(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 3 687 529 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
12.07.2023 Bulletin 2023/28

(21) Application number: **18860177.7**

(22) Date of filing: **26.09.2018**

(51) International Patent Classification (IPC):
A61K 31/395 *(2006.01)* ***A61K 31/505*** *(2006.01)*
A61K 31/519 *(2006.01)* ***C07D 471/00*** *(2006.01)*
C07D 471/02 *(2006.01)* ***C07D 471/04*** *(2006.01)*
A61P 31/14 *(2006.01)* ***C07D 487/04*** *(2006.01)*

(52) Cooperative Patent Classification (CPC):
C07D 471/04; A61P 31/14; C07D 487/04

(86) International application number:
PCT/US2018/052965

(87) International publication number:
WO 2019/067623 (04.04.2019 Gazette 2019/14)

(54) POTENT ANTIVIRAL PYRIDINE-CONTAINING COMPOUNDS

POTENTE ANTIVIRALE PYRIDINHALTIGE VERBINDUNGEN

COMPOSÉS ANTIVIRAUX PUISSANTS CONTENANT DE LA PYRIDINE

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

(30) Priority: **27.09.2017 US 201762564182 P**

(43) Date of publication of application:
05.08.2020 Bulletin 2020/32

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(56) References cited:
WO-A1-2011/073316 **WO-A1-2017/053604**
US-A1- 2016 185 797 **US-B2- 7 968 536**

- **XING et al.: "Synthesis and Structure-Activity Relationship (SAR) Studies of Novel Pyrazolopyridine Derivatives as Inhibitors of Enterovirus Replication", Journal of Medicinal Chemistry, vol. 61, no. 4, 18 January 2018 (2018-01-18), pages 1688-1703, XP055587485, DOI: 10.1021/acs.jmedchem.7b01863**

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Description

[0001] This invention was made with Government support under AI107383, awarded by the National Institutes of Health. The Government has certain rights in the invention.

FIELD

[0002] The present technology generally relates to pyridine-containing compounds useful in inhibiting an enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies in cells and/or treating subjects suffering from an enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies.

BACKGROUND

[0003] Throughout this disclosure, various publications, patents and published patent specifications are referenced by an identifying citation. Also within this disclosure are Arabic numerals referring to referenced citations, the full bibliographic details of which are provided immediately after the Examples section. The disclosures of these publications, patents and published patent specifications are provided to more fully describe the state of the art to which this invention pertains.

[0004] The human enteroviruses (EVs) are a genus of more than 110 serologically distinct, small, non-enveloped RNA viruses responsible for poliomyelitis, encephalitis, acute heart failure, fulminant sepsis in newborns, and other life-threatening infections (Cherry, J.D. et al. (2009) Enteroviruses and Parechoviruses, in Textbook of Pediatric Infectious Diseases, R.D. Feigin, et al., Editors. 2009, WB Saunders Co: Philadelphia, PA:1984-2041). While immunization has curtailed circulation of the polioviruses in most of the world, other EVs (coxsackieviruses, echoviruses, and numbered EVs) continue to cause substantial morbidity and mortality.

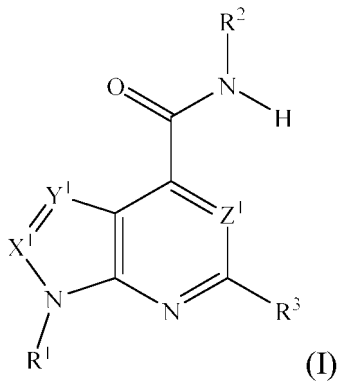
[0005] For example, enterovirus 71 (EV71) has been the cause of numerous epidemics of central nervous system infection in Europe and the Asia-Pacific Region over the last 15 years (McMinn, P. et al. (2001) Clin Infect Dis. 32(2):236-242; McMinn, P.C. (2002) FEMS Microbiol Rev. 26(1):91-107), including an outbreak earlier in 2012 in Cambodia that caused more than 60 deaths (Seiff, A. (2012) Lancet 380(9838):206). A recent outbreak of coxsackievirus B1 (CVB1) myocarditis in the United States also highlighted the mutability of enteroviruses and their epidemic potential. A new variant of CVB1 emerged in 2007 that was detected at nearly 50 sites in the U.S. linked to clusters of cases of sepsis, myocarditis, and deaths among newborns (Verma, N.A. et al. (2009) Clin Infect Dis. 49(5):759-763; Wikswo, M.E. et al. (2009) Clin Infect Dis. 49(5):e44-e51). In 2011 and 2012, cases of severe Hand, Foot, and Mouth Disease associated with coxsackievirus A6 requiring hospitalization were reported in four states.

International patent application publication number WO2017053604 discloses potent antiviral pyrazolopyridine compounds that are useful in inhibiting an enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus in a cell and/or treating subjects suffering from an enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus.

SUMMARY

[0006] In one aspect the present invention provides compounds, compositions as set out in the claims. In another aspect the present invention provides for a pharmaceutical composition for use in treating an enterovirus infection as set out in the claims. In a still further aspect the present invention provides a compound for use in a method of treating a patient or animal infected with an enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus as set out in the claims.

In an aspect, a compound represented by Formula I is provided



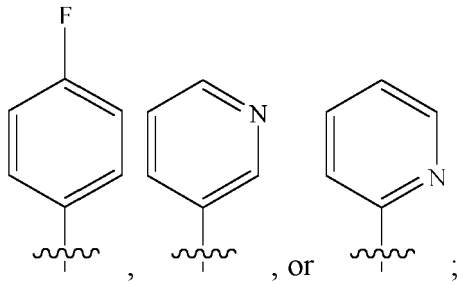
(I)

or a pharmaceutically acceptable salt thereof,
wherein

X^1 is CH, Y^1 is CH, and Z^1 is CH;

R^1 is unsubstituted C_1-C_6 alkyl;

R^2 is



and

R^3 is 2-thiophenyl or 3-thiophenyl.

[0007] In an aspect, a composition is provided that includes a compound of Formula I as set out in the claims and a pharmaceutically acceptable carrier.

[0008] In an aspect, a pharmaceutical composition for treating an enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus infection is provided where the composition includes an effective amount of a compound of Formula I as set out in the claims and a pharmaceutically acceptable excipient.

[0009] In an aspect, a compound for use in a method of treating a patient or animal infected with an enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus is provided as set out in the claims, the method including administration of an effective amount of a compound of Formula I as set out in the claims to the patient or animal. In the method, administration of the effective amount of the compound to the patient or animal treats the patient or animal infected with the enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus.

DETAILED DESCRIPTION

[0010] The following terms are used throughout as defined below.

[0011] As used herein and in the appended claims, singular articles such as "a" and "an" and "the" and similar referents in the context of describing the elements (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 are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate 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 embodiments and does not pose a limitation on the scope of the claims unless otherwise stated. No language in the specification should be construed as indicating any non-claimed element as essential.

[0012] As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent depending upon the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art, given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

[0013] Generally, reference to a certain element such as hydrogen or H is meant to include all isotopes of that element. For example, if an R group is defined to include hydrogen or H, it also includes deuterium and tritium. Compounds comprising radioisotopes such as tritium, C^{14}, P^{32} and S^{35} are thus within the scope of the present technology. Procedures for inserting such labels into the compounds of the present technology will be readily apparent to those skilled in the art based on the disclosure herein.

[0014] In general, "substituted" refers to an organic group as defined below (e.g., an alkyl group) in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to non-hydrogen or non-carbon atoms. Substituted groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom are replaced by one or more bonds, including double or triple bonds, to a heteroatom. Thus, a substituted group is substituted with one or more substituents, unless otherwise specified. A substituted group may be substituted with 1, 2, 3, 4, 5, or 6 substituents. Examples of substituent groups include: halogens (i.e., F, Cl, Br, and I); hydroxyls; alkoxy, alkenoxy, aryloxy, aralkyloxy, heterocyclyl, heterocyclylalkyl, heterocyclyloxy, and heterocyclylalkoxy groups; carbonyls (oxo); carboxylates; esters; urethanes; oximes; hydroxylamines; alkoxyamines; aralkoxyamines; thiols; sulfides; sulfoxides; sulfones; sulfonyls; pentafluorosulfanyl (i.e., SF_5), sulfonamides; amines; N-oxides; hydrazines; hydrazides; hydrazones; azides; amides; ureas; amidines; guanidines; enamines; imides; isocyanates; isothiocyanates; cyanates; thiocyanates; imines; nitro groups; nitriles (i.e., CN); and the like.

[0015] Substituted ring groups such as substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups also include rings and ring systems in which a bond to a hydrogen atom is replaced with a bond to a carbon atom. Therefore, substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups may also be substituted with substituted or unsubstituted alkyl, alkenyl, and alkynyl groups as defined below.

[0016] Alkyl groups include straight chain and branched chain alkyl groups having from 1 to 12 carbon atoms, and typically from 1 to 10 carbons or, for example, from 1 to 8, 1 to 6, or 1 to 4 carbon atoms. Examples of straight chain alkyl groups include groups such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, tert-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. Representative substituted alkyl groups may be substituted one or more times with substituents such as those listed above, and include without limitation haloalkyl (e.g., trifluoromethyl), hydroxyalkyl, thioalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, carboxyalkyl, and the like.

[0017] Cycloalkyl groups include mono-, bi- or tricyclic alkyl groups having from 3 to 12 carbon atoms in the ring(s), or, for example 3 to 10, 3 to 8, or 3 to 4, 5, or 6 carbon atoms. Exemplary monocyclic cycloalkyl groups include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. The cycloalkyl group may have 3 to 8 ring members, or the number of ring carbon atoms range from 3 to 5, 3 to 6, or 3 to 7. Bi- and tricyclic ring systems include both bridged cycloalkyl groups and fused rings, such as, but not limited to, bicyclo[2.1.1]hexane, adamantyl, decalinyl, and the like. Substituted cycloalkyl groups may be substituted one or more times with, non-hydrogen and non-carbon groups as defined above. However, substituted cycloalkyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above. Representative substituted cycloalkyl groups may be mono-substituted or substituted more than once, such as, but not limited to, 2,2-, 2,3-, 2,4- 2,5- or 2,6-disubstituted cyclohexyl groups, which may be substituted with substituents such as those listed above.

[0018] Cycloalkylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a cycloalkyl group as defined above. Cycloalkylalkyl groups may have from 4 to 16 carbon atoms, 4 to 12 carbon atoms, and typically 4 to 10 carbon atoms. Substituted cycloalkylalkyl groups may be substituted at the alkyl, the cycloalkyl or both the alkyl and cycloalkyl portions of the group. Representative substituted cycloalkylalkyl groups may be mono-substituted or substituted more than once, such as, but not limited to, mono-, di- or tri-substituted with substituents such as those listed above.

[0019] Alkenyl groups include straight and branched chain alkyl groups as defined above, except that at least one double bond exists between two carbon atoms. Alkenyl groups have from 2 to 12 carbon atoms, and typically from 2 to 10 carbons or from 2 to 8, 2 to 6, or 2 to 4 carbon atoms. An alkenyl group may have one, two, or three carbon-carbon double bonds. Examples include, but are not limited to vinyl, allyl, $-CH=CH(CH_3)$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH_2$, $-C(CH_3)=CH(CH_3)$, $-C(CH_2CH_3)=CH_2$, among others. Representative substituted alkenyl groups may be mono-substituted or substituted more than once, such as, but not limited to, mono-, di- or tri-substituted with substituents such as those listed above.

