Antiviral Drugs for Treatment or Prevention of Dengue Infection

CROSS REFERENCE TO RELATED APPLICATIONS

[00001] This application claims priority to and benefit of U.S. Provisional Application No. 60/924,628, filed May 23, 2007, the contents of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[00002] This invention relates to the use of benzenesulfonamide derivatives and analogs, as well as compositions containing the same, for the treatment or prophylaxis of viral diseases associated with the flavivirus family such as Dengue fever, Yellow fever, West Nile, St. Louis encephalitis, Hepatitis C, Murray Valley encephalitis, and Japanese encephalitis.

BACKGROUND OF THE INVENTION

[00003] Dengue fever (DF) is an acute febrile disease caused by one of four closely related virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). Dengue fever is classified based on its clinical characteristics into classical dengue fever, or the more severe forms, dengue hemorrhagic fever syndrome (DHF), and dengue shock syndrome (DSS). Recovery from infection from one serotype produces life-long immunity to that particular serotype, but provides only short-lived and limited protection against any of the other serotypes (37). Dengue is a member of the *Flaviviridae* family which are enveloped, positive-sense RNA viruses whose human pathogens also include West Nile virus (WNV), yellow fever virus (YFV), Japanese encephalitis virus (JEV), and tick-borne encephalitis virus (TBEV) among others. Dengue

transmission is via the bite of an infected *Aedes aegypti* mosquito which is found in tropical and sub-tropical regions around the world.

[00004] Each year regional epidemics of dengue cause significant morbidity and mortality, social disruption and substantial economic burden on the societies affected both in terms of hospitalization and mosquito control. Dengue is considered by the World Health Organization (WHO) to be the most important arthropod-borne viral disease with an estimated 50 million cases of dengue infection, including 500,000 DHF cases and 24,000 deaths worldwide each year (37, 38). WHO estimates that forty percent of the world's population (2.5 billion people) are at risk for DF, DHF, and DSS (37). Dengue is also a NIAID Category A pathogen and in terms of bio-defense, represents a significant threat to United States troops overseas. Dengue is an emerging threat to North America with a dramatic increase in severe disease in the past 25 years including major epidemics in Cuba and Venezuela, and outbreaks in Texas and Hawaii (4). Failure to control the mosquito vector and increases in long-distance travel have contributed to the increase and spread of dengue disease. The characteristics of dengue as a viral hemorrhagic fever virus (arthropod-borne, widely spread, and capable of inducing a great amount of cellular damage and eliciting an immune response that can result in severe hemorrhage, shock, and death) makes this virus a unique threat to deployed military personnel around the world as well as to travelers to tropical regions. Preparedness for both biodefense and for the public health challenges posed by dengue will require the development of new vaccines and antiviral therapeutics.

[00005] Dengue causes several illnesses with increasing severity being determined in part by prior infection with a different serotype of the virus. Classic dengue fever (DF) begins 3-8 days after the bite of an infected mosquito and is characterized by sudden onset of fever, headache, back pain, joint pain, a measles-like rash, and nausea and vomiting (21). DF is frequently referred to as "breakbone" fever due to these symptoms. The disease usually resolves after two weeks but a prolonged recovery with weakness and depression is common. The more severe form of the disease, dengue hemorrhagic fever (DHF) has a similar onset and early phase of illness as dengue fever. However, shortly after onset the disease is characterized by high fever, enlargement of the liver, and hemorrhagic phenomena such as bleeding from the nose, mouth, and internal organs due to vascular permeability (38). In dengue shock syndrome (DSS) circulatory failure and hypovolaemic shock resulting from plasma leakage occur and can lead to death in 12-24 hours without plasma replacement (38). The case fatality rate of DHF/DSS can be as high as 20% without treatment. DHF has become a leading cause of hospitalization and death among children in many countries with an estimated 500,000 cases requiring hospitalization each year and a case fatality rate of about 5%(37).

[00006] The pathogenesis of DHF/DSS is still being studied but is thought to be due in part to an enhancement of virus replication in macrophages by heterotypic antibodies, termed antibody-dependent enhancement (ADE) (8). During a secondary infection, with a different serotype of dengue virus, cross-reactive antibodies that are not neutralizing form virus-antibody complexes that are taken into monocytes and Langerhans cells (dendritic

cells) and increase the number of infected cells (7). This leads to the activation of cytotoxic lymphocytes which can result in plasma leakage and the hemorrhagic features characteristic of DHF and DSS (21). This antibody-dependent enhancement of infection is one reason why the development of a successful vaccine has proven to be so difficult. Although less frequent, DHF/DSS can occur after primary infection (33), so virus virulence (16) and immune activation are also believed to contribute to the pathogenesis of the disease (26).

[00007] Dengue is endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, South-east Asia and the Western Pacific. During epidemics, attack rates can be as high as 80-90% of the susceptible population. All four serotypes of the virus are emerging worldwide, increasing the number of cases of the disease as well as the number of explosive outbreaks. In 2002 for example, there were 1,015,420 reported cases of dengue in the Americas alone with 14,374 cases of DHF, which is more than three times the number of dengue cases reported in the Americas in 1995 (24).

[00008] The dengue genome, approximately 11 kb in length, consists of a linear, single stranded, infectious, positive sense RNA that is translated as a single long polyprotein (reviewed in (29). The genome is composed of seven nonstructural (NS) protein genes and three structural protein genes which encode the nucleocapsid protein (C), a membrane-associated protein (M), and an envelope protein (E). The nonstructural proteins are involved in viral RNA replication (35), viral assembly, and the inflammatory components of the disease (19). The structural proteins are involved mainly in viral particle formation (22). The precursor polyprotein is cleaved by

cellular proteinases to separate the structural proteins (18), while a virus-encoded proteinase cleaves the nonstructural region of the polyprotein (6). The genome is capped and does not have a poly(A) tail at the 3′ end but instead has a stable stem-loop structure necessary for stability and replication of the genomic RNA (3). The virus binds to cellular receptors via the E protein and undergoes receptor-mediated endocytosis followed by low-pH fusion in lysosomes (20). The viral genome is then uncoated and translated into the viral precursor polyprotein. Co- and posttranslational proteolytic processing separates the structural and nonstructural proteins. The RNA-dependent RNA polymerase along with cofactors synthesizes the minus-strand RNA which serves as a template for the synthesis of the progeny plus-strand RNA (25). Viral replication is membrane associated (1, 34). Following replication, the genome is encapsidated, and the immature virus, surrounded by a lipid envelope buds into the lumen (9). The envelope proteins become glycosylated and mature viruses are released outside the cell. Essential stages or process during the virus life cycle would be possible targets for inhibition from an antiviral drug and include binding of the virus to the cell through the E protein, uptake of the virus into the cell, the capping mechanism, the viral proteinase, the viral RNA-dependent RNA polymerase, and the viral helicase.

