). Unless otherwise specified, the term "alkyl" may include "alkylene" groups.

As used herein, either alone or in combination, the term "alkylcarbonyl" or "alkanoyl" refers to a functional group comprising an alkyl group attached to the parent molecular moiety through a carbonyl group. Examples of alkylcarbonyl groups include, without limitation, methylcarbonyl, ethylcarbonyl, and the like.

As used herein, either alone or in combination, the term "heteroalkyl" refers to a functional group comprising a straight-chain or branched-chain hydrocarbon containing from 1 to 20 atoms linked exclusively by single bonds, where at least one atom in the chain is a carbon and at least one atom in the chain is O, S, N, or any combination thereof. The heteroalkyl group can be fully saturated or contain from 1 to 3 degrees of unsaturation. The non-carbon atoms may be at any interior position of the heteroalkyl group, and up to two non-carbon atoms may be consecutive, such as, e.g., -\(\text{CH}_2\text{NH}-\). In addition, the non-carbon atoms may optionally be oxidized and the nitrogen may optionally be quaternized.

As used herein, either alone or in combination, the term "alkyloxy" or "alkoxy" refers to a functional group comprising an alkyl ether group. Examples of alkoxy groups include, without limitation, methoxy, ethoxy, \(n\)-propoxy, isoproxy, \(n\)-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

As used herein, either alone or in combination, the term "hydroxy" refers to the functional group hydroxyl (\(-\text{OH}\)).

As used herein, either alone or in combination, the term "carboxyl" or "carboxy" refers to the functional group \(-\text{C}(=\text{O})\text{OH}\) or the corresponding "carboxylate" anion \(-\text{C}(=\text{O})\text{O}^-\). Examples include, without limitation, formic acid, acetic acid, oxalic acid, benzoic acid. An "O-carboxyl" group refers to a carboxyl group having the general formula RCOO, wherein R is an organic moiety or group. A "C-carboxyl" group refers to a carboxyl group having the general formula COOR, wherein R is an organic moiety or group.

As used herein, either alone or in combination, the term "oxo" refers to the functional group \(=\text{O}\).

As used herein, the term "carbocyclic" has the broadest meaning generally understood in the art, and includes a ring or ring system wherein the ring atoms are all carbon. Examples include, but are not limited to, phenyl, naphthyl, anthracenyl, cycloalkyl, cycloalkenyl, cycloalkynyl, etc., and combinations thereof.
As used herein, the term "heterocyclic" has the broadest meaning generally understood in the art, and includes a ring or ring system wherein at least one of the ring atoms is not carbon, such as N, O, S, etc. Examples include, but are not limited to, heteroaryl, cycloheteroalkyl, cycloheteroalkenyl, cycloheteroalkynyl, etc., and combinations thereof.

As used herein, either alone or in combination, the term "cycloalkyl," "carbocycloalkyl" and "carbocycloalkyl" refers to a functional group comprising a substituted or unsubstituted non-aromatic hydrocarbon with a non-conjugated cyclic molecular ring structure of 3 to 12 carbon atoms linked exclusively with carbon-carbon single bonds in the carbon ring structure. A cycloalkyl group can be monocyclic, bicyclic or polycyclic, and may optionally include one to three additional ring structures, such as, e.g., an aryl, a heteroaryl, a cycloalkenyl, a heterocycloalkyl, or a heterocycloalkenyl.

As used herein, either alone or in combination, the term "lower cycloalkyl" refers to a functional group comprising a monocyclic substituted or unsubstituted non-aromatic hydrocarbon with a non-conjugated cyclic molecular ring structure of 3 to 6 carbon atoms linked exclusively with carbon-carbon single bonds in the carbon ring structure. Examples of lower cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

As used herein the term "aryl" has the broadest meaning generally understood in the art, and can include an aromatic ring or aromatic ring system. An aryl group can be monocyclic, bicyclic or polycyclic, and may optionally include one to three additional ring structures; such as, for example, a cycloalkyl, a cycloalkenyl, a heterocycloalkyl, a heterocycloalkenyl, or a heteroaryl. The term "aryl" includes, without limitation, phenyl (benzenyl), thiophenyl, indolyl, naphthyl, tolyl, xyl, anthracenyl, phenanthenyl, azulenyl, biphenyl, naphthenyl, 1-methylnaphthenyl, acenaphthenyl, acenaphthyl, anthracenyl, fluorenyl, phenaleny, phenanthenyl, benzo[a]anthracenyl, benzo[c]phenanthrenyl, chrysalenyl, fluoranthenyl, pyrenyl, tetracenylnaphthenyl, triphenyl, anthanthrenyl, benzopyrenyl, benzo[a]pyrenyl, benzo[e]fluoranthenyl, benzo[ghi]perylene, benzo[j]fluoranthenyl, benzo[k]fluoranthenyl, corannulenylnaphthenyl, coronenyl, dicoronarylenyl, helicenylnaphthenyl, hexacylenyl, ovalenylnaphthenyl, pentacenyl, picenylnaphthenyl, tetraphenylenyl, etc.

Additionally, as used herein, either alone or in combination, the term "aryl," "hydrocarbyl aryl" or "aryl hydrocarbon" can refer to a functional group comprising a substituted or unsubstituted aromatic hydrocarbon with a conjugated cyclic molecular ring structure of 3 to 12 carbon atoms. Substituted aryl refers to aryls substituted with one to five substituents including H, lower alkyl, aryl, alkenyl, alkynyl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkyl, alkylamino, arylamino, NH2, OH, CN, NO2, OCF3, CF3, Br, Cl, F, 1-amidino, 2-
amidino, alkylcarbonyl, morpholino, piperidinyl, dioxyanil, pyranyl, heteroaryl, furanyl, thiophenyl, tetrazolo, thiazole, isothiazolo, imidazolo, thiadiazolo, thiadiazole S-oxide, thiadiazole S,S-dioxide, pyrazolo, oxazole, isoxazole, pyridinyl, pyrimidinyl, quinoline, isoquinoline, SR, SOR, S02R1, C02R1, COR, CONR'R'', CSNR'R'', SO2NR'R'', etc.

**[00159]** As used herein, either alone or in combination, the term "lower aryl" refers to a functional group comprising a substituted or unsubstituted aromatic hydrocarbon with a conjugated cyclic molecular ring structure of 3 to 6 carbon atoms. Examples of lower aryl groups include, without limitation, phenyl and naphthyl.

**[00160]** As used herein, either alone or in combination, the term "heteroaryl" refers to a functional group comprising a substituted or unsubstituted aromatic hydrocarbon with a conjugated cyclic molecular ring structure of 3 to 12 atoms, where at least one atom in the ring structure is a carbon and at least one atom in the ring structure is O, S, N, or any combination thereof. A heteroaryl group can be monocyclic, bicyclic or polycyclic, and may optionally include one to three additional ring structures, such as, e.g., an aryl, a cycloalkyl, a cycloalkenyl, a heterocycloalkyl, or a heterocycloalkenyl. Examples of heteroaryl groups include, without limitation, acridinyl, benzidolyl, benzimidazolyl, benzisoxazolyl, benzodioxinyl, dihydrobenzodioxinyl, benzodioxyl, 1,3-benzodioxolyl, benzofuryl, benzoisoxazolyl, benzopyranyl, benzothiophenyl, benzo[c]thiophenyl, benzotriazolyl, benzoxadiazolyl, benzoxazolyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, carbazolyl, chromonyl, cinnolinyl, dihydrocinnolinyl, coumarinyl, dibenzofuranyl, furopyridinyl, furyl, indolizinyl, indoly1, dihydroindolyl, imidazolyl, indazolyl, isobenzofuryl, isoidolyl, isoidoliny1, dihydroisindolyl, isoquinolyl, dihydroisoquinolinyl, isoazolyl, isothiazolyl, oxazolyl, oxadiazolyl, phenanthroliny1, phenanthridinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrroliny1, pyrrol, pyrrolopyridinyl, quinolyl, quinoxaliny1, quinazolinyl, tetrahydroquinolinyl, tetrazolopyridazinyl, tetrahydroisoquinolinyl, thiophenyl, thiazolyl, thiadiazolyl, thienopyridinyl, thienyl, thiophenyl, triazolyl, xantheny1, and the like.

**[00161]** As used herein, either alone or in combination, the term "lower heteroaryl" refers to a functional group comprising a monocyclic or bicyclic, substituted or unsubstituted aromatic hydrocarbon with a conjugated cyclic molecular ring structure of 3 to 6 atoms, where at least one atom in the ring structure is a carbon and at least one atom in the ring structure is O, S, N, or any combination thereof.

**[00162]** The phenyl structure associated with some of the embodiments described herein is depicted below. This structure can be unsubstituted, as shown below, or can be substituted such that a substituent can independently be in any position normally occupied by a hydrogen
atom when the structure is unsubstituted. Unless a point of attachment is indicated by bond to a specific carbon atom, attachment may occur at any position normally occupied by a hydrogen atom.

![Phenyl]

[00163] The term "treat" includes one or more of the diagnosis, cure, mitigation, vaccination, or augmentation of a therapy or prevention of disease in man or other animals. Furthermore,

[00164] As used herein, the term "vertebrate" includes all living vertebrates such as, without limitation, mammals, humans, birds, dogs, cats, livestock, farm animals, free-range herds, etc.

[00165] Many RNA viruses share biochemical, regulatory, and signaling pathways. These viruses include but are not limited to influenza virus (including avian and swine isolates), respiratory syncytial virus (RSV), Hepatitis C virus (HCV), West Nile virus (WNV), severe acute respiratory syndrome (SARS)-coronavirus, human immunodeficiency virus (HIV), poliovirus, measles virus, Dengue virus, yellow fever virus, tick-borne encephalitis virus, Japanese encephalitis virus, St. Louis encephalitis virus, Murray Valley virus, Powassan virus, Rocio virus, louping-ill virus, Banzi virus, Ilheus virus, Kokobera virus, Kunjin virus, Alfuy virus, bovine diarrhea virus, and the Kyasanur forest disease virus. The compounds and methods disclosed herein can be used to treat these viruses.

[00166] Relevant taxonomic families of RNA viruses include, without limitation, Arenaviridae, Astroviridae, Birnaviridae, Bromoviridae, Bunyaviridae, Caliciviridae, Closteroviridae, Comoviridae, Cystoviridae, Flaviviridae, Flexiviridae, Hepevirus, Leviviridae, Luteoviridae, Mononegavirales, Mosaic Viruses, Nidovirales, Nodaviridae, Orthomyxoviridae, Paramyxoviridae, Picobirnavirus, Picornaviridae, Potyviridae, Reoviridae, Retroviridae, Sequiviridae, Tenuiviridae, Togaviridae, Tombusviridae, Totiviridae, and Tymoviridae. The compounds and methods disclosed herein can be used to treat viruses within these families of viruses as part of a pharmaceutically acceptable drug formulation. Other relevant virus families include, without limitation, Hepadnaviridae, Herpesviridae, and Papillomaviridae.

[00167] Particular embodiments provide for pharmaceutical compositions comprising the compounds, alone or in combination with an antigen, for the purpose of treating and/or preventing disease in an animal including a vertebrate animal. As such, in some embodiments the pharmaceutical compositions can be used as vaccines.
The disclosure also provides for the use of the compounds as adjuvants. As used herein, the term "adjuvant" refers to compounds that modify the effect of other agents on the immune system. Adjuvants are inorganic or organic chemicals, macromolecules or entire cells of certain killed bacteria, which enhance the immune response to an antigen. They may be included in a vaccine to enhance the recipient's immune response to the supplied antigen.

The compounds and methods disclosed herein can be additive or synergistic with other therapies currently in development or use. For example, ribavirin and interferon-a provide an effective treatment for HCV infection when used in combination. Their efficacy in combination can exceed the efficacy of either drug product when used alone. The compositions of the disclosure can be administered alone or in combination or conjunction with interferon, ribavirin and/or a variety of small molecules that are being developed against both viral targets (viral proteases, viral polymerase, assembly of viral replication complexes) and host targets (host proteases required for viral processing, host kinases required for phosphorylation of viral targets such as the non-structural 5A protein of hepatitis C virus (NS5A), and inhibitors of host factors required to efficiently utilize the viral internal ribosome entry site, or IRES).

The compounds and methods disclosed herein could be used in combination or conjunction with, without limitation, adamantane inhibitors, neuraminidase inhibitors, alpha interferons, non-nucleoside or nucleoside polymerase inhibitors, NS5A inhibitors, antihistamines, protease inhibitors, helicase inhibitors, P7 inhibitors, entry inhibitors, IRES inhibitors, immune stimulators, HCV replication inhibitors, cyclophilin A inhibitors, A3 adenosine agonists, and microRNA suppressors.