[0020] Cycloalkenyl groups include cycloalkyl groups as defined above, having at least one double bond between two

carbon atoms. A cycloalkenyl group may have one, two or three double bonds but does not include aromatic compounds. Cycloalkenyl groups have from 4 to 14 carbon atoms, or, for example, 5 to 14 carbon atoms, 5 to 10 carbon atoms, or even 5, 6, 7, or 8 carbon atoms. Examples of cycloalkenyl groups include cyclohexenyl, cyclopentenyl, cyclohexadienyl, cyclobutadienyl, and cyclopentadienyl.

[0021] Cycloalkenylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of the alkyl group is replaced with a bond to a cycloalkenyl group as defined above. Substituted cycloalkenylalkyl groups may be substituted at the alkyl, the cycloalkenyl or both the alkyl and cycloalkenyl portions of the group. Representative substituted cycloalkenylalkyl groups may be substituted one or more times with substituents such as those listed above.

[0022] Alkynyl groups include straight and branched chain alkyl groups as defined above, except that at least one triple bond exists between two carbon atoms. Alkynyl groups have from 2 to 12 carbon atoms, and typically from 2 to 10 carbons or, for example, from 2 to 8, 2 to 6, or 2 to 4 carbon atoms. The alkynyl group may have one, two, or three carbon-carbon triple bonds. Examples include, but are not limited to - C≡CH, -C=CCH_3, -$CH_2C{\equiv}CCH_3$, -$C{\equiv}CCH_2CH(CH_2CH_3)_2$, among others. Representative substituted alkynyl groups may be mono-substituted or substituted more than once, such as, but not limited to, mono-, di- or tri-substituted with substituents such as those listed above.

[0023] Aryl groups are cyclic aromatic hydrocarbons that do not contain heteroatoms. Aryl groups herein include monocyclic, bicyclic and tricyclic ring systems. Thus, aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, fluorenyl, phenanthrenyl, anthracenyl, indenyl, indanyl, pentalenyl, and naphthyl groups. Aryl groups may contain 6-14 carbons, of from 6 to 12 or even 6-10 carbon atoms in the ring portions of the groups. Aryl groups may be phenyl or naphthyl. Although the phrase "aryl groups" includes groups containing fused rings, such as fused aromatic-aliphatic ring systems (e.g., indanyl, tetrahydronaphthyl, and the like), it does not include aryl groups that have other groups, such as alkyl or halo groups, bonded to one of the ring members. Rather, groups such as tolyl are referred to as substituted aryl groups. Representative substituted aryl groups may be mono-substituted or substituted more than once. For example, monosubstituted aryl groups include, but are not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or naphthyl groups, which may be substituted with substituents such as those listed above.

[0024] Aralkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined above. Aralkyl groups may contain 7 to 16 carbon atoms, 7 to 14 carbon atoms, or 7 to 10 carbon atoms. Substituted aralkyl groups may be substituted at the alkyl, the aryl or both the alkyl and aryl portions of the group. Representative aralkyl groups include but are not limited to benzyl and phenethyl groups and fused (cycloalkylaryl)alkyl groups such as 4-indanylethyl. Representative substituted aralkyl groups may be substituted one or more times with substituents such as those listed above.

[0025] Heterocyclyl groups include aromatic (also referred to as heteroaryl) and non-aromatic ring compounds containing 3 or more ring members, of which one or more is a heteroatom such as, but not limited to, N, O, and S. A heterocyclyl group may contain 1, 2, 3 or 4 heteroatoms. Heterocyclyl groups include mono-, bi- and tricyclic rings having 3 to 16 ring members, whereas other such groups have 3 to 6, 3 to 10, 3 to 12, or 3 to 14 ring members. Heterocyclyl groups encompass aromatic, partially unsaturated and saturated ring systems, such as, for example, imidazolyl, imidazolinyl and imidazolidinyl groups. The phrase "heterocyclyl group" includes fused ring species including those comprising fused aromatic and non-aromatic groups, such as, for example, benzotriazolyl, 2,3-dihydrobenzo[1,4]dioxinyl, and benzo[1,3]dioxolyl. The phrase also includes bridged polycyclic ring systems containing a heteroatom such as, but not limited to, quinuclidyl. However, the phrase does not include heterocyclyl groups that have other groups, such as alkyl, oxo or halo groups, bonded to one of the ring members. Rather, these are referred to as "substituted heterocyclyl groups". Heterocyclyl groups include, but are not limited to, aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydrofuranyl, dioxolyl, furanyl, thiophenyl, pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, tetrahydrothiopyranyl, oxathiane, dioxyl, dithianyl, pyranyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, dihydropyridyl, dihydrodithiinyl, dihydrodithionyl, homopiperazinyl, quinuclidyl, indolyl, indolinyl, isoindolyl,azaindolyl (pyrrolopyridyl), indazolyl, indolizinyl, benzotriazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, benzthiazolyl, benzoxadiazolyl, benzoxazinyl, benzodithiinyl, benzoxathiinyl, benzothiazinyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[1,3]dioxolyl, pyrazolopyridyl, imidazopyridyl (azabenzimidazolyl), triazolopyridyl, isoxazolopyridyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, quinolizinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl, pteridinyl, thianaphthyl, dihydrobenzothiazinyl, dihydrobenzofuranyl, dihydroindolyl, dihydrobenzodioxinyl, tetrahydroindolyl, tetrahydroindazolyl, tetrahydrobenzimidazolyl, tetrahydrobenzotriazolyl, tetrahydropyrrolopyridyl, tetrahydropyrazolopyridyl, tetrahydroimidazopyridyl, tetrahydrotriazolopyridyl, and tetrahydroquinolinyl groups. Representative substituted heterocyclyl groups may be mono-substituted or substituted more than once, such as, but not limited to, pyridyl or morpholinyl groups, which are 2-, 3-, 4-, 5-, or 6-substituted, or disubstituted with various substituents such as those listed above.

[0026] Heteroaryl groups are aromatic ring compounds containing 5 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S. Heteroaryl groups include, but are not limited to, groups such as pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiophe-

nyl, benzothiophenyl, furanyl, benzofuranyl, indolyl, azaindolyl (pyrrolopyridinyl), indazolyl, benzimidazolyl, imidazopyridinyl (azabenzimidazolyl), pyrazolopyridinyl, triazolopyridinyl, benzotriazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups. Heteroaryl groups include fused ring compounds in which all rings are aromatic such as indolyl groups and include fused ring compounds in which only one of the rings is aromatic, such as 2,3-dihydro indolyl groups. Although the phrase "heteroaryl groups" includes fused ring compounds, the phrase does not include heteroaryl groups that have other groups bonded to one of the ring members, such as alkyl groups. Rather, heteroaryl groups with such substitution are referred to as "substituted heteroaryl groups." Representative substituted heteroaryl groups may be substituted one or more times with various substituents such as those listed above.

[0027] Heterocyclylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a heterocyclyl group as defined above. Substituted heterocyclylalkyl groups may be substituted at the alkyl, the heterocyclyl or both the alkyl and heterocyclyl portions of the group. Representative heterocyclyl alkyl groups include, but are not limited to, morpholin-4-yl-ethyl, furan-2-yl-methyl, imidazol-4-yl-methyl, pyridin-3-yl-methyl, tetrahydrofuran-2-yl-ethyl, and indol-2-yl-propyl. Representative substituted heterocyclylalkyl groups may be substituted one or more times with substituents such as those listed above.

[0028] Heteroaralkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a heteroaryl group as defined above. Substituted heteroaralkyl groups may be substituted at the alkyl, the heteroaryl or both the alkyl and heteroaryl portions of the group. Representative substituted heteroaralkyl groups may be substituted one or more times with substituents such as those listed above.

[0029] Groups described herein having two or more points of attachment (i.e., divalent, trivalent, or polyvalent) within the compound of the present technology are designated by use of the suffix, "ene." For example, divalent alkyl groups are alkylene groups, divalent aryl groups are arylene groups, divalent heteroaryl groups are divalent heteroarylene groups, and so forth. Substituted groups having a single point of attachment to the compound of the present technology are not referred to using the "ene" designation. Thus, e.g., chloroethyl is not referred to herein as chloroethylene.

[0030] Alkoxy groups are hydroxyl groups (-OH) in which the bond to the hydrogen atom is replaced by a bond to a carbon atom of a substituted or unsubstituted alkyl group as defined above. Examples of linear alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, and the like. Examples of branched alkoxy groups include but are not limited to isopropoxy, sec-butoxy, tert-butoxy, isopentoxy, isohexoxy, and the like. Examples of cycloalkoxy groups include but are not limited to cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like. Representative substituted alkoxy groups may be substituted one or more times with substituents such as those listed above.

[0031] The terms "alkanoyl" and "alkanoyloxy" as used herein can refer, respectively, to - C(O)-alkyl and -O-C(O)-alkyl groups, where for example the alkanoyl or alkanoyloxy groups may each contain 2-5 carbon atoms. Similarly, the terms "aryloyl" and "aryloyloxy" respectively refer to to -C(O)-aryl and -O-C(O)-aryl groups.

[0032] The terms "aryloxy" and "arylalkoxy" refer to, respectively, a substituted or unsubstituted aryl group bonded to an oxygen atom and a substituted or unsubstituted aralkyl group bonded to the oxygen atom at the alkyl. Examples include but are not limited to phenoxy, naphthyloxy, and benzyloxy. Representative substituted aryloxy and arylalkoxy groups may be substituted one or more times with substituents such as those listed above.

[0033] The term "carboxylic acid" as used herein refers to a compound with a -C(O)OH group. The term "carboxylate" as used herein refers to a $-C(O)O^-$ group. A "substituted carboxylate" refers to a -C(O)O-G where G is a carboxylate protecting group. Carboxylate protecting groups are well known to one of ordinary skill in the art. An extensive list of protecting groups for the carboxylate group functionality may be found in Protective Groups in Organic Synthesis, Greene, T.W.; Wuts, P. G. M., John Wiley & Sons, New York, NY, (3rd Edition, 1999) which can be added or removed using the procedures set forth therein.

[0034] The term "ester" as used herein refers to $-COOR^{70}$ groups. R^{70} is a substituted or unsubstituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heterocyclylalkyl or heterocyclyl group as defined herein.

[0035] The term "amide" (or "amido") includes C- and N-amide groups, i.e., $-C(O)NR^{71}R^{72}$, and $-NR^{71}C(O)R^{72}$ groups, respectively. R^{71} and R^{72} are independently hydrogen, or a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclylalkyl or heterocyclyl group as defined herein. Amido groups therefore include but are not limited to carbamoyl groups ($-C(O)NH_2$) and formamide groups (-NHC(O)H). The amide may be $-NR^{71}C(O)-(C_{1-5}$ alkyl) and the group is termed "carbonylamino," or the amide may be -NHC(O)-alkyl and the group is termed "alkanoylamino."

[0036] The term "nitrile" or "cyano" as used herein refers to the -CN group.

[0037] Urethane groups include N- and O-urethane groups, i.e., $-NR^{73}C(O)OR^{74}$ and $-OC(O)NR^{73}R^{74}$ groups, respectively. R^{73} and R^{74} are independently a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclylalkyl, or heterocyclyl group as defined herein. R^{73} may also be H.