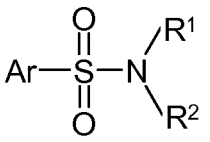
[00009] Current management of dengue virus-related disease relies solely on vector control. There are no approved antivirals or vaccines for the treatment or prevention of dengue. Ribavirin, a guanosine analogue, has been shown to be effective against a range of RNA virus infections and works against dengue in tissue culture by

inhibiting the dengue 2'-O-methyltransferase NS5 domain (2, 10). However, ribavirin did not show protection against dengue in a mouse model (15) or a rhesus monkey model (17), instead it induced anemia and thrombocytosis. While there are no currently available approved vaccines, multivalent dengue vaccines have shown some limited potential in humans (5, 12, 13, 28). However, vaccine development is difficult due to the presence of four distinct serotypes of the virus which each cause disease. Vaccine development also faces the challenge of ADE where unequal protection against the different strains of the virus could actually increase the risk of more serious disease. Therefore there is a need for antiviral drugs that target all of the serotypes of dengue. An antiviral drug administered early during dengue infection that inhibits viral replication would prevent the high viral load associated with DHF and be an attractive strategy in the treatment and prevention of disease. An antiviral drug that inhibits viral replication could be administered prior to travel to a dengue endemic region to prevent acquisition of disease, or for those that have previously been exposed to dengue, could prevent infection by another serotype of virus and decrease the chance of life-threatening DHF and DSS. Having an antiviral drug would also aid vaccine development by having a tool at hand to treat complications that may arise due to unequal immune protection against the different serotypes. Although a successful vaccine could be a critical component of an effective biodefense, the typical delay to onset of immunity, potential side-effects, cost, and logistics associated with large-scale civilian vaccinations against a low-threat risk agent suggest that a comprehensive biodefense include a separate rapid-response element.

Thus, there remains an urgent need to develop a safe and effective product to protect against flavivirus infection.

SUMMARY OF THE INVENTION

[000010] The present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the following general formula I or a pharmaceutically acceptable salt thereof:



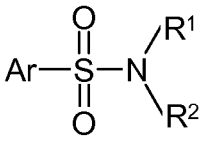
wherein R^1 and R^2 are independently hydrogen, alkyl, alkenyl, alkynyl, or unsubstituted or substituted cycloalkyl, arylalkyl, aryl, or R^1 and R^2 together may form a substituted or unsubstituted ring, which may include one or more heteroatoms in the ring; and

Ar is substituted or unsubstituted aryl or heteroaryl;

said cycloalkyl, arylalkyl, and aryl group substituents being one or more radical(s) independently selected from the group consisting of a straight- or branched chain alkyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, halogen, polyfluoroalkyl, polyfluoroalkoxy, carboxy, cyano, nitro, amido, amidoalkyl, carboxamide, alkylthio, alkylsulfinyl, alkylsulfonyl, sulfonamide, and mercapto.

[000011] The present invention also provides a method for the treatment or prophylaxis of a viral infection or disease associated therewith, comprising administering in a therapeutically effective amount to a mammal in need

thereof, a compound of Formula I below or a pharmaceutically acceptable salt thereof:



wherein R^1 and R^2 are independently hydrogen, alkyl, alkenyl, alkynyl, or unsubstituted or substituted cycloalkyl, arylalkyl, aryl, or R^1 and R^2 together may form a substituted or unsubstituted ring, which may include one or more heteroatoms in the ring; and

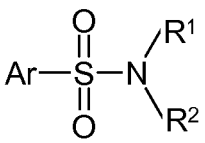
Ar is substituted or unsubstituted aryl or heteroaryl;

said cycloalkyl, arylalkyl, and aryl group substituents being one or more radical(s) independently selected from the group consisting of a straight- or branched chain alkyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, halogen, polyfluoroalkyl, polyfluoroalkoxy, carboxy, cyano, nitro, amido, amidoalkyl, carboxamide, alkylthio, alkylsulfinyl, alkylsulfonyl, sulfonamide, and mercapto.

[000012] Other objects and advantages of the present invention will become apparent from the following description and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

[000013] The compounds of the invention are of the following general Formula I:



wherein R^1 and R^2 are independently hydrogen, alkyl, alkenyl, alkynyl, or unsubstituted or substituted cycloalkyl, arylalkyl, aryl, or R^1 and R^2 together may form a substituted or unsubstituted ring, which may include one or more heteroatoms in the ring; and

Ar is substituted or unsubstituted aryl or heteroaryl;

said cycloalkyl, arylalkyl, and aryl group substituents being one or more radical(s) independently selected from the group consisting of a straight- or branched chain alkyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, halogen, polyfluoroalkyl, polyfluoroalkoxy, carboxy, cyano, nitro, amido, amidoalkyl, carboxamide, alkylthio, alkylsulfinyl, alkylsulfonyl, sulfonamide, and mercapto.

[000014] Preferably each of R^1 and R^2 is an ethyl. Also preferably, Ar is a mono-substituted phenyl such as amido-phenyl. Examples of amido-phenyl include isobutyramidophenyl, *p*-[2-(4-oxo-4H-quinazolin-3-yl)-acetamido]-phenyl and *p*-[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetamido]-phenyl. Again preferably, Ar is a di-substituted phenyl with one substituent as amido and the other one as methoxy. Examples of this type of phenyl include *m*-phenyl-acetamido-*p*-methoxy-phenyl and *m*-(3-methyl-butyramido)-*p*-methoxy-phenyl.

[000015] Most preferably, the compound of Formula I is N-(4-Diethylsulfamoyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide. Exemplary compounds according to the invention are shown below in Table 1.

[000016] The method of the present invention is for the treatment or prophylaxis of a viral infection or disease

associated therewith, comprising administering in a therapeutically effective amount to a mammal in need thereof, a compound of Formula I described above.

[000017] Preferably, the mammal is a human and the viral infection is a flavivirus infection. More preferably, the flavivirus virus is selected from the group consisting of Dengue virus, West Nile virus, yellow fever virus, Japanese encephalitis virus, and tick-borne encephalitis virus. Most preferably, the flavivirus is a Dengue virus selected from the group consisting of DEN-1, DEN-2, DEN-3, and DEN-4.

[000018] Preferably, the viral infection is associated with a condition selected from the group consisting of Dengue fever, Yellow fever, West Nile, St. Louis encephalitis, Hepatitis C, Murray Valley encephalitis, and Japanese encephalitis. Most preferably, the viral infection is associated with Dengue fever wherein said Dengue fever is selected from the group consisting of classical dengue fever, dengue hemorrhagic fever syndrome, and dengue shock syndrome.