Cytokines that could be administered in combination or conjunction with the compounds and methods disclosed herein include, without limitation, IL-2, IL-12, IL-23, IL-27, or IFN-γ. New HCV drugs that are or will be available for potential administration in combination or conjunction with the compounds and methods disclosed herein include, without limitation, ACH-1625 (Achillion); glycosylated interferon (Alios Biopharma); ANA598, ANA773 (Anadys Pharm); ATI-0810 (Arisyn Therapeutics); AVL-181 (Avila Therapeutics); LOCTERON® (Biolex); CTS-1027 (Conatus); SD-101 (Dynavax Technologies); clemizole (Eiger Biopharmaceuticals); GS-9190 (Gilead Sciences); GI-5005 (GlobalImmune BioPharma); resiquimod/R-848 (Graceway Pharmaceuticals); Albinterferon alpha-2b (Human Genome Sciences); IDX-184, IDX-320, IDX-375 (Idenix); IMO-2125 (Idera Pharmaceuticals); INX-189 (Inhibitex); ITCA-638 (Intarcia Therapeutics); ITMN-191/RG7227 (Intermune); ITX-5061, ITX-4520 (iTherx Pharmaceuticals); MB1 1362 (Metabasis Therapeutics); bavituximab (Peregrine Pharmaceuticals); PSI-7977, RG7128, PSI-938 (Pharmasset); PHX1766 (Phenomix); nitazoxanide/ALINIA® (Romark
Laboratories); SP-30 (Samaritan Pharmaceuticals); SCV-07 (SciClone); SCY-635 (Scynexis); TT-033 (Tacere Therapeutics); viramidine/taribavirin (Valeant Pharmaceuticals); Telaprevir, VCH-759, VCH-916, VCH-222, VX-500, VX-813 (Vertex Pharmaceuticals); and PEG-INF Lambda (Zymogenetics).

New influenza and West Nile virus drugs that are or will be available for potential administration in combination or conjunction with the compounds and methods disclosed herein include, without limitation, neuraminidase inhibitors (Peramivir, Laninamivir); triple therapy - neuraminidase inhibitors ribavirin, amantadine (ADS-8902); polymerase inhibitors (Favipiravir); reverse transcriptase inhibitor (ANX-201); inhaled chitosan (ANX-211); entry / binding inhibitors (Binding Site Mimetic, FLUCIDE™ (NanoViricides); entry inhibitor (FLUDASE® (NexBio); fusion inhibitor, (MGAWN1 for West Nile); host cell inhibitors (lanbiotics); cleavage of RNA genome (RNAi, RNase L); immune stimulators (Interferon, ALFERON®-LDO [Hemispherx Biopharma], Neurokininl agonist, HOMSPERA® [ImmuneRegen Biosciences], Interferon ALFERON® N for West Nile); and TG21.

Other drugs for treatment of influenza and/or hepatitis that are available for potential administration in combination or conjunction with the compounds and methods disclosed herein include, without limitation:

Table 1. Hepatitis and influenza drugs

<table>
<thead>
<tr>
<th>Branded Name</th>
<th>Generic Name</th>
<th>Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEGASYS® (Genentech)</td>
<td>PEGinterferon alfa-2a</td>
<td>Hepatitis C, Hepatitis B</td>
</tr>
<tr>
<td>PEGINTRON® (Merck)</td>
<td>PEGinterferon alfa-2b</td>
<td>Hepatitis C</td>
</tr>
<tr>
<td>COPEGUS® (Roche Pharmaceuticals)</td>
<td>Ribavirin</td>
<td>Hepatitis C</td>
</tr>
<tr>
<td>REBETOL® (Schering Plough)</td>
<td>Ribavirin</td>
<td>Hepatitis C</td>
</tr>
<tr>
<td>TAMIFLU® (Roche Pharmaceuticals)</td>
<td>Oseltamivir</td>
<td>Influenza A, B, C</td>
</tr>
<tr>
<td>RELENZA® (GlaxoSmithKline)</td>
<td>Zanamivir</td>
<td>Influenza A, B, C</td>
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<tr>
<td></td>
<td>Amantadine</td>
<td>Influenza A</td>
</tr>
<tr>
<td></td>
<td>Rimantadine</td>
<td>Influenza A</td>
</tr>
</tbody>
</table>

These agents can be incorporated as part of the same pharmaceutical composition or can be administered separately from the compounds of the disclosure, either concurrently or in accordance with another treatment schedule.

Dosing can be single dosage or cumulative (serial dosing), and can be readily determined by one skilled in the art. As a non-limiting example, an effective dose of a
compound or a composition disclosed herein can be administered once to an individual. Alternatively, treatment may comprise multiple administrations of an effective dose of a compound or a composition disclosed herein carried out over a range of time periods, such as, e.g., several times a day, daily, once every few days, weekly, or monthly. The timing of administration can vary from individual to individual, depending upon such factors as the severity of an individual's symptoms. A person of ordinary skill in the art will recognize that the condition of the individual can be monitored throughout the course of treatment and that the effective amount of a compound or a composition disclosed herein that is administered can be adjusted accordingly.

[00176] The compounds and methods disclosed herein can be additive or synergistic with other compounds and methods as a vaccine adjuvant. By virtue of their antiviral and immune enhancing properties, the compounds can be used to potentiate a prophylactic or therapeutic vaccination. The compounds need not be administered simultaneously or in combination with other vaccine components to be effective. The adjuvant applications of the compounds are not limited to the prevention or treatment of virus infection but can encompass all therapeutic and prophylactic vaccine adjuvant applications due to the general nature of the immune response elicited by the compounds.

[00177] As is understood by one of ordinary skill in the art, vaccines can be against viruses, bacterial infections, cancers, etc. and can include one or more of, without limitation, a live attenuated vaccine (LAIV), an inactivated vaccine (IIV; killed virus vaccine), a subunit (split vaccine); a sub-virion vaccine; a purified protein vaccine; or a DNA vaccine. Appropriate adjuvants include one or more of, without limitation, water/oil emulsions, non-ionic copolymer adjuvants, e.g., CRL 1005 (OPTIVAX™; Vaxcel Inc.), aluminum phosphate, aluminum hydroxide, aqueous suspensions of aluminum and magnesium hydroxides, bacterial endotoxins, polynucleotides, polyelectrolytes, lipophilic adjuvants and synthetic muramyl dipeptide (nMDP) analogs such as N-acetyl-nor-muranyl-L-alanyl-D-isoglutamine, N-acetyl-muranyl-(6-0-stearoyl)-L-alanyl-D-isoglutamine or N-Glycol-muranyl-LalphaAbu-D-isoglutamine (Ciba-Geigy Ltd.).

[00178] The pharmaceutical composition comprising a compound of the disclosure can be formulated in a variety of forms; e.g., as a liquid, gel, lyophilized, or as a compressed solid. The preferred form will depend upon the particular indication being treated and discernible by one of ordinary skill in the art. In one embodiment, the disclosed RIG-I agonists include formulations for oral delivery that can be small-molecule drugs that employ straightforward medicinal chemistry processes.
The administration of the formulations of the present disclosure can be performed in a variety of ways, including, but not limited to, orally, subcutaneously, intravenously, intracerebrally, intranasally, transdermally, intraperitoneally, intramuscularly, intrapulmonary, intrathecally, vaginally, rectally, intraocularly, or in any other acceptable manner. The formulations can be administered continuously by infusion, although bolus injection is acceptable, using techniques known in the art, such as pumps (e.g., subcutaneous osmotic pumps) or implantation. In some instances the formulations can be directly applied as a solution or spray.

An example of a pharmaceutical composition is a solution designed for parenteral administration. Although in many cases pharmaceutical solution formulations are provided in liquid form, appropriate for immediate use, such parenteral formulations can also be provided in frozen or in lyophilized form. In the former case, the composition must be thawed prior to use. The latter form is often used to enhance the stability of the active compound contained in the composition under a wider variety of storage conditions, as it is recognized by those of ordinary skill in the art that lyophilized preparations are generally more stable than their liquid counterparts. Such lyophilized preparations are reconstituted prior to use by the addition of one or more suitable pharmaceutically acceptable diluents such as, without limitation, sterile water for injection or sterile physiological saline solution.

Parenterals can be prepared for storage as lyophilized formulations or aqueous solutions by mixing, as appropriate, the compound having the desired degree of purity with one or more pharmaceutically acceptable carriers, excipients or stabilizers typically employed in the art (all of which are termed "excipients"), for example buffering agents, stabilizing agents, preservatives, isotonifiers, non-ionic detergents, antioxidants and/or other miscellaneous additives.

Buffering agents help to maintain the pH in the range which approximates physiological conditions. They are typically present at a concentration ranging from 2 mM to 50 mM. Suitable buffering agents for use with the present disclosure include both organic and inorganic acids and salts thereof such as citrate buffers (e.g., monosodium citrate-disodium citrate mixture, citric acid-trisodium citrate mixture, citric acid-monosodium citrate mixture, etc.), succinate buffers (e.g., succinic acid-monosodium succinate mixture, succinic acid-sodium hydroxide mixture, succinic acid-disodium succinate mixture, etc.), tartrate buffers (e.g., tartaric acid-sodium tartrate mixture, tartaric acid-potassium tartrate mixture, tartaric acid-sodium hydroxide mixture, etc.), fumarate buffers (e.g., fumaric acid-monosodium fumarate mixture, fumaric acid-disodium fumarate mixture, monosodium fumarate-disodium fumarate mixture,
etc.), gluconate buffers (e.g., gluconic acid-sodium glyconate mixture, gluconic acid-sodium hydroxide mixture, gluconic acid-potassium glyconate mixture, etc.), oxalate buffer (e.g., oxalic acid-sodium oxalate mixture, oxalic acid-sodium hydroxide mixture, oxalic acid-potassium oxalate mixture, etc.), lactate buffers (e.g., lactic acid-sodium lactate mixture, lactic acid-sodium hydroxide mixture, lactic acid-potassium lactate mixture, etc.) and acetate buffers (e.g., acetic acid-sodium acetate mixture, acetic acid-sodium hydroxide mixture, etc.). Additional possibilities are phosphate buffers, histidine buffers and trimethylamine salts such as Tris.

Preservatives can be added to retard microbial growth, and are typically added in amounts of 0.2%-1% (w/v). Suitable preservatives for use with the present disclosure include, without limitation, phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, octadecyldimethylbenzyl ammonium chloride, benzalkonium halides (e.g., benzalkonium chloride, bromide or iodide), hexamethonium chloride, alkyl parabens such as methyl or propyl paraben, catechol, resorcinol, cyclohexanol and 3-pentanol.

Isotonicifiers can be added to ensure isotonicity of liquid compositions and include, without limitation, polyhydric sugar alcohols, preferably trihydric or higher sugar alcohols, such as glycerin, erythritol, arabitol, xylitol, sorbitol and mannitol. Polyhydric alcohols can be present in an amount between 0.1% and 25% by weight, typically 1% to 5%, taking into account the relative amounts of the other ingredients.

Stabilizers refer to a broad category of excipients which can range in function from a bulking agent to an additive which solubilizes the therapeutic agent or helps to prevent denaturation or adherence to the container wall. Typical stabilizers can be polyhydric sugar alcohols (enumerated above); amino acids such as arginine, lysine, glycine, glutamine, asparagine, histidine, alanine, ornithine, L-leucine, 2-phenylalanine, glutamic acid, threonine, etc., organic sugars or sugar alcohols, such as lactose, trehalose, stachyose, mannitol, sorbitol, xylitol, ribitol, myoinositol, galactitol, glycerol and the like, including cyclitols such as inositol; polyethylene glycol; amino acid polymers; sulfur-containing reducing agents, such as urea, glutathione, thiocystic acid, sodium thioglycolate, thioglycerol, alpha-monothioglycerol and sodium thiosulfate; low molecular weight polypeptides (i.e., <10 residues); proteins such as human serum albumin, bovine serum albumin, gelatin or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; monosaccharides such as xylose, mannose, fructose and glucose; disaccharides such as lactose, maltose and sucrose; trisaccharides such as raffinose, and polysaccharides such as dextran. Stabilizers are typically present in the range of from 0.1 to 10,000 parts by weight based on the active compound weight.
Additional miscellaneous excipients include fillers (e.g., starch), chelating agents (e.g., EDTA), antioxidants (e.g., ascorbic acid, methionine, vitamin E) and cosolvents.

The active ingredient can also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example hydroxymethylcellulose, gelatin or poly-(methylmethacrylate) microcapsules, in colloidal drug delivery systems (for example liposomes, albumin microspheres, microemulsions, nanoparticles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington, The Science and Practice of Pharmacy, 21st Ed., published by Lippincott Williams & Wilkins, A Wolters Kluwer Company, 2005, the teachings of which are incorporated by reference herein.

Parenteral formulations to be used for in vivo administration generally are sterile. This is readily accomplished, for example, by filtration through sterile filtration membranes.

Suitable examples of sustained-release preparations include semi-permeable matrices of solid hydrophobic polymers containing the compound or composition, the matrices having a suitable form such as a film or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate) or poly(vinylalcohol)), polylactides, copolymers of L-glutamic acid and ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the PROLEASE® technology (Alkermes) or LUPRON DEPOT® (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate; Abbott Laboratories), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for long periods such as up to or over 100 days, certain hydrogels release compounds for shorter time periods.

Oral administration of the compounds and compositions is one intended practice of the disclosure. For oral administration, the pharmaceutical composition can be in solid or liquid form, e.g., in the form of a capsule, tablet, powder, granule, suspension, emulsion or solution. The pharmaceutical composition is preferably made in the form of a dosage unit containing a given amount of the active ingredient. A suitable daily dose for a human or other vertebrate can vary widely depending on the condition of the patient and other factors, but can be determined by persons of ordinary skill in the art using routine methods.

In solid dosage forms, the active compound can be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances, e.g., lubricating agents such as magnesium stearate. In the
case of capsules, tablets and pills, the dosage forms can also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

[00192] The compounds or compositions can be admixed with adjuvants such as lactose, sucrose, starch powder, cellulose esters of alkanolic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, acacia, gelatin, sodium alginate, polyvinyl-pyrrolidine, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, they can be dissolved in saline, water, polyethylene glycol, propylene glycol, ethanol, oils (such as corn oil, peanut oil, cottonseed oil or sesame oil), tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are known in the pharmaceutical art. The carrier or diluent can include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials known in the art.