[0038] The term "amine" (or "amino") as used herein refers to $-NR^{75}R^{76}$ groups, wherein R^{75} and R^{76} are independently hydrogen, or a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclylalkyl or heterocyclyl group as defined herein. The amine may be alkylamino, dialkylamino, arylamino, or alkylarylamino. The amine may be

NH_2, methylamino, dimethylamino, ethylamino, diethylamino, propylamino, isopropylamino, phenylamino, or benzylamino.

[0039] The term "sulfonamido" includes S- and N-sulfonamide groups, i.e., $-SO_2NR^{78}R^{79}$ and $-NR^{78}SO_2R^{79}$ groups, respectively. R^{78} and R^{79} are independently hydrogen, or a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclylalkyl, or heterocyclyl group as defined herein. Sulfonamido groups therefore include but are not limited to sulfamoyl groups ($-SO_2NH_2$). A sulfonamido may be $-NHSO_2$-alkyl and is referred to as the "alkylsulfonylamino" group.

[0040] The term "thiol" refers to -SH groups, while sulfides include $-SR^{80}$ groups, sulfoxides include $-S(O)R^{81}$ groups, sulfones include $-SO_2R^{82}$ groups, and sulfonyls include $-SO_2OR^{83}$. R^{80}, R^{81}, R^{82}, and R^{83} are each independently a substituted or unsubstituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl aralkyl, heterocyclyl or heterocyclylalkyl group as defined herein. A sulfide may be an alkylthio group, -S-alkyl.

[0041] The term "urea" refers to $-NR^{84}$-C(O)-$NR^{85}R^{86}$ groups. R^{84}, R^{85}, and R^{86} groups are independently hydrogen, or a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, or heterocyclylalkyl group as defined herein.

[0042] The term "amidine" refers to $-C(NR^{87})NR^{88}R^{89}$ and $-NR^{87}C(NR^{88})R^{89}$, wherein R^{87}, R^{88}, and R^{89} are each independently hydrogen, or a substituted or unsubstituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl aralkyl, heterocyclyl or heterocyclylalkyl group as defined herein.

[0043] The term "guanidine" refers to $-NR^{90}C(NR^{91})NR^{92}R^{93}$, wherein R^{90}, R^{91}, R^{92} and R^{93} are each independently hydrogen, or a substituted or unsubstituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl aralkyl, heterocyclyl or heterocyclylalkyl group as defined herein.

[0044] The term "enamine" refers to $-C(R^{94})=C(R^{95})NR^{96}R^{97}$ and $-NR^{94}C(R^{95})=C(R^{96})R^{97}$, wherein R^{94}, R^{95}, R^{96} and R^{97} are each independently hydrogen, a substituted or unsubstituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl aralkyl, heterocyclyl or heterocyclylalkyl group as defined herein.

[0045] The term "halogen" or "halo" as used herein refers to bromine, chlorine, fluorine, or iodine. For example a halogen may be fluorine. A halogen may be chlorine or bromine.

[0046] The term "hydroxyl" as used herein can refer to -OH or its ionized form, $-O^-$.

[0047] The term "imide" refers to $-C(O)NR^{98}C(O)R^{99}$, wherein R^{98} and R^{99} are each independently hydrogen, or a substituted or unsubstituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl aralkyl, heterocyclyl or heterocyclylalkyl group as defined herein.

[0048] The term "imine" refers to $-CR^{100}(NR^{101})$ and $-N(CR^{100}R^{101})$ groups, wherein R^{100} and R^{101} are each independently hydrogen or a substituted or unsubstituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl aralkyl, heterocyclyl or heterocyclylalkyl group as defined herein, with the proviso that R^{100} and R^{101} are not both simultaneously hydrogen.

[0049] The term "nitro" as used herein refers to an $-NO_2$ group.

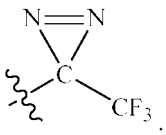
[0050] The term "trifluoromethyl" as used herein refers to $-CF_3$.

[0051] The term "trifluoromethoxy" as used herein refers to $-OCF_3$.

[0052] The term "azido" refers to $-N_3$.

[0053] The term "trialkyl ammonium" refers to a $-N(alkyl)_3$ group. A trialkylammonium group is positively charged and thus typically has an associated anion, such as halogen anion.

[0054] The term "trifluoromethyldiazirido" refers to



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[0055] The term "isocyano" refers to -NC.

[0056] The term "isothiocyano" refers to -NCS.

[0057] The term "pentafluorosulfanyl" refers to $-SF_5$.

[0058] The phrase "selectively treats" as used herein will be understood by persons of ordinary skill in the art and will vary to some extent depending upon the context in which the phrase is used. If there are uses of the phrase which are not clear to persons of ordinary skill in the art, given the context in which the phrase is used, the phrase at minimum refers to the compounds acting through a viral-specific mechanism of action, resulting in fewer off-target effects because the compounds target the virus and not the host.

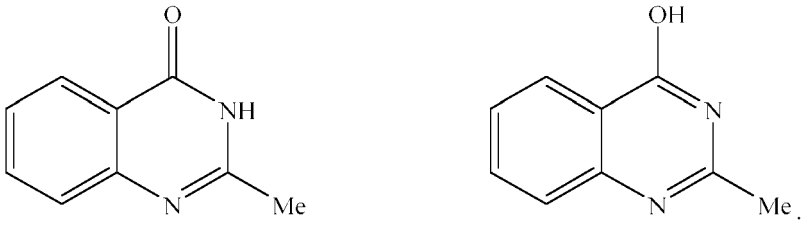
[0059] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range

discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as "up to," "at least," "greater than," "less than," and the like include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 atoms refers to groups having 1, 2, or 3 atoms. Similarly, a group having 1-5 atoms refers to groups having 1, 2, 3, 4, or 5 atoms, and so forth.

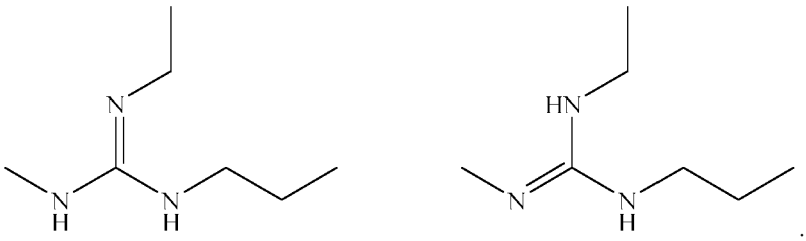
[0060] Pharmaceutically acceptable salts of compounds described herein are within the scope of the present technology and include acid or base addition salts which retain the desired pharmacological activity and is not biologically undesirable (e.g., the salt is not unduly toxic, allergenic, or irritating, and is bioavailable). When the compound of the present technology has a basic group, such as, for example, an amino group, pharmaceutically acceptable salts can be formed with inorganic acids (such as hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid), organic acids (e.g. alginate, formic acid, acetic acid, benzoic acid, gluconic acid, fumaric acid, oxalic acid, tartaric acid, lactic acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, naphthalene sulfonic acid, and p-toluenesulfonic acid) or acidic amino acids (such as aspartic acid and glutamic acid). When the compound of the present technology has an acidic group, such as for example, a carboxylic acid group, it can form salts with metals, such as alkali and earth alkali metals (e.g. Na^+, Li^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}), ammonia or organic amines (e.g. dicyclohexylamine, trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine) or basic amino acids (e.g., arginine, lysine and omithine). Such salts can be prepared in situ during isolation and purification of the compounds or by separately reacting the purified compound in its free base or free acid form with a suitable acid or base, respectively, and isolating the salt thus formed.

[0061] Those of skill in the art will appreciate that compounds of the present technology may exhibit the phenomena of tautomerism, conformational isomerism, geometric isomerism and/or stereoisomerism. As the formula drawings within the specification and claims can represent only one of the possible tautomeric, conformational isomeric, stereochemical or geometric isomeric forms, it should be understood that the present technology encompasses any tautomeric, conformational isomeric, stereochemical and/or geometric isomeric forms of the compounds having one or more of the utilities described herein, as well as mixtures of these various different forms.

[0062] "Tautomers" refers to isomeric forms of a compound that are in equilibrium with each other. The presence and concentrations of the isomeric forms will depend on the environment the compound is found in and may be different depending upon, for example, whether the compound is a solid or is in an organic or aqueous solution. For example, in aqueous solution, quinazolinones may exhibit the following isomeric forms, which are referred to as tautomers of each other:



As another example, guanidines may exhibit the following isomeric forms in protic organic solution, also referred to as tautomers of each other:



[0063] Because of the limits of representing compounds by structural formulas, it is to be understood that all chemical formulas of the compounds described herein represent all tautomeric forms of compounds and are within the scope of the present technology.

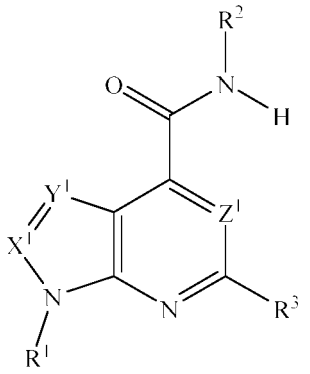
[0064] Stereoisomers of compounds (also known as optical isomers) include all chiral, diastereomeric, and racemic forms of a structure, unless the specific stereochemistry is expressly indicated. Thus, compounds used in the present

technology include enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions. Both racemic and diastereomeric mixtures, as well as the individual optical isomers can be isolated or synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these stereoisomers are all within the scope of the present technology.

[0065] The compounds of the present technology may exist as solvates, especially hydrates. Hydrates may form during manufacture of the compounds or compositions comprising the compounds, or hydrates may form over time due to the hygroscopic nature of the compounds. Compounds of the present technology may exist as organic solvates as well, including DMF, ether, and alcohol solvates among others. The identification and preparation of any particular solvate is within the skill of the ordinary artisan of synthetic organic or medicinal chemistry.

[0066] The present technology provides compounds expected to inhibit one or more of enteroviruses, paramyxoviruses, respiratory viruses, flaviviridae viruses, bunyaviridae viruses, togaviridae viruses, and rabies.