[000019] The method of the present invention may also comprise co-administration of: a)other antivirals such as Ribavirin or cidofovir; b) vaccines; and/or c) interferons or pegylated interferons.

Definitions

[000020] In accordance with this detailed description, the following abbreviations and definitions apply. It must be noted that as used herein, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

[000021] The publications discussed herein are provided solely for their disclosure. Nothing herein is to be construed as an admission regarding antedating the publications. Further, the dates of publication provided may be different from the actual publication dates, which may need to be independently confirmed.

[000022] Where a range of values is provided, it is understood that each intervening value is encompassed. The upper and lower limits of these smaller ranges may independently be included in the smaller, subject to any specifically-excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the invention. Also contemplated are any values that fall within the cited ranges.

[000023] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. Any methods and materials similar or equivalent to those described herein can also be used in practice or testing. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[000024] By "patient" or "subject" is meant to include any mammal. A "mammal," for purposes of treatment, refers to any animal classified as a mammal, including but not limited to, humans, experimental animals including rats, mice, and guinea pigs, domestic and farm animals, and zoo,

sports, or pet animals, such as dogs, horses, cats, cows, and the like.

[000025] The term "efficacy" as used herein in the context of a chronic dosage regime refers to the effectiveness of a particular treatment regime. Efficacy can be measured based on change of the course of the disease in response to an agent.

[000026] The term "success" as used herein in the context of a chronic treatment regime refers to the effectiveness of a particular treatment regime. This includes a balance of efficacy, toxicity (*e.g.*, side effects and patient tolerance of a formulation or dosage unit), patient compliance, and the like. For a chronic administration regime to be considered "successful" it must balance different aspects of patient care and efficacy to produce a favorable patient outcome.

[000027] The terms "treating," "treatment," and the like are used herein to refer to obtaining a desired pharmacological and physiological effect. The effect may be prophylactic in terms of preventing or partially preventing a disease, symptom, or condition thereof and/or may be therapeutic in terms of a partial or complete cure of a disease, condition, symptom, or adverse effect attributed to the disease. The term "treatment," as used herein, covers any treatment of a disease in a mammal, such as a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it, *i.e.*, causing the clinical symptoms of the disease not to develop in a subject that may be predisposed to the

disease but does not yet experience or display symptoms of the disease; (b) inhibiting the disease, *i.e.*, arresting or reducing the development of the disease or its clinical symptoms; and (c) relieving the disease, *i.e.*, causing regression of the disease and/or its symptoms or conditions. Treating a patient's suffering from disease related to pathological inflammation is contemplated. Preventing, inhibiting, or relieving adverse effects attributed to pathological inflammation over long periods of time and/or are such caused by the physiological responses to inappropriate inflammation present in a biological system over long periods of time are also contemplated.

[000028] "Alkenyl" refers to alkenyl group preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation.

[000029] "Alkoxy" refers to the group "alkyl-O-" which includes, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

[000030] "Alkyl" refers to linear or branched alkyl groups having from 1 to 10 carbon atoms, alternatively 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, t-butyl, n-heptyl, octyl and the like. "Amino" refers to the group $-NH_2$.

[000031] "Aryl" or "Ar" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl or anthryl) which condensed rings may or

may not be aromatic (*e.g.*, 2-benzoxazolinone, 2H-1,4-benzoxazin-3(4H)-one, and the like) provided that the point of attachment is through an aromatic ring atom. "Substituted aryl" refers to aryl groups which are substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-S(O)_2$-alkyl, $-S(O)_2$-substituted alkyl, $-S(O)_2$-cycloalkyl, $-S(O)_2$-substituted cycloalkyl, $-S(O)_2$-alkenyl, $-S(O)_2$-substituted alkenyl, $-S(O)_2$-aryl, $-S(O)_2$-substituted aryl, $-S(O)_2$-heteroaryl, $-S(O)_2$-substituted heteroaryl, $-S(O)_2$-heterocyclic, $-S(O)_2$-

substituted heterocyclic, -OS(O)$_2$-alkyl, -OS(O)$_2$-substituted alkyl, -OS(O)$_2$-aryl, -OS(O)$_2$-substiruted aryl, -OS(O)$_2$-heteroaryl, -OS(O)$_2$-substituted heteroaryl, -OS(O)$_2$-heterocyclic, -OS(O)$_2$- substituted heterocyclic, -OS(O)$_2$-NRR where R is hydrogen. or alkyl, -NRS(O)$_2$- alkyl, -NRS(O)$_2$-substituted alkyl, -NRS(O)$_2$-aryl, -NRS(O)$_2$-substituted aryl, -NRS(O)$_2$-heteroaryl, -NRS(O)$_2$-substituted heteroaryl, -NRS(O)$_2$-heterocyclic, -NRS(O)$_2$-substituted heterocyclic, -NRS(O)$_2$-NR-alkyl, -NRS(O)$_2$-NR-substituted alkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substiruted aryl, -NRS(O)$_2$-NR-heteroaryl, - NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substiruted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with -SO$_2$NRR where R is hydrogen or alkyl.

[000032] "Cycloalkyl" refers to cyclic alkyl groups of from 3 to 8 carbon atoms having a single cyclic ring including, by way of example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl and the like. Excluded from this definition are multi-ring alkyl groups such as adamantanyl, etc.

[000033] "Halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

[000034] "Heteroaryl" refers to an aromatic carbocyclic group of from 2 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within the ring or oxides thereof. Such heteroaryl groups can have a single ring (*e.g.*, pyridyl or furyl) or multiple condensed rings (*e.g.*, indolizinyl or benzothienyl) wherein one or more of the condensed rings may or may not be aromatic provided that the point of attachment is through an aromatic ring atom. Additionally, the heteroatoms of the heteroaryl group may be oxidized, *i.e.*, to form pyridine N-oxides or 1,1-dioxo-1,2,5-thiadiazoles and the like. Additionally, the carbon atoms of the ring may be substituted with an oxo (=O). The term "heteroaryl having two nitrogen atoms in the heteroaryl, ring" refers to a heteroaryl group having two, and only two, nitrogen atoms in the heteroaryl ring and optionally containing 1 or 2 other heteroatoms in the heteroaryl ring, such as oxygen or sulfur.