[00193] The present disclosure further includes the use and application of the compounds, compositions and methods herein in vitro in a number of applications including but not limited to developing therapies and vaccines against viral infections, research in modulation of the innate immune response in eukaryotic cells, etc. The compounds, compositions and methods of the present disclosure can also be used in animal models. The results of such in vitro and animal in vivo uses of the compounds, compositions and methods of the present disclosure can, for example, inform their in vivo use in humans, or they can be valuable independent of any human therapeutic or prophylactic use.

**EXAMPLES**

[00194] The Examples below describe the antiviral and pharmacological properties of exemplary compounds. The Examples are included to demonstrate particular embodiments of the disclosure. It should be appreciated by those of ordinary skill in the art that the techniques disclosed in the Examples represent techniques and compositions discovered by the inventors to function well in the practice of the disclosure, and thus can be considered to constitute preferred modes for its practice. However, those of ordinary skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure. For example, the Examples below provide in vitro methods for testing the compounds of the disclosure. Other in vitro virus infection models include but are not limited to flaviviruses such as bovine diarrheal virus, West Nile Virus, and GBV-C virus, other RNA
viruses such as respiratory syncytial virus, and the HCV replicon systems. Furthermore, any appropriate cultured cell competent for viral replication can be utilized in the antiviral assays.

EXAMPLE 1. BIOLOGICAL ACTIVITY OF KIN 1000

[00195] Luciferase assay to identify active compounds. Cultured human cells that were stably transfected with a luciferase reporter gene coupled with an RIG-I responsive promoter (IFN3, ISG56, or ISG54 promoter) were seeded and allowed to grow overnight. The compound "KIN1000" was then added and cells were grown in the presence of KIN1000 for 18-20 hours. STEADY-GLO® luciferase substrate (Promega) was added and luminescence was read on a luminometer (Berthold).

[00196] Figure 1A shows that KIN1000 as described herein was validated by demonstrating dose-dependent induction of the luciferase reporter gene coupled to the promoters for IFN3 ("IFN3-LUC," left), ISG56 ("ISG56-LUC," center), and ISG54 ("ISG54-LUC," right). Additionally, KIN1000 did not induce a nonspecific promoter (β-actin-LUC, Figure 1B).

[00197] MTS assay to determine cytotoxicity. Cultured human HeLa cells were treated with increasing amounts of compound or equivalent amounts of dimethyl sulfoxide (DMSO) diluted in media for 48 hours to see their effect on cell viability. The proportion of viable cells was calculated using a cell viability assay that measures conversion of a tetrazolium compound [3-(4,5-dimethyl-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt; or MTS] to a colored formazan compound in live cells.

[00198] The conversion of MTS to formazan was detected in a 96-well microtiter plate reader, and the resulting optical densities plotted directly to estimate cell viability. CELLTITER 96® AQueous One Solution Cell Proliferation Assay (Promega) was the one-step reagent used, as manufacturer's protocol suggested, and cells were incubated for three hours in the presence of reagent before optical density (OD) reading was done. Compounds were diluted to final concentrations of 0, 1, 5, 10, and 20 µM in media containing 0.5% DMSO. Negative control wells contained no compound, and positive control for cytotoxicity was examined using 10% DMSO. Each KIN1000 concentration and control was done in triplicate wells. KIN1000 showed no cytotoxicity to multiple cell types (MTS assay, Figure 1C).

[00199] Immunofluorescent cytochemistry assay to determine IRF-3 activation and translocation to the nucleus. The induction of interferon stimulated gene (ISG) expression mediated by RIG-I is conferred by phosphorylation, dimerization, and nuclear translocation of the IRF-3 transcription factor. Cultured human HeLa cells were treated with increasing amounts of compound or equivalent amounts of DMSO diluted in media for 20 hours. Positive control
wells were infected with 100 HA/mL Sendai virus for an equivalent time period. IRF-3 was
detected using polyclonal rabbit serum specific to IRF-3 and a secondary antibody conjugated
to DYLIGHT® 488 (Pierce Biotechnology, Inc). KIN1000 showed a dose dependent increase in
nuclear-cytoplasmic difference for IRF-3 (Figure 2A).

[00200] Immunofluorescent cytochemistry assay to determine NFKB activation. The
innate immune response dependent on RIG-1 also activates the NFKB transcription factor and
thus increases nuclear levels. Cultured human HeLa cells were treated with increasing amounts
of compound or equivalent amounts of DMSO diluted in media for 20 hours. Positive control
wells were infected with 100 HA/mL Sendai virus for an equivalent time period. NFKB was
detected using monoclonal mouse antibody specific to the p65 subunit of NFKB and a
secondary antibody conjugated to DYLIGHT® 488.

[00201 ] Quantification of immunofluorescent assays. 96-well plates containing cultured
human cells treated with compound and stained for either IRF-3 or NFKB were scanned and
quantified using the ARRAYS CAN™ instrument and software (Cellomics, Inc.). Activation of
transcription factor was evidenced by increased nuclear intensity normalized for cytoplasmic
intensity, or nuclear-cytoplasmic difference. KIN1000 shows a dose dependent increase in
nuclear-cytoplasmic difference for NFKB (Figure 2B).

[00202] Other compounds as described herein likewise can be evaluated by the methods
described in this example, and other cell types can also be used.

EXAMPLE 2. ANTIVIRAL ACTIVITY OF KIN 1000 AGAINST INFLUENZA WSN STRAIN

[00203] MRC5 cells were treated with increasing amounts of KIN1000 12-24 hours prior to
infection by influenza virus. The number of infected cells 24 hours after introduction of virus was
then quantified by an immunofluorescent assay of viral protein in cells. The KIN1000 compound
disclosed herein demonstrated efficient activity against influenza virus strain WSN. Figure 3
shows that MRC5 cells treated with increasing amounts of KIN1000 showed a dose-dependent
decrease in infection by influenza virus.

EXAMPLE 3. Ex vivo IMMUNE STIMULATORY ACTIVITY OF KIN 1000

[00204] The activity of KIN1000 in primary immune cells was assayed to determine whether
KIN1000 stimulates immune responses. Cultured human primary dendritic cells were treated
with 0, 1, or 10 μM of KIN1000 for 24 hours. Supernatant from treated wells was isolated and
tested for levels of cytokine protein. Cytokines were detected using specific antibodies
conjugated to magnetic beads and a secondary antibody that reacts with Streptavidin/Phycoerythrin to produce a fluorescent signal. The bound beads were detected and
quantified using the MAGPIX® (Luminex Corp.) instrument, although similar techniques as are known in the art may be used to measure protein production, such as for example an ELISA.

[00205] KIN1000 was shown to induce expression of the chemokines IL-8, MCP-1, MIP-1a and MIP-1β by dendritic cells (Figure 4A-D).

[00206] Other cells from which cytokine secretion can be measured include, for example but without limitation, human peripheral blood mononuclear cells, human macrophages, mouse macrophages, mouse splenocytes, rat thymocytes, and rat splenocytes.

EXAMPLE 4. ANTIVIRAL ACTIVITY AND PHARMACOLOGICAL PROPERTIES USING STRUCTURE-ACTIVITY RELATIONSHIP (SAR) STUDIES

[00207] This Example describes optimization of compounds for potency and non-toxicity. First, a small analog derivative set is used to define a structural class. The active analogs that are identified in this first stage are then used to define a subset of structural classes of interest for further optimization (Stage 2).

[00208] Stage 2 focuses on creating structural diversity and evaluating core variants. Structural derivatives are tested for biological activity in assays including IRF-3 translocation, antiviral activity, and cytotoxicity in one or more cell lines or peripheral blood mononuclear cells. Optimized molecules that show improved efficacy and low cytotoxicity are further characterized by additional measures including toxicology, mechanism of action, adjuvant activity, and breadth of antiviral activity. These characterization assays are described herein.

[00209] To design analog structures, the drug-like properties as measured by Lipinski’s Rule of Five, metabolic lability, and toxic potential of the lead compounds are analyzed. Analogs are designed to improve potency, minimize toxicity, and increase bioavailability. Structural features that that are chemically reactive or metabolically susceptible may indicate metabolic and toxicological liabilities that result in limited stability, reduced half-life, reactive intermediates, or idiosyncratic toxicity and will therefore be removed.

[00210] In vitro pharmacology studies are performed to measure performance of the most promising analogs in one or more assays of intestinal permeability, metabolic stability and toxicity. Key in vitro characterization studies include plasma protein binding evaluated by partition analysis using equilibrium dialysis; serum, plasma, and whole-blood stability in human and model organisms; intestinal permeability measured by an in vitro model using the human TC7 epithelial cell line; intrinsic clearance; stability in the presence of liver microsomes; human Ether-a-go-go (hERG) channel inhibition; and genotoxicity assays including micronucleus formation in Chinese hamster ovary (CHO) cells and mutagenicity in Salmonella typhimurium strains.
For each analog, an HPLC- and/or HPLC-mass spectrometry-based analytical method is used to evaluate drug and metabolite concentrations in various test systems. Although the specific analytical method is optimized for each molecule, reverse-phase chromatography can be used alone or in combination with quadrupole mass spectrometry to characterize the identity and purity of several of the lead molecules. Initially, drug stability over time in increasing concentrations of serum, plasma, and whole blood from mammalian species (such as mouse, cynomolgus macaque, and human) is evaluated by HPLC, and a half-life is determined.

**EXAMPLE 5. ACTIVATION OF GENE EXPRESSION BY KIN 1000 AND DERIVATIVE COMPOUNDS**

Cultured cells were treated with compound or DMSO control (HeLa cells with 20 µM, 10 µM, 5 µM; PH5CH8 cells with 10 µM, 5 µM or 1 µM; HUVEC cells with 10 µM or 1 µM) of compound or a DMSO control and incubated for up to 24 hours. HUVEC (human umbilical cord endothelial cells) primary cells were thawed and seeded in 6-well plates at 2.4x10^4 cells per well and allowed to grow to 80% confluence, typically 5 days in culture with fresh media replaced every 48 hours before use. The cells were harvested and RNA was isolated using the QIAshredder columns and RNEASY® Mini Kit (Qiagen) according to manufacturer instructions. Reverse transcription was performed and the cDNA template was used for quantitative real-time PCR. PCR reactions were performed using commercially available, validated TAQMAN® gene expression assays (Applied Biosystems/Life Technologies) according to manufacturer instructions. Gene expression levels were measured using a relative expression analysis (ΔΔCt).

Figure 5 shows induction of gene expression by KIN1000 and its derivative compound KIN1 148. Figure 5A shows gene expression levels of IFIT2 (left) and OAS1 (right) in HeLa cells over time from 4-24 hours post treatment with 10 µM KIN1000 (grey) or 10 µM KIN1 148 (black). Figure 5B shows gene expression levels of IFIT2 in PH5CH8 cells (left) treated with KIN1000 (solid grey bars) or KIN1 148 (solid black bars), and in HeLa cells (right) treated with KIN1000 (grey striped bars) or KIN1 148 (black checked bars). In each test group, the three vertical bars represent 5, 10, and 20 µM compound (KIN1000 or KIN1 148), respectively. Figure 5C shows gene expression levels of IFIT2 (left), OAS1 (center), and MxA (right) in primary HUVEC cells that were treated with 1 µM KIN1000 (grey) or 1 µM KIN1 148 (black). The difference in axis scaling demonstrates that compounds showed increased potency in a primary cell type. These data demonstrate that compounds are active in cells by inducing responsive gene expression.
Gene expression can be similarly assayed in cell types that include, without limitation: primary blood mononuclear cells, human macrophages, THP-1 cells, Huh 7 cells, A549 cells, MRC5 cells, rat splenocytes, rat thymocytes, mouse macrophages, mouse splenocytes, and mouse thymocytes. Expression of other genes can be assayed as described herein.

EXAMPLE 6. ANTIVIRAL ACTIVITY OF KIN 1000 AGAINST VARIOUS VIRUSES

To further characterize the breadth of antiviral activity of optimized molecules, cell culture infection models are used to analyze different viruses, including but not limited to different strains of influenza virus, HCV, Dengue virus, RSV, and WNV. The studies include treating cells with compound 2-24 hours prior to infection or treating cells up to 8 hours after infection. Virus production and cellular ISG expression are assessed over a time course to analyze antiviral effects of representative compounds from lead structural classes. IFNp treatment is used as a positive control.

Virus production is measured by focus-forming or plaque assay. In parallel experiments, viral RNA and cellular ISG expression are measured by qPCR and immunoblot analyses. These experiments are designed to validate compound signaling actions during virus infection, and assess compound actions to direct innate immune antiviral programs against various strains of viruses and in the setting of virus countermeasures. Detailed dose-response analyses of each compound are conducted in each virus infection system to determine the effective dose that suppresses virus production by 50% (IC50) and 90% (IC90) as compared with control cells for both the pre-treatment and post-treatment infection models.