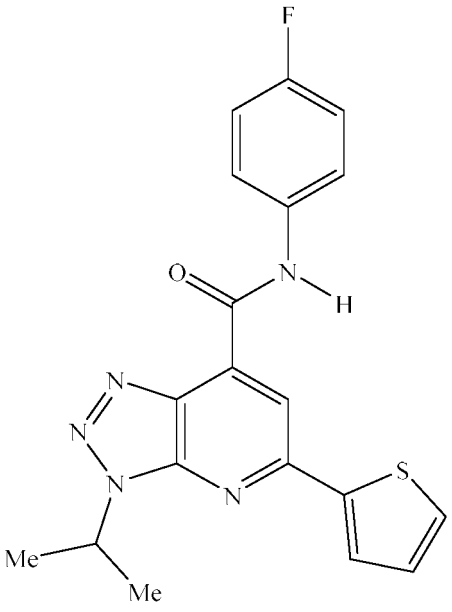
[0067] Disclosed herein is a compound represented by Formula I is provided



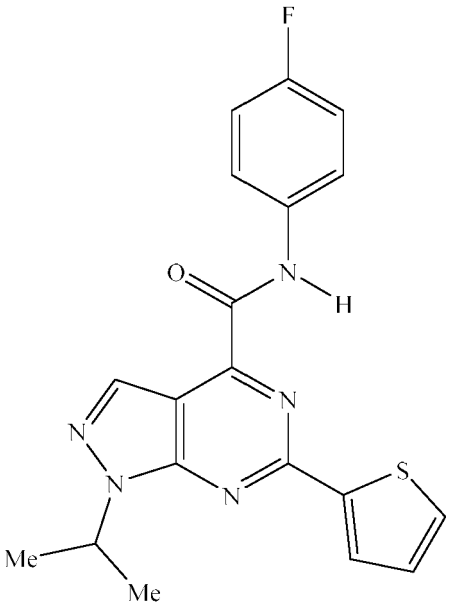
(I)

or a pharmaceutically acceptable salt thereof. In Formula I, R^1 is H, alkyl, cycloalkyl, aryl, or heteroaryl; R^2 is a substituted or unsubstituted aryl or heteroaryl; R^3 is a substituted or unsubstituted cycloalkyl, aryl, or heteroaryl; and (a) X^1 is N, Y^1 is N, and Z^1 is CH; or (b) X^1 is N, Y^1 is CH, and Z^1 is N; or (c) X^1 is CH, Y^1 is CH, and Z^1 is CH. R^1 may be a substituted or unsubstituted C_1-C_6 alkyl, unsubstituted C_4-C_7 cycloalkyl, or a substituted phenyl group. R^2 may be a heteroaryl group, preferably a six-membered nitrogen-containing heteroaryl group. R^2 may be a substituted aryl group where the aryl group bears 1, 2, or 3 substituents. R^2 may be a substituted aryl group where the substituents are selected from the group consisting of a halogen, a nitro group, cyano group, an alkanoyl group, a carbamoyl group, an ester, an amido, a sulfonyl group, a sulfonamido group, and a trifluoromethyl group. R^2 may be fluorophenyl, difluorophenyl, trifluorophenyl, sulfonamidophenyl, or trifluormethylphenyl. R^3 may be a 2-thiophenyl or 3-thiophenyl group.

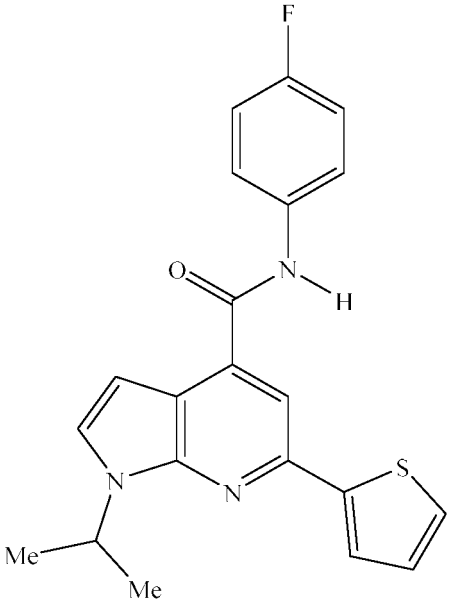
[0068] The following compounds are disclosed herein



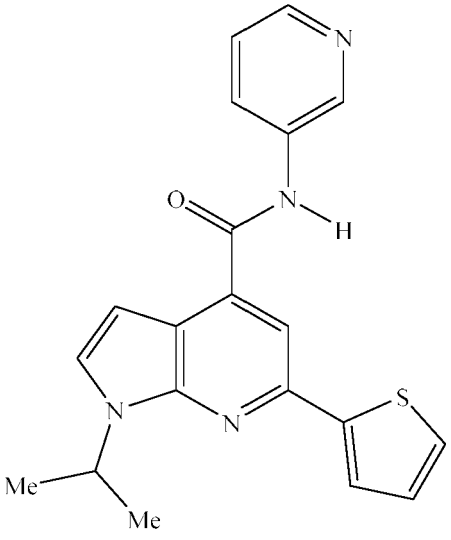
(JX-035),



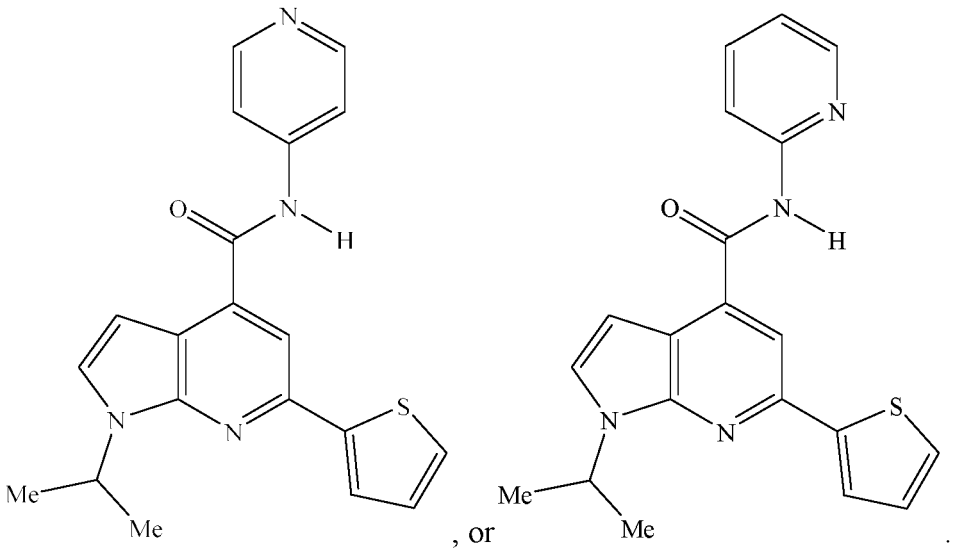
(JX-036),



(JX-037),



(JX-062),



(JX-063) , or (JX-072) .

[0069] The compounds and compositions of the present invention are set out in the claims. The present disclosure provides pharmaceutical compositions and medicaments comprising any of one of the compounds of Formula I (or a pharmaceutically acceptable salt thereof) disclosed herein and a pharmaceutically acceptable carrier or one or more excipients or fillers. The compositions may be used in the methods and treatments described herein. The pharmaceutical composition of the invention may include an effective amount of any of one of the compounds claimed herein. In any of such embodiments, the effective amount may be determined in relation to a subject. "Effective amount" refers to the amount of a compound or composition required to produce a desired effect. One example of an effective amount includes amounts or dosages that yield acceptable toxicity and bioavailability levels for therapeutic (pharmaceutical) use including, but not limited to, the treatment of an enterovirus. Another example of an effective amount includes amounts or dosages that yield acceptable toxicity and bioavailability levels for therapeutic (pharmaceutical) use including, but not limited to, the prophylaxis of an enterovirus. Another example of an effective amount includes amounts or dosages that are capable of reducing symptoms associated with an enterovirus, such as, for example, fever, headache, and/or encephalitis. As used herein, a "subject" or "patient" is a mammal, such as a cat, dog, rodent or primate. Typically the subject is a human, and, preferably, a human suffering from or suspected of suffering from an enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus. In any embodiment disclosed herein, the enterovirus may be Coxsackievirus A9, Coxsackievirus A16, Coxsackievirus B 1, Coxsackievirus B2, Coxsackievirus B3-H3, Coxsackievirus B4, Coxsackievirus B5, Enterovirus 68, Enterovirus 71, Echovirus 6, Echovirus 7, Echovirus 9, Echovirus 11, Echovirus 18, Echovirus 25, Echovirus 30, Poliovirus 1, or Poliovirus 3. The term "subject" and "patient" can be used interchangeably.

[0070] In any of the embodiments of the present technology described herein, the pharmaceutical composition may be packaged in unit dosage form. The unit dosage form is effective in treating an enterovirus. Generally, a unit dosage including a compound of the present technology will vary depending on patient considerations. Such considerations include, for example, age, protocol, condition, sex, extent of disease, contraindications, concomitant therapies and the like. An exemplary unit dosage based on these considerations may also be adjusted or modified by a physician skilled in the art. For example, a unit dosage for a patient comprising a compound of the present technology may vary from 1×10^{-4} g/kg to 1 g/kg, preferably, 1×10^{-3} g/kg to 1.0 g/kg. Dosage of a compound of the present technology may also vary from 0.01 mg/kg to 100 mg/kg or, preferably, from 0.1 mg/kg to 10 mg/kg. Suitable unit dosage forms, include, but are not limited to powders, tablets, pills, capsules, lozenges, suppositories, patches, nasal sprays, injectibles, implantable sustained-release formulations, mucoadherent films, topical varnishes, lipid complexes, etc.

[0071] The pharmaceutical compositions may be prepared by mixing one or more compounds of Formula I as set out in the claims, pharmaceutically acceptable salts thereof, stereoisomers thereof, tautomers thereof, or solvates thereof, with pharmaceutically acceptable carriers, excipients, binders, diluents or the like to prevent and treat disorders associated with the effects of increased plasma and/or hepatic lipid levels. The compounds and compositions described herein may be used to prepare formulations and medicaments that treat an enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies. Such compositions may be in the form of, for example, granules, powders, tablets, capsules, syrup, suppositories, injections, emulsions, elixirs, suspensions or solutions. The instant compositions may be formulated for various routes of administration, for example, by oral, parenteral, topical,

rectal, nasal, vaginal administration, or via implanted reservoir. Parenteral or systemic administration includes, but is not limited to, subcutaneous, intravenous, intraperitoneal, and intramuscular, injections. The following dosage forms are given by way of example and should not be construed as limiting the instant present technology.

[0072] For oral, buccal, and sublingual administration, powders, suspensions, granules, tablets, pills, capsules, gelcaps, and caplets are acceptable as solid dosage forms. These can be prepared, for example, by mixing one or more compounds of the instant present technology, or pharmaceutically acceptable salts or tautomers thereof, with at least one additive such as a starch or other additive. Suitable additives are sucrose, lactose, cellulose sugar, mannitol, maltitol, dextran, starch, agar, alginates, chitins, chitosans, pectins, tragacanth gum, gum arabic, gelatins, collagens, casein, albumin, synthetic or semi-synthetic polymers or glycerides. Optionally, oral dosage forms can contain other ingredients to aid in administration, such as an inactive diluent, or lubricants such as magnesium stearate, or preservatives such as paraben or sorbic acid, or anti-oxidants such as ascorbic acid, tocopherol or cysteine, a disintegrating agent, binders, thickeners, buffers, sweeteners, flavoring agents or perfuming agents. Tablets and pills may be further treated with suitable coating materials known in the art.

[0073] Liquid dosage forms for oral administration may be in the form of pharmaceutically acceptable emulsions, syrups, elixirs, suspensions, and solutions, which may contain an inactive diluent, such as water. Pharmaceutical formulations and medicaments may be prepared as liquid suspensions or solutions using a sterile liquid, such as, but not limited to, an oil, water, an alcohol, and combinations of these. Pharmaceutically suitable surfactants, suspending agents, emulsifying agents, may be added for oral or parenteral administration.

[0074] As noted above, suspensions may include oils. Such oils include, but are not limited to, peanut oil, sesame oil, cottonseed oil, corn oil and olive oil. Suspension preparation may also contain esters of fatty acids such as ethyl oleate, isopropyl myristate, fatty acid glycerides and acetylated fatty acid glycerides. Suspension formulations may include alcohols, such as, but not limited to, ethanol, isopropyl alcohol, hexadecyl alcohol, glycerol and propylene glycol. Ethers, such as but not limited to, poly(ethyleneglycol), petroleum hydrocarbons such as mineral oil and petrolatum; and water may also be used in suspension formulations.