[000035] "Substituted heteroaryl" refers to heteroaryl groups which are substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl,

carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-S(O)_2$-alkyl, $-S(O)_2$-substituted alkyl, $-S(O)_2$-cycloalkyl, $-S(O)_2$-substituted cycloalkyl, $-S(O)_2$-alkenyl, $-S(O)_2$-substituted alkenyl, $-S(O)_2$-aryl, $-S(O)_2$-substituted aryl, $-S(O)_2$-heteroaryl, $-S(O)_2$-substituted heteroaryl, $-S(O)_2$-heterocyclic,$-S(O)_2$-substituted heterocyclic, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$- heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where R is hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substiruted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-

substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with $-SO_2NRR$ where R is hydrogen or alkyl.

[000036] "Sulfonyl" refers to the group $-S(O)_2R$ where R is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[000037] "Pharmaceutically-acceptable carrier" means a carrier that is useful in preparing a pharmaceutical composition or formulation that is generally safe, non-toxic, and neither biologically nor otherwise undesirable, and includes a carrier that is acceptable for veterinary use as well as human pharmaceutical use. A pharmaceutically-acceptable carrier or excipient includes both one or more than one of such carriers.

[000038] "Pharmaceutically-acceptable cation" refers to the cation of a pharmaceutically-acceptable salt. "Pharmaceutically-acceptable salt" refers to salts which retain the biological effectiveness and properties of compounds which are not biologically or otherwise undesirable. Pharmaceutically-acceptable salts refer to pharmaceutically-acceptable salts of the compounds, which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

[000039] Pharmaceutically-acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases, include by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl) amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines, substituted cycloalkyl amines, disubstituted cycloalkyl amine, trisubstituted cycloalkyl amines, cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines, disubstituted cycloalkenyl amine, trisubstituted cycloalkenyl amines,

aryl amines, diaryl amines, triaryl amines, heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic amines, triheterocyclic amines, mixed di- and tri-amines where at least two of the substituents on the amine are different and are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, and the like. Also included are amines where the two or three substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group.

[000040] Examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like. It should also be understood that other carboxylic acid derivatives would be useful, for example, carboxylic acid amides, including carboxamides, lower alkyl carboxamides, dialkyl carboxamides, and the like.

[000041] Pharmaceutically-acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid,

citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like.

[000042] A compound may act as a pro-drug. Pro-drug means any compound which releases an active parent drug *in vivo* when such pro-drug is administered to a mammalian subject. Pro-drugs are prepared by modifying functional groups present in such a way that the modifications may be cleaved *in vivo* to release the parent compound. Prodrugs include compounds wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (*e.g.*, acetate, formate, and benzoate derivatives), carbamates (*e.g.*, N,N-dimethylamino-carbonyl) of hydroxy functional groups, and the like.

[000043] "Treating" or "treatment" of a disease includes:
(1) preventing the disease, *i.e.* causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,
(2) inhibiting the disease, *i.e.*, arresting or reducing the development of the disease or its clinical symptoms, or
(3) relieving the disease, *i.e.*, causing regression of the disease or its clinical symptoms.

[000044] A "therapeutically-effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically-effective amount" will vary depending on the compound, the disease,

and its severity and the age, weight, etc., of the mammal to be treated.

Pharmaceutical Formulations of the Compounds

[000045] In general, compounds will be administered in a therapeutically-effective amount by any of the accepted modes of administration for these compounds. The compounds can be administered by a variety of routes, including, but not limited to, oral, parenteral (*e.g.*, subcutaneous, subdural, intravenous, intramuscular, intrathecal, intraperitoneal, intracerebral, intraarterial, or intralesional routes of administration), topical, intranasal, localized (*e.g.*, surgical application or surgical suppository), rectal, and pulmonary (*e.g.*, aerosols, inhalation, or powder). Accordingly, these compounds are effective as both injectable and oral compositions. The compounds can be administered continuously by infusion or by bolus injection. The actual amount of the compound, *i.e.*, the active ingredient, will depend on a number of factors, such as the severity of the disease, *i.e.*, the condition or disease to be treated, age, and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors.

[000046] Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}.

[000047] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds

lies within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used, the therapeutically-effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range which includes the IC_{50} (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

[000048] The amount of the pharmaceutical composition administered to the patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions are administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as "therapeutically-effective dose." Amounts effective for this use will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the inflammation, the age, weight, and general condition of the patient, and the like.
The compositions administered to a patient are in the form of 24 pharmaceutical compositions described *supra*. These compositions may be sterilized by conventional

sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

[000049] The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically- or therapeutically-effective amount. The therapeutic dosage of the compounds will vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. For example, for intravenous administration, the dose will typically be in the range of about 0.5 mg to about 100 mg per kilogram body weight. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems. Typically, the clinician will administer the compound until a dosage is reached that achieves the desired effect.

When employed as pharmaceuticals, the compounds are usually administered in the form of pharmaceutical compositions. Pharmaceutical compositions contain as the active ingredient one or more of the compounds above, associated with one or more pharmaceutically-acceptable carriers or excipients. The excipient employed is typically one suitable for administration to human subjects or other mammals. In making the compositions, the active ingredient is usually mixed with an excipient, diluted by an excipient, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or

other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier, or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

[000050] In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, *e.g.*, about 40 mesh. Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained, or delayed-

release of the active ingredient after administration to the patient by employing procedures known in the art.

[000051] The quantity of active compound in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the manner or introduction, the potency of the particular compound, and the desired concentration. The term "unit dosage forms" refers to physically-discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

[000052] The compound can be formulated for parenteral administration in a suitable inert carrier, such as a sterile physiological saline solution. The dose administered will be determined by route of administration.
Administration of therapeutic agents by intravenous formulation is well known in the pharmaceutical industry. An intravenous formulation should possess certain qualities aside from being just a composition in which the therapeutic agent is soluble. For example, the formulation should promote the overall stability of the active ingredient(s), also, the manufacture of the formulation should be cost-effective. All of these factors ultimately determine the overall success and usefulness of an intravenous formulation.

[000053] Other accessory additives that may be included in pharmaceutical formulations and compounds as follow: solvents: ethanol, glycerol, propylene glycol; stabilizers: EDTA (ethylene diamine tetraacetic acid),

citric acid; antimicrobial preservatives: benzyl alcohol, methyl paraben, propyl paraben; buffering agents: citric acid/sodium citrate, potassium hydrogen tartrate, sodium hydrogen tartrate, acetic acid/sodium acetate, maleic acid/sodium maleate, sodium hydrogen phthalate, phosphoric acid/potassium dihydrogen phosphate, phosphoric acid/disodium hydrogen phosphate; and tonicity modifiers: sodium chloride, mannitol, dextrose.