Table 2. Virus systems and study design for antiviral analysis of lead compounds

<table>
<thead>
<tr>
<th>Virus</th>
<th>Virus Strain</th>
<th>Study Design</th>
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<tbody>
<tr>
<td>HCV</td>
<td>H77 (genotype 1a)</td>
<td>Assays</td>
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<td>JFH1 (genotype 2a)</td>
<td>Plaque or focus forming assays (infectious virus)</td>
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<td></td>
<td></td>
<td>Immunoblot and ELISA (protein levels)</td>
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<tr>
<td>FLU</td>
<td>High pathogenicity in mice</td>
<td>Study Design</td>
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<td></td>
<td>A/PR/8/34 (H1N1 mouse-adapted virus)</td>
<td>Compound treatment of cells pre- and post-infection</td>
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<td></td>
<td>A/WSN/33 (H1N1 mouse-adapted neurovirulent virus)</td>
<td>Determine EC50 and EC90</td>
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<td>Low pathogenicity in mice</td>
<td>Inhibition of viral life cycle</td>
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<td>A/Texas/36/91 (H1N1 circulating virus)</td>
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<td></td>
<td>MAD78 (lineage 2)</td>
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</table>
EXAMPLE 7. ACTIVITY OF KIN 1000 AND DERIVATIVE COMPOUNDS AGAINST RESPIRATORY SYNCYTIAL VIRUS

[00217] HeLa cells were seeded the previous day in 6-well plates at 4x1 05 cells per well. The next day, the media was replaced with RSV in media without FBS at a multiplicity of infection (MOI) of 0.1. Virus binding occurred at 37°C for 2 hours. After 2 hours the cells were washed with warm complete media and replaced with media containing compound at varying concentrations of 10 µM, 5 µM, 1 µM or a DMSO control. Cells were placed in a 37°C incubator for 48 hours.

[00218] For virus detection and titration, HeLa cells were seeded in 96-well plates at 8x1 03 cells per well 24 hours prior to collecting virus supernatant. After the 48 hour incubation period, the virus supernatant from the infected plate was harvested and used to infect these cells at a 1/10 final dilution. Cells were placed in a 37°C incubator for 24 hours.

[00219] 24 hours after infection, cells were washed twice with PBS and fixed with methanol/acetone solution. After fixing the cells were washed twice with PBS and replaced with blocking buffer (10% horse serum, 1g/ml BSA and 0.1% Triton-100X in PBS) for 1 hour. The blocking buffer is replaced with binding buffer containing a 1/2000 dilution of primary antibody for 2 hours at room temperature. The primary antibody was a mouse monoclonal antibody against RSV. The cells were washed twice with PBS and replaced with binding buffer containing 1/3000 dilution of the Alexa Fluor-488 goat anti-mouse secondary antibody and a Hoechst nuclear stain for 1 hour at room temperature. The cells were washed twice with PBS and PBS was added to all wells. The 96-well plate is sealed and fluorescence activity associated with virus infectivity was determined by immunofluorescent assay using the ARRAYSCAN™ instrument.

[00220] Figure 6 shows experiments performed using the protocol of the Example, demonstrating the antiviral activity of KIN1000 and KIN1 148 against respiratory syncytial virus. Figure 6A shows that HeLa cells treated with increasing amount of KIN1000 and KIN1 148 showed dose-dependent decrease in infection by RSV. Figure 6B shows that KIN1 148 showed antiviral activity against RSV when drug is added up to 24 hours prior to infection.

[00221] To evaluate treatment with compounds prior to infection, the compounds are added at varying time points prior to infection with virus. Virus detection and titration is conducted as described.

[00222] Antiviral activity against RSV was used as a criterion to measure activity of structural derivatives of K-1000. Table 3 shows select structural derivatives of KIN1000 that demonstrated antiviral activity against RSV. Compared to KIN1000 parent compound, these
analogs showed varying levels of antiviral activity against RSV. +++ = greater than 70% inhibition of infection, ++ = greater than 50% inhibition, + = greater than 30% inhibition, - = less than 30% inhibition.

Table 3.

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<td>H</td>
<td>H</td>
<td>+++</td>
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</tr>
</tbody>
</table>
EXAMPLE 8. ACTIVITY OF KIN1000 AND DERIVATIVE COMPOUNDS AGAINST INFLUENZA A/UDORN/72 VIRUS

[00223] Influenza A/UDORN/72 infection of H292 cells. 2x10^6 H292 cells in RPMI1640+10%FCS were treated with 2µM KIN1 148 in a final concentration of 0.5% DMSO for 6 hours. Compound-containing media was aspirated and replaced with 1X MEM containing A/UDORN/72 at an MOI of 0.1 and placed at 37°C in a CO2 incubator. Two hours post infection, virus-containing media was aspirated and replaced with 1X MEM containing 1µg/mL TPCK-treated trypsin, 2µM KIN1 148, 0.5% DMSO. Cells were placed in 37°C CO2 incubator for 18 hours. After 20 hours post-infection, virus supernatants were collected and titred on MDCK cells.

[00224] Influenza A/UDORN/72 infection of HEK293 cells. 5x10^5 HEK293 cells were infected with A/UDORN/72 at an MOI of 0.2 in 1X MEM. After 2 hours post-infection, virus-containing media was aspirated and replaced with 1X MEM containing 1µg/mL TPCK-treated trypsin, 10µM KIN1 148, 0.5% DMSO. Cells were returned to 37°C, CO2 incubator for 18 hours. After 20 hours post-infection, virus supernatants were collected and titred on MDCK cells.

[00225] Titre in MDCK cells. 10 µL of infected supernatant was added to 2x10^6 MDCK cells in the presence of 2 µg/mL TPCK-trypsin and placed in a 37°C CO2 incubator. After 8 hours, supernatant was removed and cells were fixed and stained with FITC-conjugated antibody specific for influenza nucleoprotein (NP). Number of foci was quantitated using the ARRAYSCAN™ instrument and software.

[00226] Figure 7 shows antiviral activity of KIN1 148 against Influenza A virus UDORN/72. H292 cells (left) and HEK293 cells (right) treated with 2µM (H292) or 10µM (HEK293) of KIN1 148 showed decrease in infection by virus.

EXAMPLE 9. ACTIVITY OF KIN 1000 AND DERIVATIVE COMPOUNDS AGAINST DENGUE VIRUS

[00227] Titre in Huh 7 cells. Huh 7 cells were seeded in 6-well plates with 4x10^5 cells per well. The next day, the media was replaced with Dengue virus type 2 in media without FBS at an MOI of 0.25. Virus binding occurred at 37°C for 1 hour. After 1 hour the cells were washed with warm complete media and replaced with media containing KIN1 148 at varying concentrations of 10 µM, 5 µM, 1 µM or a DMSO control. Cells were placed in a 37°C incubator for 48 hours.

[00228] Titre in Vero cells. Vero cells were seeded in 96-well plates at 8x10^3 cells per well 24 hours prior to collecting virus supernatant. After 48 hours, the virus supernatant was harvested and used to infect Vero cells at a 1/100 final dilution.
24 hours after infection, Vero cells were washed twice with PBS and fixed with methanol/acetone for 15 minutes. After fixing the cells were washed twice with PBS and replaced with blocking buffer for 30-45 minutes. The blocking buffer was replaced with binding buffer containing a 1/2000 dilution of primary monoclonal antibody targeting the envelope protein for 2 hours. After 2 hours, the cells were washed twice with PBS and replaced with binding buffer containing 1/3000 dilution of the Alexa Fluor-488 goat anti-mouse secondary antibody and a Hoechst nuclear stain for 45 minutes. After 45 minutes cells were washed twice with PBS and PBS was added to all the wells. The 96-well plate was sealed and fluorescence activity associated with virus infectivity was determined by immunofluorescence-based assay using the ARRAYSCAN™ instrument and software.

Figure 8 shows the results of experiments performed using the protocol of this Example, demonstrating the antiviral activity of KIN1 148 against Dengue virus type 2. Huh 7 cells treated with increasing amounts of KIN1 148 showed dose-dependent decrease in infection by virus.

In a separate experiment, Huh 7 cells were seeded the previous day in 6-well plates with 4x10^5 cells per well. The next day, the media was replaced with Dengue virus type 2 in media without FBS at an MOI of 0.1. Virus binding occurred at 37°C for 2 hours. After 2 hours the cells were washed with warm complete media and replaced with media containing compound at varying concentrations of 5 µM, 2.5 µM, 1.2 µM, 0.6 µM, or a DMSO control. Cells were placed in a 37°C incubator for 48 hours. Titre was assayed as previously described.

Figure 9 shows the results of this experiment performed as described, demonstrating that compounds KIN1311 and KIN1054 both had dose-dependent antiviral activity against Dengue virus type 2.

In an experiment to assess the effect of time of addition on antiviral activity, THP-1 cells were infected similarly to Huh 7 cells. Compound was added at concentrations of 5 µM, 1 µM, 0.5 µM, 0.2 5µM, or a DMSO control at 24 hours post-infection.

Figure 10 shows the results of this experiment performed using THP-1 cells. Figure 10A shows that KIN1 148 and KIN1 160 demonstrated antiviral activity against Dengue virus when administered to cells 24 hours post-infection. KIN1 160 showed a dose-dependent inhibition of Dengue virus at 0.25 - 5 µM. Figure 10B shows that KIN1 148 and KIN1 160 both induced expression of the antiviral genes IFIT2 and OASL in THP-1 cells.

**EXAMPLE 10. ACTIVITY OF KIN 1000 AND DERIVATIVE COMPOUNDS AGAINST HEPATITIS B VIRUS**

HepAD38 cells (Hep 2 cells expressing a regulated HBV genome) were grown for 72 hours in the presence of compound (concentrations 1-10 µM in 0.5% DMSO media). HepAD38
cells that do not express HBV were used as a negative control. Following 72 hours of treatment
100 µL of media was used in an ELISA to measure HBV surface antigen. The amount of HBV
surface antigen produced by the cells was measured in the supernatants by ELISA commercially available HBV sAg ELISA (Creative Diagnostics).

[00236] Figure 11 shows the results of experiments performed using the protocol of this
Example, demonstrating the antiviral activity of KIN1 148 against Hepatitis B virus. HepAD38
cells treated with increasing amounts of KIN1 148 showed dose-dependent decrease in
supernatant levels of virus.

EXAMPLE 11. ACTIVITY OF KIN 1000 AND DERIVATIVE COMPOUNDS AGAINST HUMAN CORONAVIRUS

[00237] HCoV-OC43 human coronavirus was bound to cultured MRC5 cells for 3 hours. After
3 hours the cells were washed with warm complete media and replaced with media containing
compound at varying concentrations of 5 µM, 1 µM, 0.5 µM, or a DMSO control. Cells were
placed in a 37°C incubator for 5 days. After 5 days, virus supernatant was collected and tittered
in Huh 7 cells 48 hours post-infection. Virus titer was assayed as described above.

[00238] Figure 12 shows the results of experiments performed using the protocol of this
Example, demonstrating the antiviral activity of KIN1 160 against human coronavirus. KIN1 160
showed dose-dependent antiviral activity against human coronavirus.

EXAMPLE 12. IN VIVO PHARMACOKINETIC, TOXICCOLOGICAL, AND ANTIVIRAL PROPERTIES OF
OPTIMIZED DRUG LEADS IN RELEVANT PRECLINICAL ANIMAL MODELS

[00239] The in vivo pharmacokinetic (PK) profile and tolerability/toxicity of KIN1000 and
related compounds are evaluated in order to conduct further characterization of their antiviral
activity in animal models of virus infection. A reverse-phase, HPLC-MS/MS detection method is
used for measuring the concentration of each compound in mouse plasma. Prior to PK profiling,
an initial oral and injectable formulation for each compound is developed using a limited
formulation component screen that is largely focused on maximizing aqueous solubility and
stability over a small number of storage conditions. Any of the analytical methods as are known
in the art can be used to measure formulation performance. A formulation is developed for each
compound following a three tiered strategy:

[00240] Tier 1: pH (pH 3 to 9), buffer, and osmolality adjustment

[00241] Tier 2: addition of ethanol (<10%), propylene glycol (<40%), or polyethylene glycol
(PEG) 300 or 400 (<60%) co-solvents to enhance solubility

[00242] Tier 3: addition of /V-/V-dimethylacetamide (DMA, <30%), A/-methyl-2-pyrrolidone
(NMP, <20%), and/or dimethyl sulfoxide (DMSO, <20%) co-solvents or the cyclodextrins (<40%)
as needed to further improve solubility.
For compounds that demonstrate adequate performance in in vitro assays as described herein, a preliminary mouse PK study is performed. See Table 4. Each compound is administered as a single dose to animals by oral gavage (<10 mL/kg) or intravenous bolus injection (<5 mL/kg) after an overnight fast. Multiple animals are dosed for each dosing group such that 3 animals can be sampled at each time point. Blood samples are collected by retro-orbital sinus prior to dosing and at 5, 15, and 30 minutes, and 1, 2, 4, 8, and 24 hours post-dosing. Drug concentrations are measured according to the previously developed bioanalytical method. Pharmacokinetic parameters are evaluated using the WinNonlin® software (Pharsyght).