[0075] Injectable dosage forms generally include aqueous suspensions or oil suspensions which may be prepared using a suitable dispersant or wetting agent and a suspending agent. Injectable forms may be in solution phase or in the form of a suspension, which is prepared with a solvent or diluent. Acceptable solvents or vehicles include sterilized water, Ringer's solution, or an isotonic aqueous saline solution. Alternatively, sterile oils may be employed as solvents or suspending agents. Typically, the oil or fatty acid is non-volatile, including natural or synthetic oils, fatty acids, mono-, di- or tri-glycerides.

[0076] For injection, the pharmaceutical formulation and/or medicament may be a powder suitable for reconstitution with an appropriate solution as described above. Examples of these include, but are not limited to, freeze dried, rotary dried or spray dried powders, amorphous powders, granules, precipitates, or particulates. For injection, the formulations may optionally contain stabilizers, pH modifiers, surfactants, bioavailability modifiers and combinations of these.

[0077] Compounds of the present technology may be administered to the lungs by inhalation through the nose or mouth. Suitable pharmaceutical formulations for inhalation include solutions, sprays, dry powders, or aerosols containing any appropriate solvents and optionally other compounds such as, but not limited to, stabilizers, antimicrobial agents, antioxidants, pH modifiers, surfactants, bioavailability modifiers and combinations of these. The carriers and stabilizers vary with the requirements of the particular compound, but typically include nonionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aqueous and nonaqueous (e.g., in a fluorocarbon propellant) aerosols are typically used for delivery of compounds of the present technology by inhalation.

[0078] Dosage forms for the topical (including buccal and sublingual) or transdermal administration of compounds of the present technology include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, and patches. The active component may be mixed under sterile conditions with a pharmaceutically-acceptable carrier or excipient, and with any preservatives, or buffers, which may be required. Powders and sprays can be prepared, for example, with excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. The ointments, pastes, creams and gels may also contain excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof. Absorption enhancers can also be used to increase the flux of the compounds of the present technology across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane (e.g., as part of a transdermal patch) or dispersing the compound in a polymer matrix or gel.

[0079] Besides those representative dosage forms described above, pharmaceutically acceptable excipients and carriers are generally known to those skilled in the art and are thus included in the instant present technology. Such excipients and carriers are described, for example, in "Remingtons Pharmaceutical Sciences" Mack Pub. Co., New Jersey (1991).

[0080] The formulations of the present technology may be designed to be short-acting, fast-releasing, long-acting, and sustained-releasing as described below. Thus, the pharmaceutical formulations may also be formulated for controlled

release or for slow release.

[0081] The instant compositions may also comprise, for example, micelles or liposomes, or some other encapsulated form, or may be administered in an extended release form to provide a prolonged storage and/or delivery effect. Therefore, the pharmaceutical formulations and medicaments may be compressed into pellets or cylinders and implanted intramuscularly or subcutaneously as depot injections or as implants such as stents. Such implants may employ known inert materials such as silicones and biodegradable polymers.

[0082] Specific dosages may be adjusted depending on conditions of disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs. Any of the above dosage forms containing effective amounts are well within the bounds of routine experimentation and therefore, well within the scope of the instant present technology.

[0083] Various assays and model systems can be readily employed to determine the therapeutic effectiveness of the treatment according to the present technology.

[0084] For each of the indicated conditions described herein, test subjects will exhibit a 10%, 20%, 30%, 50% or greater reduction, up to a 75-90%, or 95% or greater, reduction, in one or more symptom(s) caused by, or associated with, the disorder in the subject, compared to placebo-treated or other suitable control subjects.

[0085] In an aspect, a compound disclosed herein may be for use in a method for inhibiting the replication of an enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus in a cell infected with the enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus is provided. The method includes contacting an effective amount of any one of the compounds of Formula I (or a pharmaceutically acceptable salt thereof) disclosed herein with the cell infected with the enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus, thereby inhibiting the replication of the enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus in the cell. The enterovirus may be Coxsackievirus A9, Coxsackievirus A16, Coxsackievirus B1, Coxsackievirus B2, Coxsackievirus B3-H3, Coxsackievirus B4, Coxsackievirus B5, Enterovirus 68 (also known as Enterovirus D68), Enterovirus 71, Echovirus 6, Echovirus 7, Echovirus 9, Echovirus 11, Echovirus 18, Echovirus 25, Echovirus 30, Poliovirus 1, or Poliovirus 3. The contacting step may include administration of a pharmaceutical composition, where the pharmaceutical composition includes an effective amount of any one of the compounds of Formula I disclosed herein (or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable carrier. The effective amount may be from about 0.01 μg to about 1 mg of the compound per gram of the composition, and preferably from about 0.1 μg to about 500 μg of the compound per gram of the composition.

[0086] In an aspect, a compound disclosed herein may be for use in a method of inhibiting death of a cell infected with an enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus is disclosed, the method comprising contacting an effective amount of any one of the compounds of Formula I disclosed herein (or a pharmaceutically acceptable salt thereof)with the cell infected with the enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus, thereby inhibiting the death of the cell. The enterovirus may be Coxsackievirus A9, Coxsackievirus A16, Coxsackievirus B1, Coxsackievirus B2, Coxsackievirus B3-H3, Coxsackievirus B4, Coxsackievirus B5, Enterovirus 68 (also known as Enterovirus D68), Enterovirus 71, Echovirus 6, Echovirus 7, Echovirus 9, Echovirus 11, Echovirus 18, Echovirus 25, Echovirus 30, Poliovirus 1, or Poliovirus 3. The contacting step may include administration of a pharmaceutical composition, where the pharmaceutical composition includes an effective amount of any one of the compounds of Formula I disclosed herein (or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable carrier. The effective amount may be from about 0.01 μg to about 1 mg of the compound per gram of the composition, and preferably from about 0.1 μg to about 500 μg of the compound per gram of the composition.

[0087] In an aspect, a compound for use in a method of treating a patient or animal infected with an enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus is provided as set out in the claims, the method including administration of an effective amount of a compound of any one of the above embodiments of the present technology to the patient or animal. In the method, administration of the effective amount of a compound of any one of the above embodiments of the present technology to the patient or animal treats the patient or animal infected with the enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus. The enterovirus may be Coxsackievirus A9, Coxsackievirus A16, Coxsackievirus B1, Coxsackievirus B2, Coxsackievirus B3-H3, Coxsackievirus B4, Coxsackievirus B5, Enterovirus 68 (also known as Enterovirus D68), Enterovirus 71, Echovirus 6, Echovirus 7, Echovirus 9, Echovirus 11, Echovirus 18, Echovirus 25, Echovirus 30, Poliovirus 1, or Poliovirus 3. It may be that administration of the effective amount of the compound of any one of the above embodiments of the present technology selectively treats the enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus.

[0088] In any of the embodiments claimed herein, the method of treating a patient or animal infected with an enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus, may include administration of a pharmaceutical composition, where the pharmaceutical composition includes an effective amount of

any one of the embodiments of the compounds of the present technology or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. The enterovirus may be Coxsackievirus A9, Coxsackievirus A16, Coxsackievirus B1, Coxsackievirus B2, Coxsackievirus B3-H3, Coxsackievirus B4, Coxsackievirus B5, Enterovirus 68 (also known as Enterovirus D68), Enterovirus 71, Echovirus 6, Echovirus 7, Echovirus 9, Echovirus 11, Echovirus 18, Echovirus 25, Echovirus 30, Poliovirus 1, or Poliovirus 3. The effective amount may be from about 0.01 μg to about 1 mg of the compound per gram of the composition, and preferably from about 0.1 μg to about 500 μg of the compound per gram of the composition. In any of the embodiments claimed, the compound or composition may be administered orally, parenterally, rectally, or transdermally.

[0089] The examples herein are provided to illustrate advantages of the present technology and to further assist a person of ordinary skill in the art with preparing or using the compounds of the present technology or salts, or pharmaceutical compositions claimed herein. The examples herein are also presented in order to more fully illustrate the preferred aspects of the present technology. The examples should in no way be construed as limiting the scope of the present technology, as defined by the appended claims.

EXAMPLES

[0090] Compounds of the present technology may be synthesized by synthetic medicinal chemistry procedures well known to one of ordinary skill in the art. The compounds of the present technology may be purified by normal synthetic medicinal chemistry procedures, usually column chromatography and their structures determined by high field NMR spectroscopy. Exemplary procedures and methods include, but are not limited to, those described and referenced in U.S. Pat. Publ. No. 2015/0164910.

Biological Testing of Representative Compounds of the Present Technology

[0091] Virus cytopathic effect assay: Cells growing in 96 well plates are infected with a given virus at given low multiplicities of infection pre-determined to result in 100% cytopathic effects (CPE) in the cultures after 3-4 days incubation. Cultures are monitored daily for microscopic signs of typical CPE: rounding of cells and detachment. When CPE appears maximal in the control wells without the antiviral compounds, the cells are fixed with 4% formaldehyde before staining with 0.25% crystal violet solution. Dead cells and debris are washed out and the remaining blue stain intensity in each well is quantified by spectrophotometry at a wavelength of 590nm (OD_{590}) as a measurement of viability.

[0092] *In vitro* evaluation of antiviral activities: Each compound is initially tested against each virus at 10 μM in a virus CPE assay. A compound that is active against a virus, protecting the cells from CPE, is further evaluated for its 50% effective concentration (EC_{50}) value and 50% cytotoxicity concentration (CC_{50}) value. Serial 2-fold dilutions of an active compound are prepared. For EC_{50} value determination, a 7-point dose-response curve is constructed using a virus CPE assay and EC_{50} value is estimated using four parameter model or sigmoidal model. For CC_{50} value determination, cells are incubated with serial 2-fold dilutions of a compound for the same period as the virus CPE assay, and then cells were fixed, stained and read as in the virus CPE assay.

[0093] Exemplary *in vitro* evaluation of anti-rabies activity: T-150 flasks of confluent BHK-21 cells are prepared and subsequently trypsinized and made into cell suspensions. 50 μL of a 5×10^5 cells/mL cell suspension (25,000 cells/well) are loaded into each well of a 96-well, white walled, clear bottom cell culture plate, with the exception of row H which is reserved for Media only (see Scheme 2 below). Concentrations of double the final intended concentration ("2X Drug") of the well are made with the antivirals (Isoprinosine and test compounds). At least 6 concentration points are usually performed. Add 100 μL per well that will be tested for effective concentration ("drug wells") and cytotoxic concentration ("tox wells"). The rabies virus is diluted 1:1000 and 50 μL of this dilution is added per well in the drug wells and virus control wells. Additional media is added to the tox, Control, Virus Control, and Media only wells to ensure the final volume is 200 μL - *e.g.*, tox wells should be 100 μL 2X Drug, 50 μL cells (5×10^5 cells/mL), and 50 μL media; Media only wells (row H of Scheme 2) should be 200 μl media. The 96 well plates are then covered and incubated for 5 days at 37 °C in a 5 % CO_2 atmosphere. Upon completion of the 5-day incubation period, the well plate is visually checked to determine the difference in the Control wells and Virus Control wells as well as any visible toxicity from the compounds. A Promega CellTiter-Glo Luminescent Cell Viability Assay is then performed using the Fluoroskan FL to scan for luminescence.