[000054] The presence of a buffer is necessary to maintain the aqueous pH in the range of from about 4 to about 8. The buffer system is generally a mixture of a weak acid and a soluble salt thereof, *e.g.*, sodium citrate/citric acid; or the monocation or dication salt of a dibasic acid, *e.g.*, potassium hydrogen tartrate; sodium hydrogen tartrate, phosphoric acid/potassium dihydrogen phosphate, and phosphoric acid/disodium hydrogen phosphate.

[000055] The amount of buffer system used is dependent on (1) the desired pH; and (2) the amount of drug. Generally, the amount of buffer used is in a 0.5:1 to 50:1 mole ratio of buffenalendronate (where the moles of buffer are taken as the combined moles of the buffer ingredients, *e.g.*, sodium citrate and citric acid) of formulation to maintain a pH in the range of 4 to 8 and generally, a 1:1 to 10:1 mole ratio of buffer (combined) to drug present is used.
A useful buffer is sodium citrate/citric acid in the range of 5 to 50 mg per ml. sodium citrate to 1 to 15 mg per ml. citric acid, sufficient to maintain an aqueous pH of 4-6 of the composition.

[000056] The buffer agent may also be present to prevent the precipitation of the drug through soluble metal

complex formation with dissolved metal ions, *e.g.*, Ca, Mg, Fe, Al, Ba, which may leach out of glass containers or rubber stoppers or be present in ordinary tap water. The agent may act as a competitive complexing agent with the drug and produce a soluble metal complex leading to the presence of undesirable particulates.

[000057] In addition, the presence of an agent, *e.g.*, sodium chloride in an amount of about of 1-8 mg/ml, to adjust the tonicity to the same value of human blood may be required to avoid the swelling or shrinkage of erythrocytes upon administration of the intravenous formulation leading to undesirable side effects such as nausea or diarrhea and possibly to associated blood disorders. In general, the tonicity of the formulation matches that of human blood which is in the range of 282 to 288 mOsm/kg, and in general is 285 mOsm/kg, which is equivalent to the osmotic pressure corresponding to a 0.9% solution of sodium chloride.

[000058] An intravenous formulation can be administered by direct intravenous injection, i.v. bolus, or can be administered by infusion by addition to an appropriate 'infusion solution such as 0.9% sodium chloride injection or other compatible infusion solution.

[000059] The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to

produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

[000060] The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.
For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 2000 mg of the active ingredient.

[000061] The tablets or pills may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in

the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[000062] The liquid forms in which the novel compositions may be incorporated for administration orally or by injection include aqueous solutions suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

[000063] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically-acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically-acceptable excipients as described *supra*. Compositions in pharmaceutically-acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered from devices which deliver the formulation in an appropriate manner.

[000064] The compounds can be administered in a sustained release form. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the compounds, which

matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (*e.g.*, poly(2- hydroxyethyl-methacrylate) as described by Langer *et al.*, *J. Biomed. Mater. Res.* 15: 167-277 (1981) and Langer, *Chem. Tech.* 12: 98-105 (1982) or poly(vinyl alcohol)), polylactides (U.S. Patent No. 3,773,919), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman *et al.*, *Biopolymers* 22: 547-556, 1983), non-degradable ethylene-vinyl acetate (Langer *et al.*, *supra*), degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (*i.e.*, injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid (EP 133,988).

[000065] The compounds can be administered in a sustained-release form, for example a depot injection, implant preparation, or osmotic pump, which can be formulated in such a manner as to permit a sustained-release of the active ingredient. Implants for sustained-release formulations are well-known in the art. Implants may be formulated as, including but not limited to, microspheres, slabs, with biodegradable or non-biodegradable polymers. For example, polymers of lactic acid and/or glycolic acid form an erodible polymer that is well-tolerated by the host.

[000066] Transdermal delivery devices ("patches") may also be employed. Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.*, U.S. Patent No. 5,023,252, issued June 11, 1991, herein incorporated

by reference. Such patches may be constructed for continuous, pulsatile, or on-demand delivery of pharmaceutical agents.

Direct or indirect placement techniques may be used when it is desirable or necessary to introduce the pharmaceutical composition to the brain. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system used for the transport of biological factors to specific anatomical regions of the body is described in U.S. Patent No. 5,011,472, which is herein incorporated by reference. Indirect techniques usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid-soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

[000067] In order to enhance serum half-life, the compounds may be encapsulated, introduced into the lumen of liposomes, prepared as a colloid, or other conventional techniques may be employed which provide an extended serum half-life of the compounds. A variety of methods are available for preparing liposomes, as described in, *e.g.*, *Szoka et al.*, U.S. Patent Nos. 4,235,871, 4,501,728 and 4,837,028 each of which is incorporated herein by reference.

[000068] Pharmaceutical compositions are suitable for use in a variety of drug delivery systems. Suitable formulations for use in the present invention are found in *Remington's Pharmaceutical Sciences*, Mace Publishing Company, Philadelphia, PA, 17th ed. (1985).

[000069] The provided compounds and pharmaceutical compositions show biological activity in treating and preventing viral infections and associated diseases, and, accordingly, have utility in treating viral infections and associated diseases, such as Hemorrhagic fever viruses, in mammals including humans.

[000070] Hemorrhagic fever viruses (HFVs) are RNA viruses that cause a variety of disease syndromes with similar clinical characteristics. HFVs that are of concern as potential biological weapons include but are not limited to: Arenaviridae (Junin, Machupo, Guanarito, Sabia, and Lassa), Filoviridae (Ebola and Marburg viruses), Flaviviridae (yellow fever, Omsk hemorrhagic fever and Kyasanur Forest disease viruses), and Bunyaviridae (Rift Valley fever and Crimean-Congo hemorrhagic fever). The naturally-occurring arenaviruses and potential engineered arenaviruses are included in the Category A Pathogen list according to the Centers for Disease Control and Prevention as being among those agents that have greatest potential for mass casualties.

[000071] Risk factors include: travel to Africa or Asia, handling of animal carcasses, contact with infected animals or people, and/or arthropod bites. Arenaviruses are highly infectious after direct contact with infected blood and/or bodily secretions. Humans usually become infected through contact with infected rodents, the bite

of an infected arthropod, direct contact with animal carcasses, inhalation of infectious rodent excreta and/or injection of food contaminated with rodent excreta. The Tacaribe virus has been associated with bats. Airborne transmission of hemorrhagic fever is another mode. Person-to-person contact may also occur in some cases.

[000072] All of the hemorrhagic fevers exhibit similar clinical symptoms. However, in general the clinical manifestations are non-specific and variable. The incubation period is approximately 7-14 days. The onset is gradual with fever and malaise, tachypnea, relative bradycardia, hypotension, circulatory shock, conjunctival infection, pharyngitis, lymphadenopathy, encephalitis, myalgia, back pain, headache and dizziness, as well as hyperesthesia of the skin. Some infected patients may not develop hemorrhagic manifestations.