Table 4

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental design</th>
<th>Route of administration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse PK</td>
<td>Single dose pharmacokinetic study</td>
<td>IV, IP, SC, or IM Oral</td>
<td>Serum concentration at up to 24hrs post treatment, Cmax, t1/2, CL, Vd, AUC0-24,0-∞</td>
</tr>
<tr>
<td>Mouse tolerability</td>
<td>Phase 1: ascending dose tolerability and MTD determination; Phase 2: placebo controlled 7-day toxicity at MTD</td>
<td>Oral</td>
<td>MTD, acute toxicity, hematology, serum chemistry, gross pathology</td>
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</table>

Based upon performance in exploratory PK studies, compounds are further evaluated for preliminary tolerability and toxicity in mice prior to their characterization in antiviral models. Tolerability studies are performed in two stages: an initial dose escalation stage (up to 5 doses, each separated by a 5-day washout period) to determine the maximum tolerable dose (MTD, Phase 1), followed by seven daily administrations of the MTD to evaluate acute toxicity (Stage 2). See Table 4. All doses are administered by oral gavage. In an exemplary experiment, five animals of each sex are placed on-study in stage 1 and 15 animals per sex per dosing group in Stage 2. Study endpoints include a determination of the MTD, physical examination, clinical observations, hematology, serum chemistry and animal bodyweights. Gross pathology is performed on all animals whether found dead, euthanized in extremis, or at the intended conclusion of the experiment. The toxicology studies are primarily exploratory in nature and intended to identify early toxicological endpoints, and drive selection of lead candidates for antiviral animal models.
Table 5. *In vivo* studies of compound antiviral actions

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Analysis</th>
<th>Outcomes</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective compound dose determination</td>
<td>Viral burden analysis in serum</td>
<td>Mortality, viral titer in serum and target organs, body weight, clinical observations, cytokine levels, innate immune gene expression, markers of inflammation</td>
<td>Define <em>in vivo</em> EC&lt;sub&gt;50&lt;/sub&gt; and EC&lt;sub&gt;90&lt;/sub&gt; for each compound and for each virus</td>
</tr>
<tr>
<td>Viral pathogenesis study 1: EC&lt;sub&gt;50&lt;/sub&gt; and EC&lt;sub&gt;90&lt;/sub&gt; treatment</td>
<td>Time to moribund state, clinical scoring for pathologic signs of infection</td>
<td></td>
<td>Define compound action toward limiting viral pathogenesis</td>
</tr>
<tr>
<td>Viral pathogenesis study 2: EC&lt;sub&gt;50&lt;/sub&gt; and EC&lt;sub&gt;90&lt;/sub&gt; treatment and time course analysis</td>
<td>Viral burden analysis in serum and various target organs</td>
<td></td>
<td>Define compound action toward limiting virus replication and spread</td>
</tr>
<tr>
<td>Viral pathogenesis study 3: (neuroinvasion model) EC&lt;sub&gt;50&lt;/sub&gt; and EC&lt;sub&gt;90&lt;/sub&gt; treatment</td>
<td>Time to moribund state, clinical scoring for pathologic signs of infection</td>
<td></td>
<td>Define compound action toward limiting viral pathogenesis in the CNS</td>
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</table>

*Numbers reflect an average of at least two iterations of each experiment*

[00245] Evaluation of antiviral properties and immune protection using mouse infection models. Optimized compounds are selected based on compound pharmacokinetic, antiviral, and innate immune actions for further evaluation in preclinical mouse models of infection. See Table 5.

[00246] **General study design.** Challenge doses of virus infection range from 1x the determined LD<sub>50</sub> (median lethal dose) up to 50x LD<sub>50</sub>. Compounds from the KIN 1000 family of compounds are administered daily over the entire course of infection (up to 2 weeks) at 2 or more dose levels plus a placebo control group. Compound treatments are initiated up to 24 hours prior to virus infection or initiated at times ranging between 0-24 hours after infection. Compounds are administered at doses ranging from 1 mg/kg to 50 mg/kg. Compounds are administered by routes including but not limited to: oral gavage; injected intraperitoneally, subcutaneously, intravenously, or intramuscularly; intranasal or other mucosal route. Daily dosing is subject to the determined plasma half-life of the compound. At least 5 animals per sex and per treatment group are evaluated for endpoints, including but not limited to daily clinical observations, mortality, body weight, and body temperature. Three animals per sex are used to measure virus titer in serum and in target organs including heart, lung, kidney, liver, and brain. Expression of cytokines and of innate immune genes at various time points during infection in compound-treated versus control animals are assayed. Viral loads, cytokine levels, and innate immune gene expression levels are determined at 24-hour intervals following compound
treatment by assays including qPCR of viral or cellular RNA, immunoblot analyses, and ELISA. Compound dose-response analysis and infection time course studies are conducted to evaluate compound efficacy to: 1) limit serum viral load, 2) limit virus replication and spread in target organs, and 3) protect against viral pathogenesis. Incorporated in the design of these experiments is the determination of an effective dose for 50% and 90% suppression of serum viral load (ED50 and ED90) by each compound after a standard challenge of virus. Virus challenge models include but are not limited to the selected virus models that are described below.

[00247] Mouse WNV model. Subcutaneous footpad infection of wild-type C57Bl/6 mice with the virulent lineage 1 strain of WNV (WNV-TX) are performed. Mice are monitored for morbidity and mortality over a range of challenge doses (such as, 10 to 1,000 pfu of virus) either alone or in combination with compound treatment as described above. Viral burden is assessed in serum, lymph nodes, spleen, and brain. The compound actions are tested at the ED50 and ED90 toward limiting WNV pathogenesis in the cerebral nervous system using a WNV neuroinvasion model of infection. Mice are monitored for morbidity and mortality after standard intracranial challenge of 1 pfu of WNV-MAD, either alone or in combination with compound treatment beginning 24 hours after infection.

[00248] Mouse influenza model. Non-surgical tracheal instillation is performed for influenza virus strains A/PR/8/34, A/WSN/33, and A/Udorn/72. The influenza virus strains used for certain experiments are of two different subtypes (H1N1 and H3N2) and exhibit varying pathogenic properties and clinical presentations in C57Bl/6 mice. Compound treatment is performed as described above. In addition to serum, viral burden is assessed in the target organs heart, lung, kidney, liver, and brain.

[00249] Mouse RSV model. Non-surgical tracheal instillation of respiratory syncytial virus A2 long strain is performed. BALB-c mice are infected at a dose of RSV A2 virus that does not cause cytopathic effects. Compound treatment is performed as described above.

[00250] Mouse SARS coronavirus model. Non-surgical tracheal instillation of mouse hepatitis virus strain 2 (MHV-1) is performed. A/J mice are infected with MHV-1 virus at challenge doses. Compound treatment is performed as described above.

[00251] In one experiment to test compound activity against SARS coronavirus, dosing of vehicle and compounds was done beginning 24 hours prior to infection of MHV-1 (500 PFU) and administered daily through day 5. KIN1 160 was administered orally at a dose of 50 mg/kg per day. Mice were weighed daily for 10 days. Weight loss was measured as an indicator of infection. Figure 13 shows the results of one experiment performed as described. KIN1 160
treated mice showed weight loss comparable to uninfected mice, and less weight loss than mice treated with vehicle alone.

**EXAMPLE 13. ADJUVANT ACTIVITY OF KIN 1000, KIN 1148, AND DERIVATIVE COMPOUNDS IN VIVO**

[00252] To characterize the breadth of adjuvant activity of KIN1000 and related compounds, *in vivo* animal models of vaccination and vaccination plus protection are used. The studies include priming animals including but not limited to rats and mice with compound alone or in combination with an antigen and then assessing the adjuvant effect.

[00253] Adjuvant effect is measured by assays for modified, enhanced immune humoral and cellular responses. Humoral responses are assessed over time at discrete times post vaccination and/or boosting by collecting blood for sera and determining relative concentrations of antibody classes (IgM, IgG, IgA or IgE) and/or isotypes including IgG1, IgG2a, IgG2b, IgG2c, IgG3 for IgG antibodies. Moreover, affinity and avidity of the generated antibodies is also determined. In instances in which the vaccine preparation includes a combination of compound and antigen, the neutralizing activity of the generated antibodies is also determined.

[00254] Cellular mediated immune responses induced by the compounds are measured by established methods in the field including *ex vivo* stimulation of peripheral blood mononuclear cells, lymph nodes, splenocytes or other secondary lymphoid organs with the antigen and measurement of cytokine or chemokine production in the supernatant at several times thereafter. Cytokines measured include Th1 type of cytokines including but not limited to IFN gamma and TNF alpha, Th2 type cytokines including but not limited to IL-4, IL-10, IL-5 and IL-13 and Th17 cytokines including but not limited to IL-17, IL-21 and IL-23. Chemokines elicited by the compounds are also measured including but not limited to RANTES, IP-10, MIP1a, MIP1b, and IL-8. T cell antigen specific production of cytokines can also be measured by intracellular cytokine staining with fluorescently labeled specific antibodies and flow cytometry or by ELISPOT. Both CD4+ and CD8+ T cell populations are studied.

[00255] Measurement of adjuvant activity at the cellular level is also determined by immunophenotyping of surface markers of activation by flow cytometry. CD8 T cell antigen-specific responses are also evaluated by intracellular cytokine staining of perforin, cell surface marker expression or proliferation assays including thymidine incorporation.

[00256] These experiments are designed to validate compound adjuvant activity in different combinations of prime-boost schemes and assess how the effects of KIN1000 or related compounds on the innate immune antiviral programs shape the adaptive immune responses mounted to the antigen in the vaccine preparations.
Detailed immune response analyses of each compound as described above are conducted with each selected antigen to determine the immune correlates for that particular antigen(s) and compound formulation. These results guide the protection studies in which animals vaccinated and boosted with combinations of select optimized compounds and desired antigen(s) formulations from select infectious agents are later challenged with doses of infectious agent that are known to result in disease or death of the animal. Protection afforded by vaccination is typically measured by monitoring of clinical symptoms and survival.

A proof of concept experiment was performed. LEWIS female rats at 10-12 weeks of age were primed with suspensions of antigen (ovalbumin, 0.2 mg/Kg) and KIN1000 (1 mg/kg) or KIN1 148 (1 mg/mL) in phosphate saline buffer (PBS) on day zero. Control animals received ovalbumin (OVA, InvivoGen Inc.) in PBS or OVA with poly I:C (0.1 mg/kg, InvivoGen Inc.). Animals were boosted at weeks 2 and 8. Injections were delivered subcutaneously in the footpad and base of the tail for priming and on the footpad and flank for the boosts (0.025 mL/site). Blood samples were collected by tail bleed and processed to serum at 0, 1, 2, 4, 6, and 9 weeks post priming. Titers of OVA specific antibodies were determined by ELISA using anti-IgM, anti IgG and anti-IgG isotype specific antibodies. Figure 14 shows IgG antibody levels relative to OVA alone vaccinated controls in OVA+KIN1000 and OVA+KIN1 148 vaccinated animals.

Measurement of cell-mediated adjuvant activity was also determined by determining delayed type hypersensitivity (DTH) to an antigen (OVA). In the same proof of concept experiment, cellular responses were evaluated by determining the delayed type hypersensitivity reaction to challenge with OVA 2 weeks after the first boost. Animals were sedated with isoflurane and injected with PBS or OVA (0.02 mL of 1mg/mL solution of OVA in PBS) in the pinna of the left and right ears, respectively. 24 hours later the difference in ear thickness was calculated. Figure 15 shows measured difference between right ear and left ear thickness.

Inactivated influenza virus vaccine model. 8-12wk old C57Bl/6 mice were vaccinated with a single dose (prime) of 1 µg of inactivated whole virion influenza A/Puerto Rico/8/1934 (PR8) or PR8 plus 100 µg KIN1 148 in PBS. Vaccinated mice along with naïve controls were challenged 3 weeks post priming with live mouse-adapted PR8 virus at 10X LD50 (10,000 pfu/mouse in 30 µL of PBS) by intranasal instillation. By day 10, survival was 20% of placebo group, 40% of PR8 alone group, and 75% of KIN1 148/PR8 group, indicating that animals vaccinated with KIN1 148/PR8 showed higher protection (Figure 16A). Animals vaccinated with KIN1 148 lost significantly less weight following PR8 challenge than animals vaccinated with antigen alone or with placebo. The adjuvanted group regained weight earlier
than the other groups (Figure 16B). Microneutralization assays of serum samples collected from vaccinated animals 2 days before challenge demonstrated a consistently higher titer of neutralizing antibodies to PR8 in the KIN1 148 adjuvanted animals versus unadjuvanted controls (Figure 16C). These same serum samples were also able to neutralize the heterologous H1N1 A/Brisbane/59/2007 strain (Figure 16D).

To further characterize the adjuvanting properties of KIN1 148, a prime/boost strategy for influenza vaccination was investigated. Animals were primed with inactivated whole virion PR8 +/- KIN1 148 and boosted two weeks later with an additional dose of PR8 either with or without adjuvant. All mice were challenged 3 weeks post priming with live mouse-adapted PR8 virus at 10X LD50 (10,000 pfu/mouse in 30 μL of PBS) by intranasal instillation. Measures of total IgG and neutralizing antibodies in the serum of vaccinated animals, weight loss and clinical score served as endpoints for vaccine efficacy. In general the prime/boost strategy resulted in enhanced protection across all study groups. The animals that received unadjuvanted vaccine exhibited less weight loss than unvaccinated animals; however, there was a significant improvement in both weight loss and clinical score for animals that received the KIN1 148-adjuvanted vaccine (Figure 17A). Mice that received KIN1 148 had a significant increase in serum IgG levels that correlated with the enhanced protection following a lethal challenge (Figure 17B). The serum of adjuvanted animals collected 2 weeks post priming demonstrated a high titer of neutralizing antibody against PR8 (Figure 17C) and titer was increased in serum collected 2 weeks following the booster (Figure 17D).