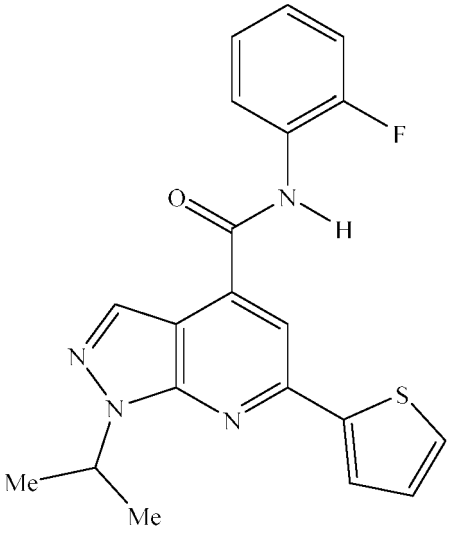
Scheme 2.

[0094]

	1	2	3	4	5	6	7	8	9	10	11	12
A B C	Drug 1 1000μM	Drug 1 333μM	Drug 1 111μM	Drug 1 37μM	Drug 1 12.3μM	Drug 1 4μM	Drug 2 100μM	Drug 2 33μM	Drug 2 11μM	Drug 2 3.7μM	Drug 2 1.2μM	Drug 2 0.4μM
D	Cells + 150μl media (Control)			Cells+virus+100μl media (Virus control)			Cells + 150μl media (Control)			Cells+virus+100μl media (Virus control)		
E F G	Tox 1 1000μM	Tox 1 333μM	Tox 1 111μm	Tox 1 37μM	Tox 1 12.3μM	Tox 1 4μM	Tox 2 100μM	Tox 2 33.3μM	Tox 2 11.1μM	Tox 2 3.7μM	Tox 2 1.2μM	Tox 2 0.4μM
H	Media only						Media only					

Drug = 100μl 2x drug, 50μl cells (5e5 cells/ml), 50μl virus (1:1000)
Tox = 100μl 2x drug, 50μl cells (5e5 cells/ml), 50μl media

[0095] Cell-based assays evaluating the antiviral activities of compounds of the present technology with certain enteroviruses, paramyxoviruses, respiratory viruses, flaviviridae viruses, bunyaviridae viruses, togaviridae viruses, and rabies viruses may be compared to positive controls. One such positive control is JX-001, the structure of which is illustrated below.



(JX-001)

Compounds of Formula I are expected to inhibit one or more of enteroviruses, paramyxoviruses, respiratory viruses, flaviviridae viruses, bunyaviridae viruses, togaviridae viruses, and rabies viruses.

[0096] Tables 1 and 2 provide the results of evaluating the antiviral activities of certain representative compounds of the present technology with certain enteroviruses. The data in Tables 1 and 2 are EC_{50} values in μM units. Abbreviations are as follows:

CVB3-H3: Coxsackievirus B3-H3
PV1: Poliovirus 1
PV3: Poliovirus 3
CVB 1: Coxsackievirus B1
CVB2: Coxsackievirus B2
CVB4: Coxsackievirus B4
CVB5: Coxsackievirus B5
EV71: Enterovirus 71
COX A9: Coxsackievirus A9
ECHO06: Echovirus 6
ECHO07: Echovirus 7
ECHO09: Echovirus 9
ECHO11: Echovirus 11
ECHO25: Echovirus 25
ECHO30: Echovirus 30

Table 1. Evaluation of Compounds of the Present Technology Against Enteroviruses

Compound (JX #)	**CVB3-H3**	**PV1**	**PV3**	**CVB1**	**CVB2**	**CVB4**	**CVB5**
JX-001	1.4 ± 0.6	7 ± 0.0	7 ± 0.0	2.4 ± 0.2	2.8 ± 0.4	2.3 ± 0.0	2.3 ± 0.0
JX-035	>10	>10	>10	>10	>10	>10	>10
JX-036	>10	>10	>10	>10	>10	>10	>10
JX-037	3.1 ± 0.1	>25	>25	3.6 ± 0.6	3.6 ± 0.6	3.1 ± 0.1	2.7 ± 0.6
JX-062	1.3	>10	>10	1.2	1.2	1.2	1.2

(continued)

Compound (JX #)	CVB3-H3	PV1	PV3	CVB1	CVB2	CVB4	CVB5
JX-063	>10	>10	>10	>10	>10	>10	>10
JX-072	2.2 ± 0.4	>10	>10	1.56	2.33		

1. *In Vitro* antiviral testing was done in HeLa-RW cells.
2. x.x ± x.x: mean ± standard deviation (sd). EC_{50} values of single experiments are shown as x.x.
3. >10 and >25 entries: compounds were tested in 10 μM or 25 μM, respectively, and no antiviral activities were observed.
4. TBD: A compound is active against an enteroviral infection in 10 μM concentration; EC_{50} not yet determined.

Table 2. Evaluation of Compounds of the Present Technology Against Enteroviruses (cont.)

Compound (JX #)	EV71	COX A9	ECHO06	ECHO07	ECHO09	ECHO11	ECHO25	ECHO30
JX-001	2.3 ± 1.2	2.6 ± 0.9	2.3 ± 0.9	2.4	2.1 ± 1.2	1.5 ± 0.4	3	1.2
JX-035	>10	>10	>10	>10	>10	>10	>10	>10
JX-036	>10	>10	>10	>10	>10	>10	>10	>10
JX-037	2.2							
JX-062	0.8	TBD	TBD	TBD	0.4	1.2	TBD	TBD
JX-063	TBD	TBD	TBD	TBD	TBD	TBD	TBD	TBD
JX-072	1.2	TBD	TBD	3	TBD	TBD	TBD	TBD

1. *In Vitro* antiviral testing was done in LLC cells.
2. x.x ± x.x: mean ± standard deviation (sd). EC_{50} values of single experiments are shown as x.x.
3. >10 and >25 entries: compounds were tested in 10 μM or 25 μM, respectively, and no antiviral activities were observed.
4. TBD: A compound is active against an enteroviral infection in 10 μM concentration; EC_{50} not yet determined.
5. A blank cell indicates that the referenced compound has not yet been tested with the indicated enterovirus.

[0097] Table 3 provides the compound concentration in μM units that reduces cell viability of the host cell by 50% (CC_{50}) for certain compounds of the present technology for HeLa-RW and LLC cells. Blank cells indicate that the cytotoxicity assessment is not yet complete.

Table 3. Evaluation of CC_{50} of Compounds of the Present Technology

Compound (JX #)	HeLa-RW	LLC
JX-001	12.5	50
JX-037	>200	100
JX-062	18	25
JX-072	18.8	>200

[0098] Table 4 provides the results of cell-based assays with RD cells evaluating the antiviral activities of certain representative compounds of the present technology with certain strains of Enterovirus D68, namely strains Fermon ("D68/Fermon"), US/Mo/14-18949 ("D68/US/Mo/14-18949"), and US/KY/14-18953 ("D68/US/KY/14-18953"). The values indicated in the strain columns are EC_{50} values in μM units. The CC_{50} values (in μM units) for RD cells are also provided for evaluation of SI_{50}.

Table 4. Evaluation of Activities of Compounds of the Present Technology Against strains of Enterovirus D68

Compound (JX #)	Fermon	US/Mo/14-18949	US/KY/14-18953	CC_{50} (RD)
JX-001	0.35 ± 0.05	0.33 ± 0.05	0.50 ± 0.17	200

(continued)

Compound (JX #)	**Fermon**	**US/Mo/14-18949**	**US/KY/14-18953**	**CC_{50} (RD)**
JX-037	0.86 ± 0.31	0.57 ± 0.15	1.1 ± 0.3	>200
JX-062	0.16 ± 0.03	0.13 ± 0.03	0.26 ± 0.07	25
JX-072	<0.4		0.6	25
1. In Vitro antiviral testing was done in RD cells. 2. x.x ± x.x: mean ± standard deviation (sd). EC_{50} values of single experiments are shown as x.x. EC_{50} values of a few experiments are listed out as a series of values. 3. A blank cell indicates that the referenced compound has not yet been tested with the indicated Enterovirus D68 strain.				

[0099] The data for the strains provided in these examples illustrate that the compounds of the present technology have high activity while concurrently exhibiting excellent SI values. For example, JX-037, JX-062, and JX-072 each have at least one strain against which the compound has an EC_{50} less than 1 μM while concurrently having a SI greater than 25. As a further example, for the 2014 epidemic strain of Enterovirus D68/US/Mo/14-18949, JX-037 has an SI of over 350 (>200/0.57 = >350).

Exemplary mouse studies of inhibition of viruses

[0100] *Compound preparation and dosing:* Compounds will be formulated with an appropriate vehicle for the study, such as a suspension in a 0.5% xanthan gum-1% Tween 80 vehicle. The compound will be administered intragastrically with a 0.5-ml Glaspak syringe fitted with a 24-gauge feeding needle (Popper and Sons, Inc., New York, N.Y.).

[0101] *Infection of suckling mice:* Newborn ICR mouse pups of both sexes (weight, 1.2 to 1.9 g), born within 24 h of receipt, will obtained with their dams. The pups will be pooled, weighed, and distributed to the nursing dams in groups of 10. Three cages (30 pups) will be included for each dosage group. Each mouse pup will infected subcutaneously over the right shoulder within 24 h of birth with the virus. The amount of virus inoculated will be titrated to produce approximately 80% mortality in untreated animals over the 13-day observation period. The compound of interest will be administered as a single, 0.03-ml dose 2.5 days postinfection. Mouse pups will be checked daily for evidence of paralysis or death (paralyzed animals will be killed). It is expected that a suitable dosage of compounds of the present technology will be determined that will enable at least eighty percent of treated virus-infected animals to survive the entire 14-day observation period.

REFERENCES:

[0102]

1. Cherry, J.D., Krogstad P.K., Enteroviruses and Parechoviruses, in Textbook of Pediatric Infectious Diseases, R.D. Feigin, et al., Editors. 2009, WB Saunders Co: Philadelphia, PA. p. 1984-2041.

2. a) McMinn, P., et al., Neurological manifestations of enterovirus 71 infection in children during an outbreak of hand, foot, and mouth disease in Western Australia. Clin Infect Dis, 2001. 32(2): p. 236-42. b) McMinn, P.C., An overview of the evolution of enterovirus 71 and its clinical and public health significance. FEMS Microbiol Rev, 2002. 26(1): p. 91-107.

3. Seiff, A., Cambodia unravels cause of mystery illness. Lancet, 2012. 380(9838): p. 206.

4. a) Verma, N.A., et al., Outbreak of life-threatening coxsackievirus B1 myocarditis in neonates. Clin Infect Dis, 2009. 49(5): p. 759-63. b) Wikswo, M.E., et al., Increased activity of Coxsackievirus B1 strains associated with severe disease among young infants in the United States, 2007-2008. Clin Infect Dis, 2009. 49(5): p. e44-51.

5. a) Notes from the field: severe hand, foot, and mouth disease associated with coxsackievirus A6 - Alabama, Connecticut, California, and Nevada, November 2011-February 2012. MMWR Morb Mortal Wkly Rep, 2012. 61(12): p. 213-4. b) Flett, K., et al., Hand, foot, and mouth disease caused by coxsackievirus a6. Emerg Infect Dis, 2012. 18(10): p. 1702-4. c) Mathes, E.F., et al., "Eczema Coxsackium" and Unusual Cutaneous Findings in an Enterovirus Outbreak. Pediatrics, 2013.

6. a) Nonpolio enterovirus and human parechovirus surveillance --- United States, 2006-2008. MMWR Morb Mortal Wkly Rep, 2010. 59(48): p. 1577-80. b) Progress toward interruption of wild poliovirus transmission - worldwide, january 2011-march 2012. MMWR Morb Mortal Wkly Rep, 2012. 61: p. 353-7. c) De Palma, A.M., et al., Selective inhibitors of picornavirus replication. Med Res Rev, 2008. 28(6): p. 823-84.