[000073] Methods of diagnosis at specialized laboratories include antigen detection by antigen-capture enzyme-linked immunosorbent assay (ELISA), IgM antibody detection by antibody-capture enzyme-linked immunosorbent assay, reverse transcriptase polymerase chain reaction (RT-PCR), and viral isolation. Antigen detection (by enzyme-linked immunosorbent assay) and reverse transcriptase polymerase chain reaction are the most useful diagnostic techniques in the acute clinical setting. Viral isolation is of limited value because it requires a biosafety level 4 (BSL-4) laboratory.

Example 1 - Determining Anti Dengue-2 Activity of Compounds of the Invention:

[000074] A sensitive and reproducible high-throughput screening (HTS) assay has been established to measure

dengue virus-induced cytopathic effect (CPE). To determine the amount of dengue virus stock required to produce complete CPE in 5 days, Vero cell monolayers were seeded on 96-well plates and infected with 10-fold serial dilutions of the dengue virus stock representing a multiplicity of infection (MOI) of approximately 0.001 PFU/cell to 0.1 PFU/cell. At 5 days post-infection, the cultures were fixed with 5% glutaraldehyde and stained with 0.1% crystal violet. Virus-induced CPE was quantified spectrophometrically at OD_{570}. From this analysis, an MOI of 0.1 PFU/cell of dengue virus stock was chosen for use in the HTS assay. To establish the signal-to-noise ratio (S/N) of the 96-well assay and evaluate the well-to-well and assay-to-assay variability, five independent experiments were performed. Vero cell monolayers were infected with 0.1 PFU/cell of dengue virus stock. Each plate contained the following controls: quadruplicate virus-infected wells, quadruplicate uninfected cell wells and a dose response curve in duplicate for ribavirin at 500, 250, 125 and 62 µM, as reference standards. At day 5 post-infection, the plates were processed as described above.

[000075] Compounds were dissolved in DMSO and diluted in medium such that the final concentration in each well was 5 µM compound and 0.5% DMSO. The compounds were added robotically to the culture medium using the PerkinElmer MultiPROBE® II HT PLUS robotic system. Following compound addition, cultures were infected with dengue virus (DEN-2 strain New Guinea C). After 5 days incubation, plates were processed and CPE quantified on a PerkinElmer EnVision II plate reader system.

[000076] The results of these experiments indicated that the 96-well assay format is robust and reproducible. The S/N ratio (ratio of signal of cell control wells (signal) to virus control wells (noise)) was 5.0 ± 1.2. The well-to-well variability was determined for each individual plate and found to have a coefficient of variance of less than 10% for both positive control and negative control wells, and overall assay-to-assay variability was less than 15%. Using this assay, the EC_{50} values for ribavirin were determined to be 125 ± 25 μM, respectively. The effectiveness of ribavirin against dengue varies with the cell type used, but the values obtained were within the range of published values for this compound (2, 14, 32). Taken together, these results show that a sensitive and reproducible HTS assay has been successfully developed to evaluate our compound library for inhibitors of dengue virus replication.

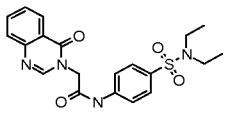
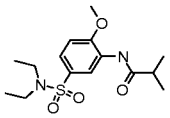
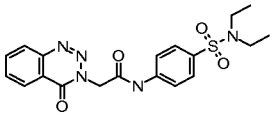
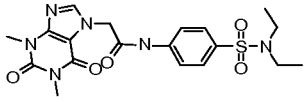
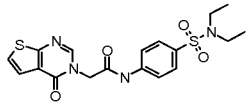
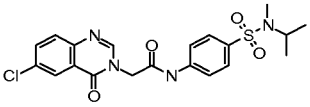
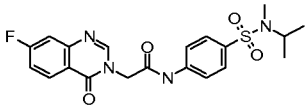
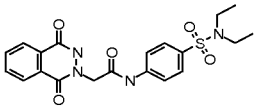
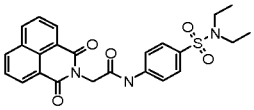
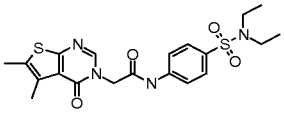
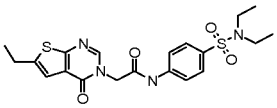
[000077] This assay was the basis of a high-throughput screen for dengue virus inhibitors, against which a library of 210,000 compounds was tested. Compounds that inhibited dengue virus induced CPE by at least 50% were further investigated for chemical tractability, potency, and selectivity.

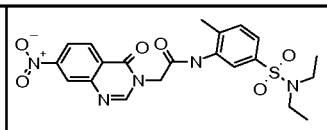
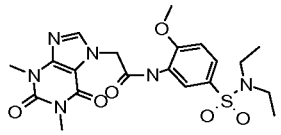
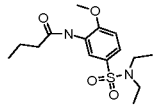
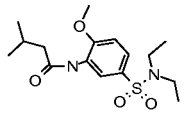
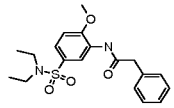
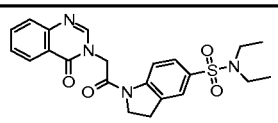
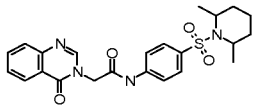
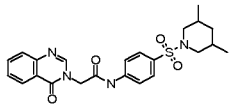
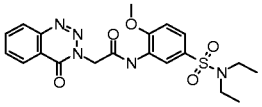
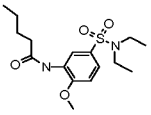
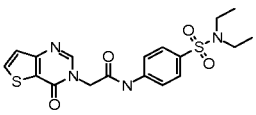
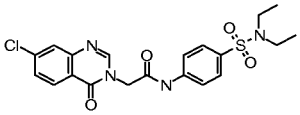
[000078] Initially, the chemical structures of the hit compounds were examined for chemical tractability. A chemically tractable compound is defined as one that is synthetically accessible using reasonable chemical methodology, and which possesses chemically stable functionalities and potential drug-like qualities. Hits that passed this medicinal chemistry filter were evaluated for their potency. Compound potency was determined by evaluating inhibitory activity across a broad range of