Inactivated split influenza virus vaccine model. Mice were vaccinated with a single subcutaneously injected dose (prime) of inactivated split virion influenza A/California/07/2009 (NMYCX-179A) with or without 100 μg KIN1 148. In this study, antigen dose was 0.2 μg, 0.6 μg, 1.8 μg, or 5.4 μg. All mice were challenged 3 weeks post priming with live mouse-adapted influenza A/California/04/07 at 5X LD50 (~250 pfu/mouse) by intranasal instillation. Animals vaccinated with KIN1 148 and at least 0.6 μg antigen showed lower levels of weight loss following virus challenge than animals vaccinated with antigen alone or with placebo. The adjuvanted group regained weight earlier than the other groups (Figure 18A). By day 15 post-challenge, survival was greater in KIN1 148 vaccinated groups at all antigen doses, indicating that animals vaccinated with KIN1 148/PR8 showed higher protection (Figure 18B).

In order to characterize an alternative route of vaccine administration, mice were vaccinated with a single intramuscularly injected dose (prime) of inactivated split virion influenza A/California/07/2009 (CA09) with or without 50 μg KIN1 148. In this study, antigen dose was 0.26 μg, 0.78 μg, or 2.35 μg. All mice were challenged 3 weeks post priming with live mouse-
adapted influenza A/California/04/07 at 5X LD50 (1,250 pfu/mouse) by intranasal instillation. Animals vaccinated with KIN1148/CA09 showed lower levels of weight loss following virus challenge than animals vaccinated with antigen alone or with placebo (Figure 19A). By day 15 post-challenge, survival was greater in KIN1148 vaccinated groups at all antigen doses and was 100% in animals that were vaccinated with KIN1148 and 2.35 µg antigen, indicating that animals vaccinated with KIN1148/CA09 showed higher protection (Figure 19B). Mice that received KIN1148 had a significant increase in serum IgG levels that correlated with the enhanced protection following a lethal challenge (Figure 19C).

**Adjuvant and antigen dose optimization.** Prime and/or prime-boost strategies are optimized for each vaccine formulated with KIN1148 and/or other adjuvant compounds from the KIN1000 family of compounds. Furthermore, the effective dose of adjuvant compound is determined for each adjuvant-vaccine combination; this dose can range from 0.1 to 100 µg per dose of vaccine. The effects of antigen sparing through administration of adjuvantated vaccine will also be assessed.

**Injection site analysis after administration of KIN1148.** We assayed whether administration of the KIN1000 family of compounds would have localized effects at the site of injection. One hundred micrograms of each compound was injected subcutaneously into 4 mice per treatment group. Injection site tissue was harvested and homogenized at 4, 24, and 48 hours after injection. Seventy diverse cytokines related to inflammation were measured. Levels of pro-inflammatory cytokines including IL-6, TNFa, and IFNy were not increased over vehicle control samples that received injections of phosphate-buffered saline (PBS). Furthermore, there was no detectable increase in C reactive protein levels compared to vehicle control samples. Figure 20 shows that KIN1148 induced an increase in levels of the chemokines MIP-1α (Fig. 20A), MIP-1β (Fig. 20B), MIP-2 (Fig. 20C), MCP-1 (Fig. 20D), and MDC (Fig. 20E) at the injection site. KIN1000 also showed less potent increases in chemokine levels. These data suggest that KIN1148 and related compounds induce a localized immune stimulation at the site of injection.

**KIN1148 and/or analog compounds can be tested for adjuvanting activity in other vaccine models, such as vaccines against viruses including Japanese encephalitis virus, Dengue virus, and West Nile virus. For example, mice are vaccinated with whole inactivated West Nile virus strain WNV-TX02 with or without 25-100 µg KIN1148. Two to three weeks post priming, mice are challenged with at least 1,000 pfu WNV-TX02. Protection is assessed similarly to the above described studies including survival, clinical observations, and antibody titers.
EXAMPLE 14. IRF-3 ACTIVITY FOR STRUCTURES WITH AMIDE ISOSTERE LINKING GROUPS

[00267] Antiviral compounds of Formula III having amide isostere linking structures were synthesized and tested for IRF-3 activity, using methodology as reported herein. Antiviral compounds having linking groups L with the following structures were prepared and analyzed for IRF-3 activity. The structures and activity are reported in Table 6 (relative units). All structures prepared displayed activity for IRF-3.

Table 6. IRF-3 Activity for Linker Analogs.

<table>
<thead>
<tr>
<th>Structure ID</th>
<th>IRF-3 Activity</th>
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<tbody>
<tr>
<td>315</td>
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</tr>
<tr>
<td>316</td>
<td>8</td>
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EXAMPLE 15. SYNTHESIS OF KIN 1148

[00268] Typical amide bond formation procedures

[00269] Carbonyl diimidazole coupling

[00270] To a solution of 0.15 g [1,3]thiazolo[5,4-e][1,3]benzothiazol-2-amine in 10 mL dry dioxane was added 0.135 g carbonyl diimidazole. The mixture was stirred at 60°C for 2 hours. Then 0.135 g of 2-naphthylamine was added and the mixture was refluxed for 5 hours. The separated solid was filtered off, washed with water and dried to give 0.29 g of crude product. Chromatographic purification yielded 0.025 g of pure 1-naphthalen-2-yl-3-[1,3]thiazolo[5,4-e][1,3]benzothiazol-2-ylurea.

[00271] Acid chloride coupling

[00272] To a suspension of 0.15 g 7-methyl[1,3]thiazolo[5,4-g][1,3]benzoxazol-2-amine in 2.5 mL dry pyridine was added 0.078 mL thiophene-2-carbonyl chloride. The reaction was stirred for
5 hours at 80°C then cooled to room temperature. 4 mL of water was added and the precipitate was filtered off, washed with water and dried to yield 0.154 g of N-(7-methyl[1,3]thiazolo[5,4-g][1,3]benzoxazol-2-yl)thiophene-2-carboxamide.

**[00273]** HATU coupling

![HATU coupling reaction](image)

**[00274]** A mixture of 0.1 g [1,3]thiazolo[5,4-e][1,3]benzothiazol-2-amine, 0.094 g pyrazolo[1,5-a]pyridine-2-carboxylic acid, 0.275 g HATU, and 0.156 g DIEA were stirred at 50°C in 9 mL of dry THF for 8 hours. The mixture was diluted with water and the precipitate was recrystallized from methanol/DMF to yield 0.07 g of N-([1,3]thiazolo[5,4-e][1,3]benzothiazol-2-yl)pyrazolo[1,5-a]pyridine-2-carboxamide.

**[00275]** Examples of tricyclic scaffolds

![Tricyclic scaffolds](image)
Synthesis of Scaffolds

Scaffold A

[1,3]thiazolo[5,4-e][1,3]benzothiazol-2-amine

A suspension of 1g (0.00665 mole) of commercially available 6-aminobenzothiazole, 1.52 g (0.02 mole) ammonium thiocyanate in 30 mL glacial acetic acid was cooled to 15°C and 0.33 mL (0.00665 mole) bromine was added dropwise. The mixture was allowed to stir at room temperature overnight. The precipitate was filtered off, washed with acetic acid and water, then dissolved in 50 mL hot water and filtered to remove insoluble impurities. The filtrate was neutralized with sodium acetate, cooled and the precipitate was filtered, washed with water, and dried to yield 0.89 g (65%) of [1,3]thiazolo[5,4-e][1,3]benzothiazol-2-amine. \(\text{MH}^+ 208\).

7-methyl[1,3]thiazolo[5,4-e][1,3]benzothiazol-2-amine

3 g (0.0183 mol) of the commercially available amine was dissolved in 70 mL of acetic acid was added with stirring 4.17 g of (0.0548 mol) of ammonium thiocyanate. Then, at a temperature below 15°C was added dropwise 2.9 g (0.0183 mol) of bromine. Stirring was continued at room temperature until the end of the working day and left overnight.

1-methyl-3-(2-methyl-1,3-benzothiazol-5-yl)thiourea

2-methyl-1,3-benzothiazol-5-amine (2g, 0.012 mol) and 2 drops of triethylamine in 30 mL ethanol was treated dropwise with methyl isothiocyanate (1.07g, 0.0146 mol) and refluxed for 2 hours. After cooling the precipitate was filtered off, washed with ethanol, and dried to yield 2.1 g of the product.

N,7-dimethyl[1,3]thiazolo[5,4-e][1,3]benzothiazol-2-amine

To a stirred suspension of 0.5 g (0.0021 mol) of thiourea in 15 mL of dry chloroform at 20-25°C was added dropwise 0.34 g (0.0021 mol) of bromine. The reaction was heated under
vigorous stirring 6 hours. The precipitate was filtered, washed with chloroform and dried. The solid was dissolved in 20 ml of hot water and insoluble impurities were filtered off. The hot filtrate was treated with aqueous ammonia to bring the solution to pH 9. After cooling to room temperature the precipitate was filtered, washed with water, and dried to give 0.3 g of product.

[00286] Scaffold B

\[
\begin{align*}
\text{S\textsuperscript{N}} & \quad \rightarrow \\
\text{S\textsuperscript{N}} & \\
\text{OH} & \\
\text{NH} & \\
\text{O} & \\
\end{align*}
\]

[00287] 0.6 g of commercially available 5-azido-2-methyl-1,3-benzothiazole and 5 g of acetic acid were heated to 100°C for 20 minutes. Evaporation and column chromatography purification of the residue yielded 0.43 g of N-(4-hydroxy-2-methyl-1,3-benzothiazol-5-yl)acetamide.

\[
\begin{align*}
\text{S\textsuperscript{N}} & \quad \rightarrow \\
\text{OH} & \\
\text{NH} & \\
\text{O} & \\
\end{align*}
\]

[00288] 0.4 g of the acetamide was treated with 2 mL concentrated HCl. Evaporation provided 0.38 g of 5-amino-2-methyl-1,3-benzothiazol-4-ol as the di-HCl salt.

\[
\begin{align*}
\text{S\textsuperscript{N}} & \quad \rightarrow \\
\text{OH} & \\
\text{NH}_{2} & \\
\text{O} & \\
\end{align*}
\]

[00289] To a solution of 5 mL 3:4 methanol:water solution cooled to 0 C was added 0.08 mL bromine followed by 0.12 g of KCN in portions. When the bromine color was gone the cyanogen bromide solution was added to 0.38 g of the amine dihydrochloride in 20 mL water and 0.252 g sodium bicarbonate and the reaction was left overnight. The reaction was filtered and the filtrate was treated with sodium bicarbonate and concentrated under vacuum. The residue was dissolved in ethanol and the solution was filtered. The filtrate was concentrated to a residue which was purified by chromatography to yield 0.14 of 7-methyl[1,3]thiazolo[5,4-g][1,3]benzoxazol-2-amine.
Following the general procedure used to make Scaffold A, 1 g (0.0067 mol) of the commercially available amine dissolved in 30 ml of acetic acid was treated with 1.55 g (0.02 mol) ammonium thiocyanate. At temperatures below 15°C, 1.07 g (0.0067 mol) of bromine was added and the reaction was stirred at room temperature. Workup provided 7-methyl-6H-imidazo[4,5-g][1,3]benzothiazol-2-amine. NMR 2.73 (s, 3H), 7.53 (d, 1H), 7.46 (s, 1H), MH+ 205.

**Scaffold D**

2-methyl-1,3-benzoxazol-5-amine

Following the general procedure to make Scaffold A, a solution of 1.5 g (0.01 mol) of the amine in 30 mL of glacial acetic acid was treated with 2.31 g (0.03 mol) ammonium thiocyanate followed by dropwise addition of 1.62 g bromine at a temperature below 15°C, forming 1.0 g of the cyclized product.

**Scaffold E**

N-(2,1,3-benzothiadiazol-4-yl)acetamide
To a solution of 5 g (0.033 mol) of commercially available 2,1,3-benzothiadiazol-4-amine in 50 mL of abs. toluene was added 3.38 g (0.033 mol) of acetic anhydride. The mixture was refluxed for two hours, evaporated to dryness, and the precipitate was washed with ether and dried to yield 5.5 g of product.

N-(2,1,3-benzothiadiazol-4-yl)ethanethioamide

To a solution of 1.9 g (0.0098 mole) of the amide in 20 mL dry toluene was added 0.7 g (0.0016 mol) pentasulfide phosphorus and heated at 110°C for 1.5 hours. The reaction solution was decanted from the oily residue and evaporated to dryness in vacuo. To the residue was added 20 mL of 10% NaOH solution. The precipitate dissolved and the resulting solution was filtered. To the filtrate was added acetic acid with stirring. The precipitate was filtered off, washed with water and dried, yielding 1.2 g of product.

7-methyl[1,3]thiazolo[4,5-e][2,1,3]benzothiadiazole

To a cooled solution of 5°C, 4.72 g (0.0143 mole) of potassium ferricyanide in 60 mL of water was added dropwise a solution of 3 g (0.0143 mole) of thioacetamide in 66 mL 4% sodium hydroxide solution. The mixture was stirred for 1 hour at room temperature. The precipitate was filtered off, washed with water, and dried to yield 1.4 g of product.

2-methyl-1,3-benzothiazole-4,5-diamine

0.7 g of starting material was reduced in aqueous HCl with 4.8 g of SnCl₂·H₂O to yield 0.95 g of product. MH+ 253.
[00306] 0.5 g of diamine treated with BrCN generated from 0.28 g bromine and 0.13 g KCN. 0.17 g of product was obtained. MH+ 205.

[00307] Scaffold F

[00308] Commercially available as 7-methyl [1,3]thiazolo [4,5-g][1,3]benzothiazol-2-amine.