7. Pamukcu, R.; Piazza, G. A. US Patent 5942520, 24 Aug 1999.

8. a) MacKy, M.; Nortcliffe, A.; McNab, H.; Hulme, A. N. Gas-Phase Synthesis of Pyrazolo[3,4-b]pyridin-4-ones Synthesis (2015), 47(2), 242-248. b) Ji, N.; Meredith, E.; Liu, D.; Adams, C. M.; Artman, G. D., III; Jendza, K. C.; Ma, F.; Mainolfi, N.; Powers, J. J.; Zhang, C. Synthesis of 1-substituted-3-aminopyrazoles Tetrahedron Letters (2010), 51(52), 6799-6801.

9. Chen, H. et al. (2014) ; Knerr, L.; Aakerud, T.; Hallberg, K.; Oester, L.; Rohman, M.; Oesterlund, K.; Beisel, H.-G.; Olsson, T.; Brengdhal, J. et al. Discovery of a novel pyrazole series of group X secreted phospholipase A2 inhibitor (sPLA2X) via fragment based virtual screening Bioorganic & Medicinal Chemistry Letters (2014), 24(22), 5251-5255.

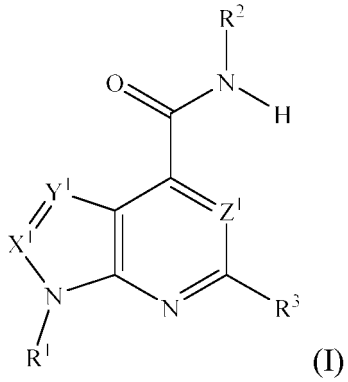
[0103] The embodiments, illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising," "including," "containing," etc. shall be read expansively and without limitation. Additionally, the phrase "consisting essentially of" will be understood to include those elements specifically recited and those additional elements that do not materially affect the basic and novel characteristics of the claimed technology. The phrase "consisting of" excludes any element not specified.

[0104] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[0105] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as "up to," "at least," "greater than," "less than," and the like, include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member.

Claims

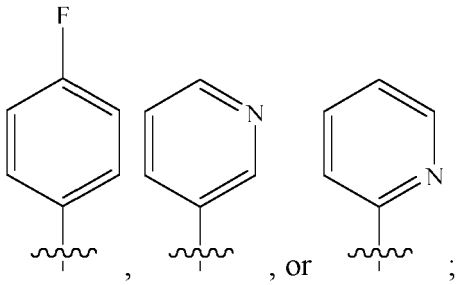
1. A compound according to Formula I:



(I)

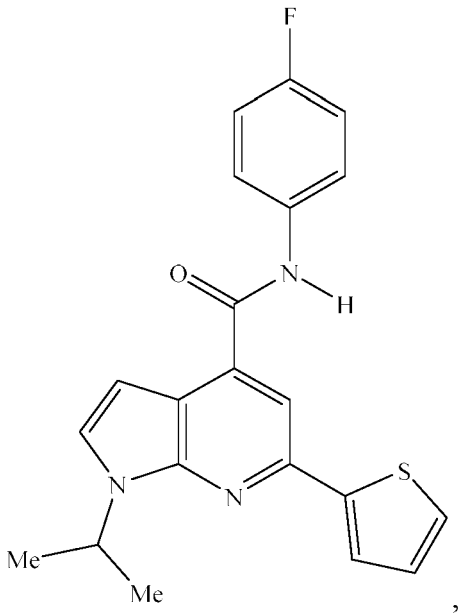
or a pharmaceutically acceptable salt thereof, wherein
X^1 is CH, Y^1 is CH, and Z^1 is CH;

R^1 is unsubstituted C_1-C_6 alkyl;
R^2 is



and
R^3 is 2-thiophenyl or 3-thiophenyl.

2. The compound of claim 1, wherein the compound is:



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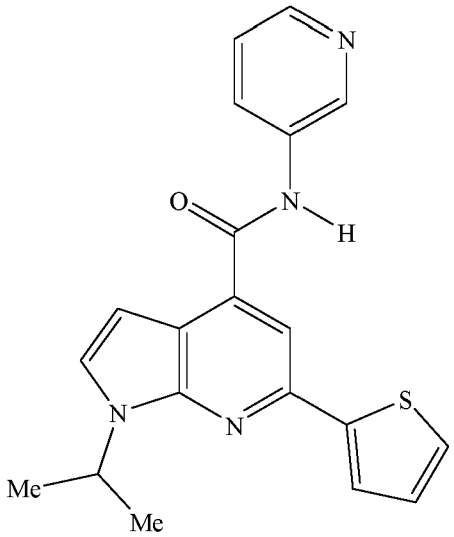

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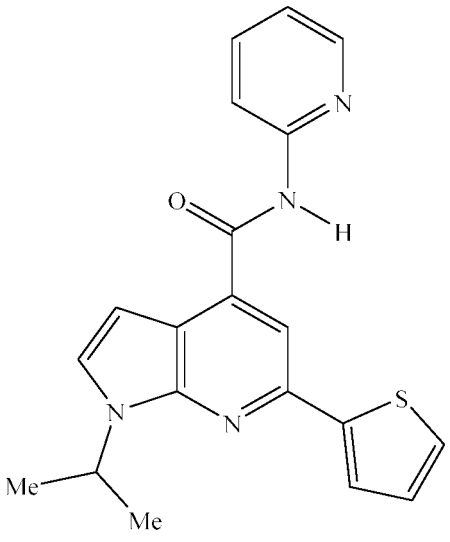


,

or a pharmaceutically acceptable salt of any one thereof.

3. A composition comprising a compound of claim 1 or 2, and a pharmaceutically acceptable carrier.

4. A pharmaceutical composition for use in treating an enterovirus infection, the composition comprising an effective amount of a compound of claim 1 or 2 and a pharmaceutically acceptable excipient;

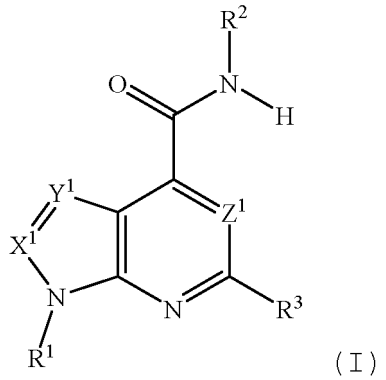
wherein, optionally, the pharmaceutical composition is packaged in unit dosage form;
and / or wherein, optionally, the enterovirus is Coxsackievirus A9, Coxsackievirus A16, Coxsackievirus B1, Coxsackievirus B2, Coxsackievirus B3-H3, Coxsackievirus B4, Coxsackievirus B5, Enterovirus 68, Enterovirus 68, Enterovirus 71, Echovirus 6, Echovirus 7, Echovirus 9, Echovirus 11, Echovirus 18, Echovirus 25, Echovirus 30.

5. A compound according to claim 1 or 2, for use in a method of treating a patient or animal infected with an enterovirus, paramyxovirus, respiratory virus, flaviviridae virus, bunyaviridae virus, togaviridae virus, or rabies virus, the use comprising administration of an effective amount of the compound to the patient or animal;

wherein, optionally, the enterovirus is Coxsackievirus A9, Coxsackievirus A16, Coxsackievirus B1, Coxsackievirus B2, Coxsackievirus B3-H3, Coxsackievirus B4, Coxsackievirus B5, Enterovirus 68, Enterovirus 71, Echovirus 6, Echovirus 7, Echovirus 9, Echovirus 11, Echovirus 18, Echovirus 25, or Echovirus 30; and / or
wherein, optionally, the administration comprises oral administration, parenteral administration, or nasal administration.

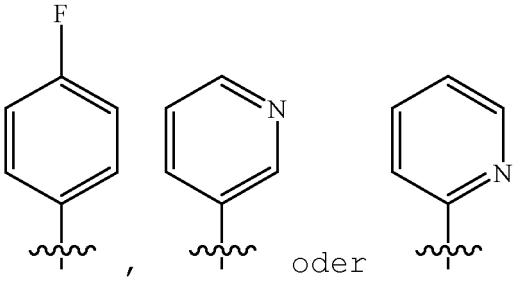
Patentansprüche

1. Verbindung gemäß Formel I:



(I)

oder pharmazeutisch verträgliches Salz davon, wobei
X^1 CH ist, Y^1 CH ist und Z^1 CH ist;
R^1 unsubstituiertes C_1-C_6-Alkyl ist;
R2

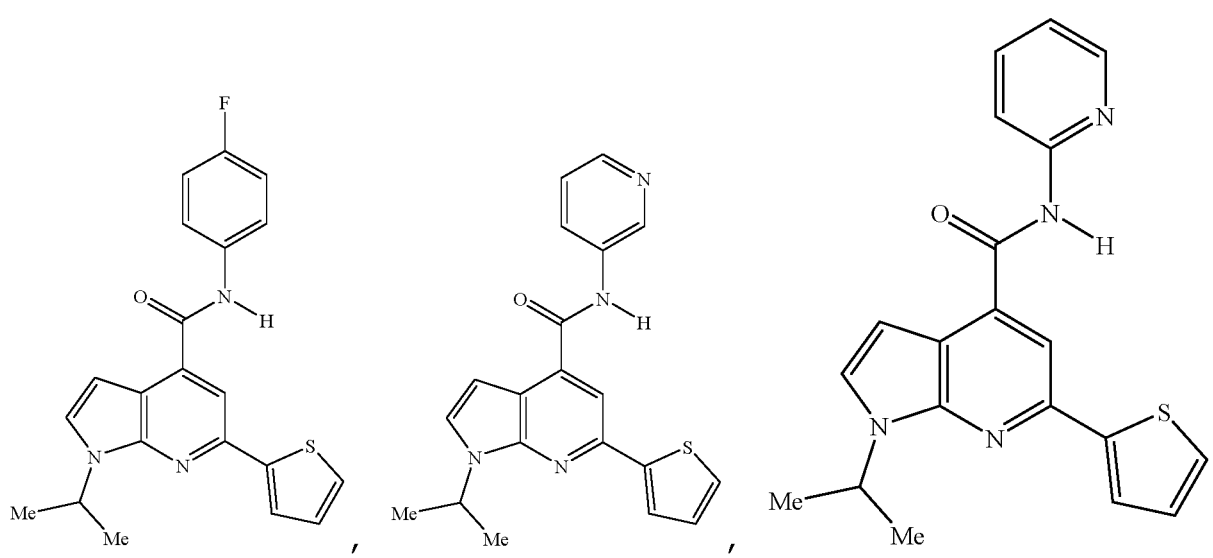


oder

ist; und

R^3 2-Thiophenyl oder 3-Thiophenyl ist.

2. Verbindung nach Anspruch 1, wobei die Verbindung:



oder ein pharmazeutisch verträgliches Salz davon ist.