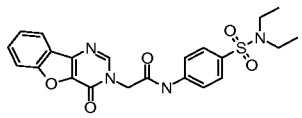
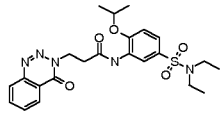
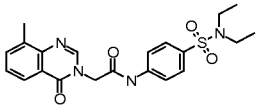
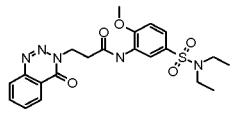
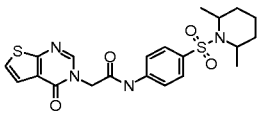
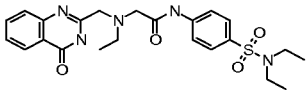
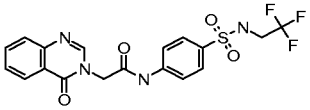
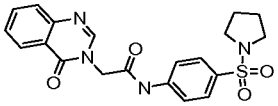
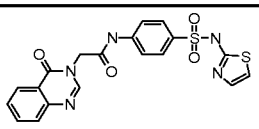
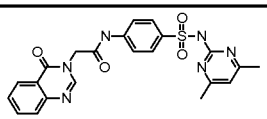
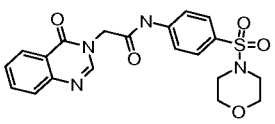
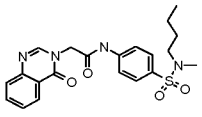
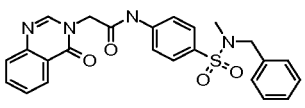
concentrations. Nonlinear regression was used to generate best-fit inhibition curves and to calculate the 50% effective concentration (EC50).

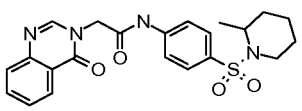
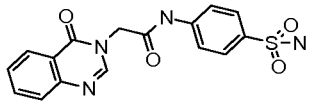
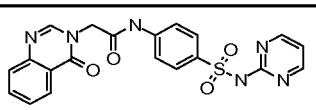
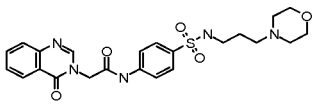
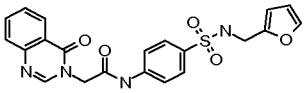
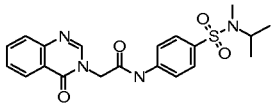
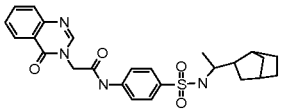
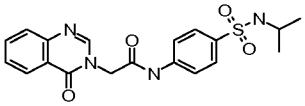
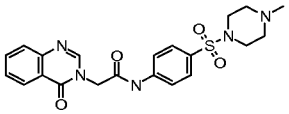
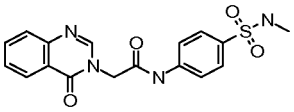
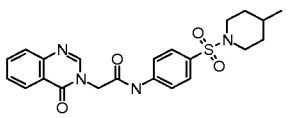
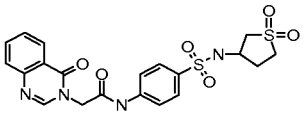
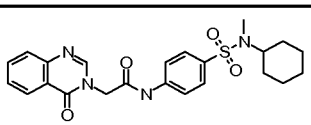
[000079] Compounds that were active in the primary screen were also tested for activity in viral yield assays. Table 1 below shows some of the compounds that were tested for activity against Dengue-2 (Strain New Guinea C) in a viral yield assay at a range of concentrations. Vero cells in 12-well plates were infected with dengue-2 virus at a multiplicity of infection (MOI) of 0.1, treated with compound (or DMSO as a control), incubated at 37°C, harvested 48 hours post infection and titered on Vero cells as described above. The EC50 was calculated through ExcelFit. Those compounds with activity below 1 µM are indicated with "A", those with activity between 1 and 10 µM are indicated with "B", those with activity between 10 and 25 µM with "C", and those with activity above 25 µM are indicated with "D".

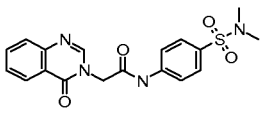
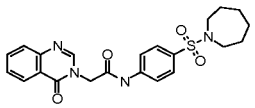
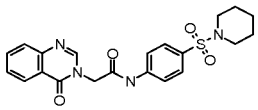
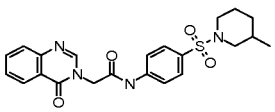
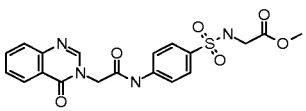
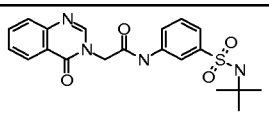
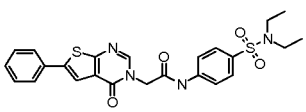
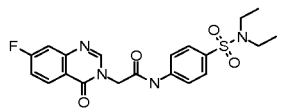
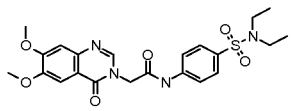
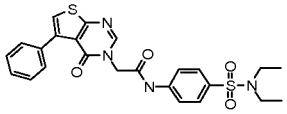
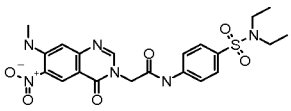
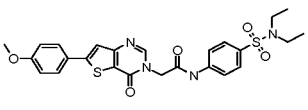
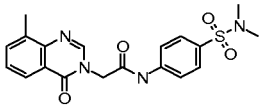
Table 1 – List of compounds of the present invention and their anti-dengue 2 viral activity.