[00309] Scaffold G

[00310] A solution of 25 g of commercially available N-(2-methyl-1,3-benzothiazol-5-yl)acetamide and 14.4 mL acetic anhydride was boiled in 50 mL anhydrous pyridine for 2 hours. The mixture was cooled and water was added to precipitate the product which was filtered off, washed with water and dried to give 28.9 g N-(2-methyl-1,3-benzothiazol-5-yl)acetamide.

[00311] 28.4 g of amide in 200 mL sulfuric acid was treated with 69.6 g potassium nitrate over 0.5 hour, maintaining the reaction temperature between 0 and 5°C. The reaction was stirred an additional 0.5 hour then poured onto ice and neutralized to pH 7 with ammonium hydroxide. The solid was filtered, washed with water and dried to yield 23 g of product as a mixture of isomers which was separated by column chromatography to provide N-(2-methyl-4-nitro-1,3-benzothiazol-5-yl)acetamide.
[00312] 7.8 g of N-(2-methyl-4-nitro-1,3-benzothiazol-5-yl)acetamide was hydrolyzed in 39 mL cone. HCl to afford 6.35 g of 2-methyl-4-nitro-1,3-benzothiazol-5-amine.

[00313] 5.5 g of 2-methyl-4-nitro-1,3-benzothiazol-5-amine was dissolved in 32 mL sulfuric acid and treated with 1.87 g NaN₃. A solution of 4.23 g FeSO₄·7H₂O in 10 mL water was added. Workup provided 1.3 g of 2-methyl-4-nitro-1,3-benzothiazole.

[00314] 1.27 g of 2-methyl-4-nitro-1,3-benzothiazole was hydrogenated over 0.13 g Pd/C catalyst in 150 mL methanol. Filtration and evaporation gave 0.94 g 2-methyl-1,3-benzothiazol-4-amine.

[00315] 0.5 g of amine intermediate in 9 mL acetic acid was treated with 0.7 g ammonium thiocyanate then keeping the temperature below 15°C, 9.5 g of liquid bromine was added dropwise. The reaction mixture was allowed to stir overnight. The precipitate was washed with acetic acid then dissolved in water and filtered. The filtrate was neutralized to yield 7-methyl[1,3]thiazolo[4,5-e][1,3]benzothiazol-2-amine as a precipitate, 0.35 g.

[00316] Scaffold H
19.8 g of commercially available 3-nitroaniline was boiled with 13.6 mL acetic anhydride in toluene for 2 hours. After cooling the reaction mixture the solid was filtered, washed with toluene and dried to yield 17.1 g of N-(3-nitrophenyl)acetamide.

A mixture of 12.5 g of amide and 5.14 g of P4S10 was heated in 125 mL toluene for 2 hours then evaporated to any oily product. The material was treated with NaOH and filtered, yielding 7.2 g of N-(3-nitrophenyl)ethanethioamide.

A mixture of 6.2 g thioamide in 158 mL 4% NaOH solution was treated with 20.8 g of potassium ferricyanide. The solid disappeared and a new precipitate formed. The reaction was stirred another hour. Workup provided 4.9 g of 2-methyl-7-nitro-1,3-benzothiazole.

Reduction of 1.1 g of nitro compound with 0.11 g Pd/C in 150 mL methanol under 5 atm of hydrogen at 30°C afforded 1.0 g of 2-methyl-1,3-benzothiazol-7-amine.

Following the procedure of the last step in the preparation of scaffold G, 0.5 g of 2-methyl-1,3-benzothiazol-7-amine converted to 0.17 g of 2-methyl[1,3]thiazolo[5,4-e][1,3]benzothiazol-7-amine.

Scaffold I

6-chloro-1,3-benzodioxol-5-amine
To a solution of 7 g (0.051 mol) of the commercially available 1,3-benzodioxol-5-
amine in 80 mL of acetonitrile was added 7.16 g (0.054 mol) N-chlorosuccinimide. The mixture was refluxed for 1 hour. After cooling, the precipitate was filtered, washed with water and dried to yield 2.3 g of product. NMR 400 MHz, DMSO-d6: 6.81 (s, 1), 6.46 (s, 1), 5.87 (s, 2)

Scaffold J

1,6-dihydroimidazo[4,5-e]benzimidazol-2-amine

To a water-methanol mixture (6 mL methanol and 8 mL water) was added 0.24 mL bromine and was cooled to 0°C. 0.32 g KCN was added in portion and the reaction was stirred for 1 hour until the color of bromine had dissipated. The diamine (di-HCl salt) was dissolved in 40 mL water containing 0.76 g sodium bicarbonate and cooled to 0°C. The solution of cyanogen bromide was added dropwise then the reaction was left overnight. Filtration removed a solid impurity and the filtrate was treated with sodium bicarbonate and concentrated under vacuum. To the residue was added 50 mL ethanol and the inorganic salt was filtered off. The filtrate was concentrated under vacuum to yield 1.2 g of crude product which was purified by column chromatography to yield 0.35 g of product. MH+ 174/

Scaffold K

2-amino-3,7-dimethyl[1,3]thiazolo[5,4-e][1,3]benzothiazol-3-ium iodide

0.5 g of 7-methyl[1,3]thiazolo[5,4-e][1,3]benzothiazol-2-amine and 0.5 mL of iodomethane were mixed in 50 mL ethanol and held at 25-30°C. The reaction was monitored by LCMS and an additional 0.5 mL of iodomethane was added after 6 days. The reaction was 98% complete after 76 days. The mixture was evaporated under reduced pressure to near dryness. The solid which separated was filtered off, washed with ethanol and ether then dried yielding 0.75 g of 2-amino-3,7-dimethyl[1,3]thiazolo[5,4-e][1,3]benzothiazol-3-ium iodide.
Table 7. Examples of A-L-B linkers of Formula 4

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<td>g</td>
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<td>c</td>
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<td>h</td>
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</tr>
<tr>
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<td>-CH₂NH-</td>
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**Syntheses of example linkers**

**[00331]** Linker a

N-(3-bromobenzyl)[1,3]thiazolo[5,4-e][1,3]benzothiazol-2-amine

![Synthesis of Linker a](image1)

Commercially available 2-bromo-7-methyl[1,3]thiazolo[5,4-e][1,3]benzothiazole (0.1 g) and 1-(3-bromophenyl)methanamine (0.26 g) in DMF were heated to 150°C for 3 hours. The reaction mixture was evaporated and purified by chromatography to provide 0.08 g of amine.

**[00335]** Linker b

N-(naphthalen-2-yl)[1,3]thiazolo[5,4-e][1,3]benzothiazole-2-carboxamide

![Synthesis of Linker b](image2)

A mixture of acid (0.2 g), 2-naphthylamine (0.09 g), TBTU (0.31 g) and diisopropylethylamine (0.18 mL) in acetonitrile at 35°C for 3.5 hours. The reaction mixture was washed with aqueous potassium carbonate and concentrated. The residue was purified by chromatography to yield 0.052 g of amide product.

**[00338]** Linker c

N-(1,3-benzothiazol-5-yl)-3-(naphthalen-2-yl)propanamide

![Synthesis of Linker c](image3)

Commercially available aminobenzothiazole (0.75 g) was dissolved in 35 mL methylene chloride containing 0.63 mL N-methylmorpholine. Thionyl chloride (0.42 mL) was
added dropwise. After 30 minutes added 1.05 g of commercially available 3-(naphthalen-2-yl)propanoic acid was added. After 1 hour the reaction mixture was evaporated and the residue was purified by chromatography to afford 1.21 g of the amide.

[00341] N-(1,3-benzothiazol-5-yl)-3-(naphthalen-2-yl)propanethioamide

[00342] The amide (1.45 g) was heated with Lawesson's reagent (1.06 g) in toluene at 110°C for 1.5 hours. The solvent was removed and the residue was purified by chromatography to provide 1.28 g of thiourea.

[00343] 2-[2-(naphthalen-2-yl)ethyl][1,3]thiazolo[5,4-e][1,3]benzothiazole

[00344] The thioamide (0.1 g) and AIBN (0.06 g) were dissolved in 10 mL nitrobenzene and heated to 180°C for 10 hours. The solvent was removed by vacuum and the remaining mixture was purified by chromatography to yield 0.082 g of product.

[00345] Linker d

[00346] 2-(naphthalen-2-ylmethoxy)[1,3]thiazolo[5,4-e][1,3]benzothiazole

[00347] Commercially available naphthalen-2-ylmethanol (0.146 g) was added in portions to a suspension of 0.04 g sodium hydride in 25 mL anhydrous THF so as to maintain the temperature below 50°C. The bromobenzobisthiazole (0.25 g) was added and the reaction was stirred at room temperature for 96 hour. Evaporation of the solvent and purification of the residue by chromatography yielded 0.22 g of product.

[00348] Linker e

[00349] N-(1,3-thiazolo[5,4-e][1,3]benzothiazol-2-ylmethyl)naphthalen-2-amine
Commercially available 2-(bromomethyl)[1,3]thiazolo[5,4-e][1,3]benzothiazole (0.142 g) and 2-naphthylamine (0.143 g) were refluxed in 10 mL acetonitrile for 2 hours. Evaporation of the solvent and purification by chromatography provided 0.125 g of product.

A mixture of 2-(bromomethyl)[1,3]thiazolo[5,4-e][1,3]benzothiazole-2-amine (0.8 g) and copper(II) bromide (1.73 g) in anhydrous DMF was cooled to -5°C and isoamyl nitrite (0.874 mL) was added. After 24 hours the reaction mixture was diluted with water and extracted with methylene chloride. Evaporation of solvent and purification yielded 0.53 g of product.
[00360] 2-[(naphthalen-2-ylmethyl)sulfanyl][1,3]thiazolo[5,4-e][1,3]benzothiazole

[00361] Naphthalen-2-ylmethanethiol (0.28 g) was added to a suspension of 0.071 g sodium hydride in 35 mL anhydrous THF, maintaining the temperature between 50 and 60°C. 2-Bromo[1,3]thiazolo[5,4-e][1,3]benzothiazole (0.39 g in 5 mL THF) was added and the reaction mixture was stirred for 24 hours. Evaporation of the solvent and purification of the residue provided 0.4 g of thioether.

[00362] Linker I

[00363] N-[(1,3]thiazolo[5,4-e][1,3]benzothiazol-2-yl)naphthalene-2-sulfonamide

[00364] A solution of [1,3]thiazolo[5,4-e][1,3]benzothiazol-2-amine (0.02 g) and commercially available naphthalene-2-sulfon chloride (0.024 g) was heated 2 hours in 2 mL dry pyridine. The mixture was taken to dryness under vacuum and purified by chromatography to afford 0.007 g of sulfonamide.

[00365] 3-bromo-N-[(1,3]thiazolo[5,4-e][1,3]benzothiazol-2-yl]benzamide (KIN 1062)

[00366] Following the general procedure for amide formation using an acid chloride, a reaction of 0.1 g (0.00048 mol) of the amine and 0.106 g (0.00048 mol) 3-bromobenzoyl chloride afforded 1.5 g of the product. MH+ 391.

[00367] Additional examples of compounds

[00368] N-[(1,3]thiazolo[5,4-e][1,3]benzothiazol-2-yl)naphthalene-2-carboxamide (KIN 148)

[00369] 1H NMR (400 MHz, DMSO-d6) δ 13.3 (bs, NH), 8.87 (s, 1H), 8.22 (d, 2H), 8.10 (t, 2H), 8.04 (d, 1H), 7.92 (d, 1H), 7.67 (m, 2H). MH+ 362
3-bromo-N-(7-methyl-6H-imidazo[4,5-g][1,3]benzothiazol-2-yl)benzamide (KIN 1080)

\[
\begin{align*}
\text{HN} & \quad \text{S} \\
\text{S} & \quad \text{NH}_2 \\
\text{Cl} & \quad \text{Br} \\
\end{align*}
\]

0.1 g (0.00049 mol) of the amine dissolved in 3 ml absolute pyridine was added 0.097 g (0.00044 mol) chloride and refluxed for 2 hours. Cooled to room temperature and 4 ml of water was added. The precipitate was filtered, washed with water and dried. Yield: 0.105 g (55%) MS MH+ doublet 387.389.

3,4-dichloro-N-([1,3]thiazolo[5,4-e][1,3]benzothiazol-2-yl)benzamide

\[
\begin{align*}
\text{S} & \quad \text{N} \\
\text{S} & \quad \text{NH}_2 \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{O} \\
\end{align*}
\]

To 0.1g (0.00052 mol) of acid in 10 ml dry acetonitrile was added 0.193g (0.0006 mol) TBTU and 0.09g (0.00068 mol) DIPEA and heated at 50°C for 0.5 hours. Then added 0.109g (0.00052 mole) of the amine and boiled for 5 hours. The precipitate was filtered, washed with acetonitrile and dried. Yield: 0.115g. (58%).

2-methyl-5-nitro-1,3-benzoxazole

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{O} & \quad \text{N} \\
\end{align*}
\]

To 11 g (0.071 mol) of 2-amino-4-nitrophenol in 200 ml of absolute toluene was added 7.3 g (0.071 mol) acetic anhydride and refluxed for 1 hour. Then added 2.72 g (0.0143 mol) of p-toluenesulfonic acid and boiled for 5 hours with a Dean-Stark trap. The hot solution was filtered. The filtrate was allowed to cool to overnight. The substance was filtered off, washed with dry toluene and dried in a water pump vacuum at 25°C for 4 hours. Yield: 8 g

3-bromo-N-(2-methyl[1,3]thiazolo[5,4-e][1,3]benzoxazol-7-yl)benzamide

\[
\begin{align*}
\text{S} & \quad \text{N} \\
\text{S} & \quad \text{NH}_2 \\
\text{Cl} & \quad \text{Br} \\
\end{align*}
\]

To a solution of 0.1 g (0.00049 mol) of the amine in 3 ml of abs. pyridine was added 0.107 g (0.00049 mol) of 3-bromobenzoyl chloride and refluxed for 2 hours. Cooled to room temperature and 4 ml of water was added. The resulting precipitate was filtered, washed with
water, ether and dried under water pump vacuum at a temperature of 30-35°C. Yield: 0.1 g of amide.