3. Zusammensetzung, umfassend eine Verbindung nach Anspruch 1 oder 2 und einen pharmazeutisch verträglichen Träger.

4. Pharmazeutische Zusammensetzung zur Verwendung beim Behandeln einer Enterovirus-Infektion, wobei die Zusammensetzung eine wirksame Menge einer Verbindung nach Anspruch 1 oder 2 und einen pharmazeutisch verträglichen Hilfsstoff umfasst;

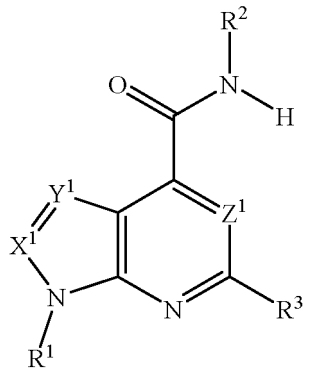
wobei die pharmazeutische Zusammensetzung optional in Einheitsdosisform verpackt ist;
und/oder wobei das Enterovirus optional Coxsackievirus A9, Coxsackievirus A16, Coxsackievirus B1, Coxsackievirus B2, Coxsackievirus B3-H3, Coxsackievirus B4, Coxsackievirus B5, Enterovirus 68, Enterovirus 68, Enterovirus 71, Echovirus 6, Echovirus 7, Echovirus 9, Echovirus 11, Echovirus 18, Echovirus 25, Echovirus 30 ist.

5. Verbindung nach Anspruch 1 oder 2 zur Verwendung in einem Verfahren zum Behandeln eines Patienten oder Tieres, der bzw. das mit einem Enterovirus, Paramyxovirus, Atemwegsvirus, Flaviviridae-Virus, Bunyaviridae-Virus, Togaviridae-Virus oder Tollwutvirus infiziert ist, wobei die Verwendung eine Verabreichung einer wirksamen Menge der Verbindung an den Patienten oder das Tier umfasst;

wobei das Enterovirus optional Coxsackievirus A9, Coxsackievirus A16, Coxsackievirus B1, Coxsackievirus B2, Coxsackievirus B3-H3, Coxsackievirus B4, Coxsackievirus B5, Enterovirus 68, Enterovirus 71, Echovirus 6, Echovirus 7, Echovirus 9, Echovirus 11, Echovirus 18, Echovirus 25 oder Echovirus 30 ist; und/oder
wobei die Verabreichung optional orale Verabreichung, parenterale Verabreichung oder nasale Verabreichung umfasst.

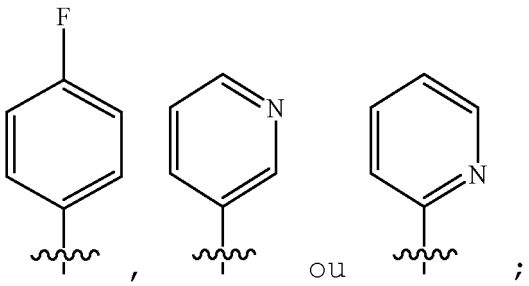
Revendications

1. Composé selon la Formule I :



(I)

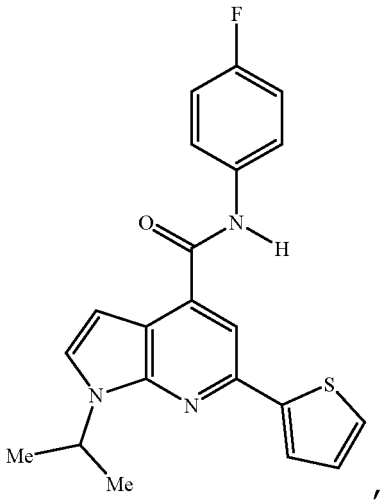
ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel
X^1 est CH, Y^1 est CH et Z^1 est CH ;
R^1 est un alkyle en C_1-C_6 non substitué ;
R^2 est



;

et
R^3 est 2-thiophényle ou 3-thiophényle.

2. Composé selon la revendication 1, dans lequel le composé est :



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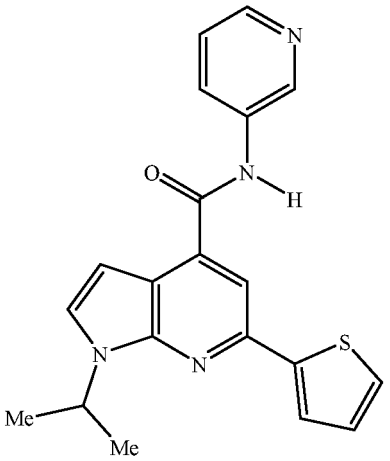

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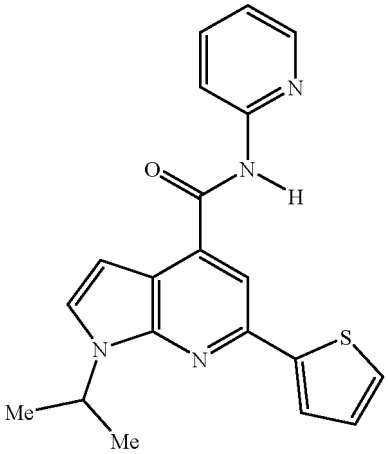

ou un sel pharmaceutiquement acceptable de l'un quelconque de celui-ci.

3. Composition comprenant un composé selon la revendication 1 ou 2, et un support pharmaceutiquement acceptable.

4. Composition pharmaceutique destinée à être utilisée dans le traitement d'une infection à entérovirus, la composition comprenant une quantité efficace d'un composé selon la revendication 1 ou 2 et un excipient pharmaceutiquement acceptable ;

dans laquelle, éventuellement, la composition pharmaceutique est conditionnée sous forme posologique unitaire ;
et/ou dans laquelle, éventuellement, l'entérovirus est Coxsackievirus A9, Coxsackievirus A16, Coxsackievirus B1, Coxsackievirus B2, Coxsackievirus B3-H3, Coxsackievirus B4, Coxsackievirus B5, Enterovirus 68, Enterovirus 68, Enterovirus 71, Echovirus 6, Echovirus 7, Echovirus 9, Echovirus 11, Echovirus 18, Echovirus 25, Echovirus 30.

5. Composé selon la revendication 1 ou 2, destiné à être utilisé dans un procédé de traitement d'un patient ou d'un animal infecté par un entérovirus, un paramyxovirus, un virus respiratoire, un virus des flaviviridae, un virus des bunyaviridae, un virus des togaviridae ou un virus de la rage, l'utilisation comprenant l'administration d'une quantité efficace du composé pour le patient ou l'animal ;

dans lequel, éventuellement, l'entérovirus est Coxsackievirus A9, Coxsackievirus A16, Coxsackievirus B1, Coxsackievirus B2, Coxsackievirus B3-H3, Coxsackievirus B4, Coxsackievirus B5, Enterovirus 68, Enterovirus 71, Echovirus 6, Echovirus 7, Echovirus 9, Echovirus 11, Echovirus 18, Echovirus 25, Echovirus 30 ; et/ou
dans lequel, éventuellement, l'administration comprend l'administration orale, l'administration parentérale ou l'administration nasale.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 2017053604 A **[0005]**
- US 20150164910 A **[0090]**
- US 5942520 A, Pamukcu, R.; Piazza, G. A **[0102]**

Non-patent literature cited in the description

- Enteroviruses and Parechoviruses. **CHERRY, J.D et al.** Textbook of Pediatric Infectious Diseases. WB Saunders Co, 2009, 1984-2041 **[0004]**
- **MCMINN, P et al.** *Clin Infect Dis,* 2001, vol. 32 (2), 236-242 **[0005]**
- **MCMINN, P.C.** *FEMS Microbiol Rev,* 2002, vol. 26 (1), 91-107 **[0005]**
- **SEIFF, A.** *Lancet,* 2012, vol. 380 (9838), 206 **[0005]**
- **VERMA, N.A et al.** *Clin Infect Dis,* 2009, vol. 49 (5), 759-763 **[0005]**
- **WIKSWO, M.E et al.** *Clin Infect Dis,* 2009, vol. 49 (5), e44-e51 **[0005]**
- **GREENE, T.W ; WUTS, P. G. M.** Protective Groups in Organic Synthesis. John Wiley & Sons, 1999 **[0033]**
- Remingtons Pharmaceutical Sciences. Mack Pub. Co, 1991 **[0079]**
- Enteroviruses and Parechoviruses. **CHERRY, J.D. ; KROGSTAD P.K. et al.** Textbook of Pediatric Infectious Diseases. WB Saunders Co, 2009, 1984-2041 **[0102]**
- **MCMINN, P. et al.** Neurological manifestations of enterovirus 71 infection in children during an outbreak of hand, foot, and mouth disease in Western Australia. *Clin Infect Dis,* 2001, vol. 32 (2), 236-42 **[0102]**
- **MCMINN, P.C.** An overview of the evolution of enterovirus 71 and its clinical and public health significance. *FEMS Microbiol Rev,* 2002, vol. 26 (1), 91-107 **[0102]**
- **SEIFF, A.** Cambodia unravels cause of mystery illness. *Lancet,* 2012, vol. 380 (9838), 206 **[0102]**
- **VERMA, N.A. et al.** Outbreak of life-threatening coxsackievirus B1 myocarditis in neonates. *Clin Infect Dis,* 2009, vol. 49 (5), 759-63 **[0102]**
- **WIKSWO, M.E. et al.** Increased activity of Coxsackievirus B1 strains associated with severe disease among young infants in the United States, 2007-2008. *Clin Infect Dis,* 2009, vol. 49 (5), e44-51 **[0102]**
- Notes from the field: severe hand, foot, and mouth disease associated with coxsackievirus A6 - Alabama, Connecticut, California, and Nevada, November 2011-February 2012. *MMWR Morb Mortal Wkly Rep,* 2012, vol. 61 (12), 213-4 **[0102]**
- **FLETT, K. et al.** Hand, foot, and mouth disease caused by coxsackievirus a6. *Emerg Infect Dis,* 2012, vol. 18 (10), 1702-4 **[0102]**
- **MATHES, E.F. et al.** Eczema Coxsackium'' and Unusual Cutaneous Findings in an Enterovirus Outbreak. *Pediatrics,* 2013 **[0102]**
- Nonpolio enterovirus and human parechovirus surveillance --- United States, 2006-2008. *MMWR Morb Mortal Wkly Rep,* 2010, vol. 59 (48), 1577-80 **[0102]**
- Progress toward interruption of wild poliovirus transmission - worldwide, january 2011-march 2012. *MMWR Morb Mortal Wkly Rep,* 2012, vol. 61, 353-7 **[0102]**
- **DE PALMA, A.M. et al.** Selective inhibitors of picornavirus replication. *Med Res Rev,* 2008, vol. 28 (6), 823-84 **[0102]**
- **MACKY, M. ; NORTCLIFFE, A ; MCNAB, H ; HULME, A. N.** *Gas-Phase Synthesis of Pyrazolo[3,4-b]pyridin-4-ones Synthesis,* 2015, vol. 47 (2), 242-248 **[0102]**
- **JI, N. ; MEREDITH, E ; LIU, D ; ADAMS, C. M ; ARTMAN, G. D., III ; JENDZA, K. C. ; MA, F ; MAINOLFI, N ; POWERS, J. J ; ZHANG, C.** *Synthesis of 1-substituted-3-aminopyrazoles Tetrahedron Letters,* 2010, vol. 51 (52), 6799-6801 **[0102]**
- **CHEN, H ; KNERR, L ; AAKERUD, T ; HALLBERG, K ; OESTER, L ; ROHMAN, M. ; OESTERLUND, K ; BEISEL, H.-G ; OLSSON, T ; BRENGDHAL, J et al.** *Discovery of a novel pyrazole series of group X secreted phospholipase A2 inhibitor (sPLA2X) via fragment based virtual screening Bioorganic & Medicinal Chemistry Letters,* 2014, vol. 24 (22), 5251-5255 **[0102]**