[00378] N-[(6-chloro-1,3-benzodioxol-5-yl)carbamothioyl]benzamide

\[
\begin{array}{c}
\text{O} \\
\text{Cl} \\
\text{N} \\
\text{NH}_2 \\
\end{array}
+ \begin{array}{c}
\text{O} \\
\text{Cl} \\
\text{C} \\
\text{O} \\
\end{array}
+ \begin{array}{c}
\text{N} \\
\text{H}_2 \\
\text{S} \\
\text{C} \\
\end{array}
\rightarrow \begin{array}{c}
\text{O} \\
\text{Cl} \\
\text{N} \\
\text{S} \\
\text{N} \\
\end{array}
\]

[00379] To 1.88 g (0.025 mol) of anhydrous ammonium thiocyanate in 40 ml acetone was added dropwise 3.2 g (0.023 mol) of benzoyl chloride. The resulting mixture was heated to reflux. Heating was removed and a solution of 3.8 g (0.022 mol) of the amine in 15 ml dry acetone was added at a rate to maintain the mixture at boiling. After an additional 15 minutes reflux the reaction was cooled and the precipitate was filtered off. The precipitate was washed with acetone and dried to yield 5.5 g of the product.

[00380] 1-(6-chloro-1,3-benzodioxol-5-yl)thiourea

\[
\begin{array}{c}
\text{O} \\
\text{Cl} \\
\text{S} \\
\text{C} \\
\text{N} \\
\text{S} \\
\text{NH}_2 \\
\end{array}
\]

[00381] 20 ml of 10% sodium hydroxide solution was heated to 90-95°C. The thiourea (5.4 g, 0.017 mol) was added and the reaction was held at this temperature for 10 minutes. After cooling the precipitate was filtered off and the filtrate was acidified with acetic acid to pH 7. The precipitate was filtered off, washed with water and dried to yield 2.3 g of product.

[00382] 5-chloro[1,3]dioxolo[4,5-g][1,3]benzothiazol-7-amine

[00383] To a stirred suspension of 2.2 g (0.00075 mol) of thiourea in 30 ml dry chloroform at 20-25°C is added 1.53 g (0.00095 mol) of bromine dropwise. The mixture was heated to boiling and a precipitate gradually formed. The precipitate was filtered off, washed with chloroform, dried, then taken up in hot water and stirred and filtered. The precipitate was placed in a dilute solution of ammonia, stirred for 10 minutes, then filtered, washed with water and dried to yield 1.35 g of product.
N-[(2E)-3,7-dimethyl[1,3]thiazolo[5,4-e][1,3]benzothiazol-2(3H)-ylidene]naphthalene-2-carboxamide

[00385] Scaffold K (0.15 g) was dissolved in 5 mL dry pyridine and 2-naphthoyl chloride (0.083 g) was added. The mixture was refluxed for 3 hours and the separated solid was filtered off, washed with pyridine, water, and dried to yield 0.025 g of product.

Table 8. Compounds containing scaffold A

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[00386] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about.” Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that can vary depending upon the desired properties sought to be obtained by the present disclosure. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[00387] Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the disclosure are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

[00388] The terms “a,” “an,” “the” and similar referents used in the context of describing the disclosure (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated
herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the disclosure and does not pose a limitation on the scope of the disclosure otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the disclosure.

[00389] Groupings of alternative elements or embodiments of the disclosure disclosed herein are not to be construed as limitations. Each group member can be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group can be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

[00390] Certain embodiments of this disclosure are described herein, including the best mode known to the inventors for carrying out the disclosure. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the disclosure to be practiced otherwise than specifically described herein. Accordingly, this disclosure includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the disclosure unless otherwise indicated herein or otherwise clearly contradicted by context.

[00391] Specific embodiments disclosed herein may be further limited in the claims using consisting of or and consisting essentially of language. When used in the claims, whether as filed or added per amendment, the transition term "consisting of" excludes any element, step, or ingredient not specified in the claims. The transition term "consisting essentially of" limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s). Embodiments of the disclosure so claimed are inherently or expressly described and enabled herein.

[00392] It is to be understood that the embodiments of the disclosure disclosed herein are illustrative of the principles of the present disclosure. Other modifications that may be employed are within the scope of the disclosure. Thus, by way of example, but not of limitation, alternative
configurations of the present disclosure may be utilized in accordance with the teachings herein. Accordingly, the present disclosure is not limited to that precisely as shown and described.
1. (Original) A compound represented by the formula

wherein a dashed line indicates the presence or absence of a π bond; A and B are each independently single or double covalent bonds; A-L-B is A-C(=R X )-NR-B, A-S0 2 NR-B, A-NR-B, SO 2 B, A-CH(CF 3 )-NR-B, A-NR-CH(CF 3 )-B.
where \( m \) and \( n \) are independently an integer from 0-5 such that \( m+n \geq 1 \),

\[ R^1 \text{ is } R^a, \text{OR}^2 \text{ or } \text{NR}^2\text{R}^3; \]

each \( R^a \) is independently \( H \), optionally substituted hydrocarbyl, optionally substituted aryl, or optionally substituted heteroaryl;

\( R^2 \) and \( R^3 \) are each independently \( R^a \), COR\(^a\), C(=0)OR\(^a\), or S0\(^2\)R\(^a\);

\( Y^1, Y^2, Y^3, \) and \( Y^4 \) are each independently CR\(^4\) or N;

\( Y^5, Y^6, Y^7, \) and \( Y^8 \) are each independently CR\(^4\), N, or R\(^5\);

each \( R^4 \) is independently \( R^a, \text{OR}^a, \text{NR}^2\text{R}^3, \text{SR}^a, \text{SOR}^a, \text{S}0\(^2\)\text{R}^a, \text{S}0\(^2\)\text{NHR}^a, \text{N(R}^5\text{)COR}^a, \)
halogen, trihalomethyl, CN, S=0, or nitro;

each \( R^5 \) is independently \( R^a, \text{COR}^a, \text{S}0\(^2\)R^a, \) or is not present;

\( W \) and \( X \) are each independently \( N, \text{NR}^a, \text{O, S, CR}^2\text{R}^4 \text{ or CR}^4; \)

each \( R^x \) is independently \( \text{O, S, CR}^2\text{R}^3, \) or \( \text{NR}^5; \)

\( R^y \) is S, N-CN, or CHR\(^4\); and

\( Z^1 \) and \( Z^2 \) are each independently C, CR\(^2\), or N.

2. A compound of claim 1, further represented by a formula

![Formula Image]

wherein \( R^{10}, R^{13}, R^{14}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, \) and \( R^{22} \) are independently \( R^b, \text{OR}^b, \text{SR}^b, \text{COR}^b, \text{C}0\(^2\)\text{R}^b, \text{OCOR}^b, \text{NR}^b\text{R}^c, \text{CONR}^b\text{R}^c, \text{NR}^b\text{COR}^c, \text{S}0\(^2\)\text{NR}^b\text{R}^c, \text{CF}_3, \text{CN, N}_0\(^2\), F, Cl, Br, \)

\( i, \) or C\(_2-5\) heterocycl; each \( R^b \) is independently \( H \) or C\(_{1.3}\) hydrocarbyl, and each \( R^c \) is independently \( H \) or C\(_{1.3}\) alkyl.

3. A compound of claim 1, wherein \( W \) is S and \( X \) is N.

4. A compound of claim 1, wherein:
Y₁ and Y₂ are both CR⁴, and together form an additional heterocyclic ring optionally substituted by R⁴;
Y³ is CR⁴; and
Y⁴ is CR⁴.

5. A compound of claim 1, wherein R¹ is optionally substituted naphthyl or optionally substituted phenyl.

6. A compound of claim 1, further represented by a formula:

7. A compound of claim 1, wherein R⁵ is H or C₁₋₃ alkyl.

8. A compound of claim 1, wherein Y³ is CR⁴, wherein R⁴ is R⁶, OR⁵, COR⁵, CO₂R⁰, OCOR⁵, NR⁰R⁵, CF₃, CN, NO₂, F, Cl, Br, or I, wherein R⁵ and R⁶ are independently H or C₁₋₃ alkyl.

9. A compound of claim 1, wherein Y⁴ is CR⁴, wherein R⁴ is R⁶, OR⁵, COR⁵, CO₂R⁰, OCOR⁵, NR⁰R⁵, CF₃, CN, NO₂, F, Cl, Br, or I, wherein R⁵ and R⁶ are independently H or C₁₋₃ alkyl.

10. A compound of claim 1, further represented by the formula

wherein R⁶, R¹¹, R¹², R¹³, R¹⁴, and R¹⁵ are independently R⁵, OR⁵, COR⁵, CO₂R⁰, OCOR⁵, NR⁰R⁵, CF₃, CN, NO₂, F, Cl, Br, or I, wherein R⁵ and R⁶ are independently H or C₁₋₃ alkyl; and, R⁶ is H or C₁₋₃ alkyl.

11. A compound of claim 10, wherein R¹⁸ is CH₃.

12. A compound of claim 10, wherein R¹³ is Br.

13. A compound of claim 1, further represented by the formula
14. A compound of claim 1, wherein the compound is represented by the formula:

![Chemical structure image]


17. A method of treating or preventing a viral infection in a vertebrate comprising administering to the vertebrate a pharmaceutical composition comprising the compound of claim 1.

18. A method of claim 17, wherein the viral infection is caused by a virus from one or more of the families Arenaviridae, Astroviridae, Birnaviridae, Bromoviridae, Bunyaviridae, Caliciviridae, Closteroviridae, Comoviridae, Cystoviridae, Flaviviridae, Flexiviridae, Hepevirus,
Leviviridae, Luteoviridae, Mononegavirales, Mosaic Viruses, Nidovirales, Nodaviridae, Orthomyxoviridae, Picobirnavirus, Picornaviridae, Potyviridae, Reoviridae, Retroviridae, Sequiviridae, Tenuivirus, Togaviridae, Tombusviridae, Totiviridae, Tymoviridae, Hepadnaviridae, Herpesviridae, Paramyxoviridae, or Papillomaviridae.

19. The method of claim 16, wherein the viral infection is influenza virus, Hepatitis C virus, West Nile virus, SARS-coronavirus, poliovirus, measles virus, Dengue virus, yellow fever virus, tick-borne encephalitis virus, Japanese encephalitis virus, St. Louis encephalitis virus, Murray Valley virus, Powassan virus, Rocio virus, louping-ill virus, Banzi virus, Ilheus virus, Kokobera virus, Kunjin virus, Alfuy virus, bovine diarrhea virus, Kyasanur forest disease virus, respiratory syncytial virus, or human immunodeficiency virus (HIV).

19. A method of claim 17, wherein the pharmaceutical composition is administered as an adjuvant for a prophylactic or therapeutic vaccine.

20. A method of claim 19 wherein the vaccine is against influenza virus, Hepatitis C virus, West Nile virus, SARS-coronavirus, poliovirus, measles virus, Dengue virus, yellow fever virus, tick-borne encephalitis virus, Japanese encephalitis virus, St. Louis encephalitis virus, Murray Valley virus, Powassan virus, Rocio virus, louping-ill virus, Banzi virus, Ilheus virus, Kokobera virus, Kunjin virus, Alfuy virus, bovine diarrhea virus, Kyasanur forest disease virus, respiratory syncytial virus, or HIV.

21. A method of modulating the innate immune response in a eukaryotic cell, comprising administering to the cell a compound of claim 1, wherein the cell is in vivo or in vitro.
FIG. 1
FIG. 2

A

B

FIG. 3

Influenza infected cells

Influenza infected cells
FIG. 4
A. 10μM KIN1148

B. PH5CH8, HeLa

FIG. 5
FIG. 5 Continued

FIG. 6
FIG. 8

DENV2 Infection

FIG. 9

Inhibition of Dengue Virus-2

Concentration (μM)
A

**DENV2 antiviral activity of 1160 in THP-1 cells**

![Graph showing DENV2 antiviral activity of 1160 in THP-1 cells.](image)

B

**AV gene induction: 1160 vs. 1148**

![Graph showing AV gene induction for IFIT2 and OASL.](image)

**FIG. 10**
**HBV ELISA 72 HOUR PI**

- **KIN 1148**
- **NO HBV CELLS**

**FIG. 11**

**Inhibition of Human coronavirus OC43**

- **KIN 1160**

**FIG. 12**
FIG. 16

A

Naive

1µg PR8

1µg PR8 + 1148

% survival

Days post challenge

B

Median weight (%)

Naive

1µg PR8

1µg PR8 + 1148

Days post challenge

C

PR8 (H1N1)

Titer (log2)

1µg PR8

1µg PR8 + 1148

10

9

8

7

6

5

4

D

Brisbane (H1N1)

Titer (log2)

1µg PR8

1µg PR8 + 1148

13

12

11

10

9

8

7

6

5

4
FIG. 17
FIG. 19
FIG. 19 Continued