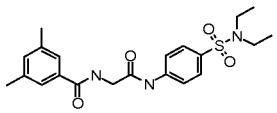
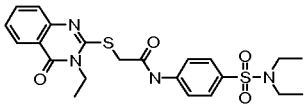
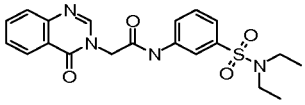
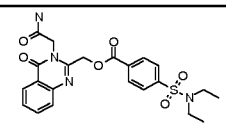
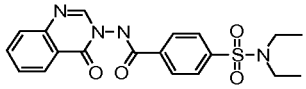
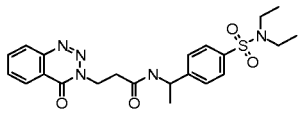
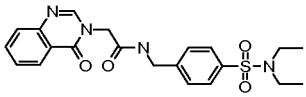
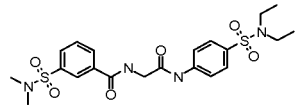
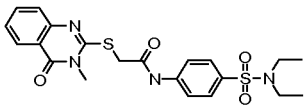
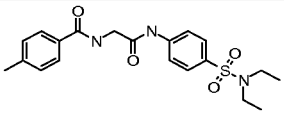
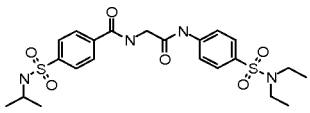
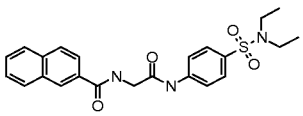
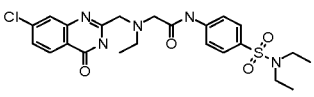
Compound	Chemical Structure	Molecular Weight	Chemical Name	Activity A: EC_{50}<1 uM; B: 1<EC_{50}<10 uM; C: 10<EC_{50}<25 uM; D: EC_{50}>25 uM
1		414.5	N-(4-Diethylsulfamoyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	A
2		328.4	N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-isobutyramide	A
3		415.5	N-(4-Diethylsulfamoyl-phenyl)-2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetamide	B
4		448.5	N-(4-Diethylsulfamoyl-phenyl)-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-yl)-acetamide	B
5		420.5	N-(4-Diethylsulfamoyl-phenyl)-2-(4-oxo-4H-thieno[2,3-d]pyrimidin-3-yl)-acetamide	B
6		448.9	2-(6-Chloro-4-oxo-4H-quinazolin-3-yl)-N-[4-(isopropyl-methyl-sulfamoyl)-phenyl]-acetamide	B
7		432.5	2-(7-Fluoro-4-oxo-4H-quinazolin-3-yl)-N-[4-(isopropyl-methyl-sulfamoyl)-phenyl]-acetamide	B
8		430.5	N-(4-Diethylsulfamoyl-phenyl)-2-(1,4-dioxo-3,4-dihydro-1H-phthalazin-2-yl)-acetamide	B
9		465.5	N-(4-Diethylsulfamoyl-phenyl)-2-(1,3-dioxo-1H,3H-benzo[de]isoquinolin-2-yl)-acetamide	B
10		448.6	N-(4-Diethylsulfamoyl-phenyl)-2-(5,6-dimethyl-4-oxo-4H-thieno[2,3-d]pyrimidin-3-yl)-acetamide	B
11		448.6	N-(4-Diethylsulfamoyl-phenyl)-2-(6-ethyl-4-oxo-4H-thieno[2,3-d]pyrimidin-3-yl)-acetamide	B

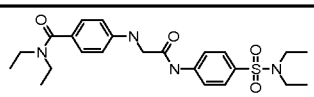
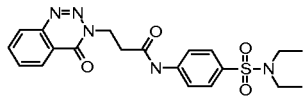
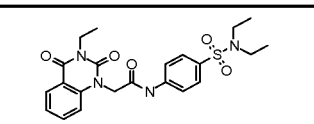
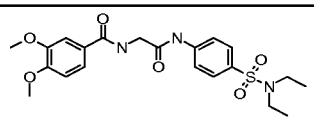
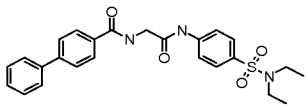
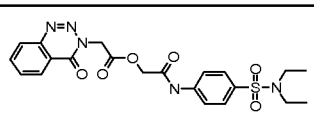
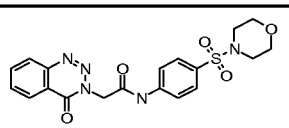
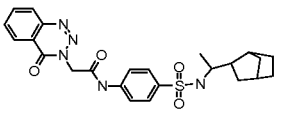
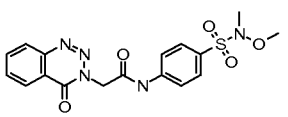
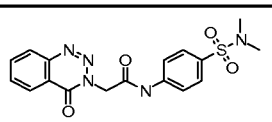
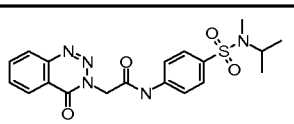
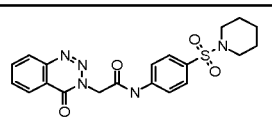
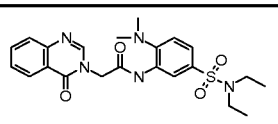
12		473.5	N-(5-Diethylsulfamoyl-2-methyl-phenyl)-2-(7-nitro-4-oxo-4H-quinazolin-3-yl)-acetamide	B
13		478.5	N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-yl)-acetamide	B
14		328.4	N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-butyramide	B
15		342.5	N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-3-methyl-butyramide	B
16		376.5	N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-2-phenyl-acetamide	B
17		440.5	1-[2-(4-Oxo-4H-quinazolin-3-yl)-acetyl]-2,3-dihydro-1H-indole-5-sulfonic acid diethylamide	B
18		454.5	N-[4-(2,6-Dimethyl-piperidine-1-sulfonyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	B
19		454.5	N-[4-(3,5-Dimethyl-piperidine-1-sulfonyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	B
20		445.5	N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetamide	B
21		342.5	Pentanoic acid (5-diethylsulfamoyl-2-methoxy-phenyl)-amide	C
22		420.5	N-(4-Diethylsulfamoyl-phenyl)-2-(4-oxo-4H-thieno[3,2-d]pyrimidin-3-yl)-acetamide	C
23		448.9	2-(7-Chloro-4-oxo-4H-quinazolin-3-yl)-N-(4-diethylsulfamoyl-phenyl)-acetamide	C

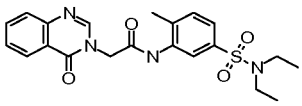
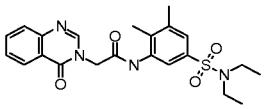
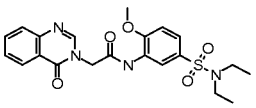
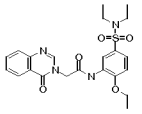
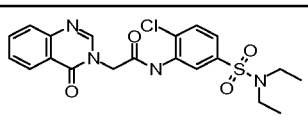
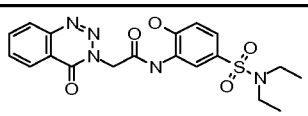
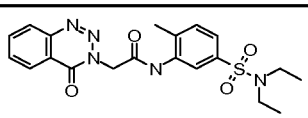
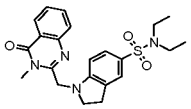
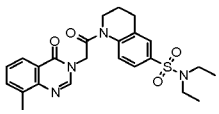
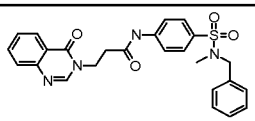
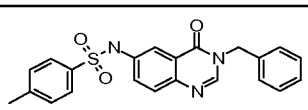
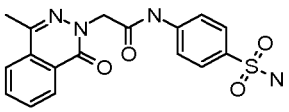
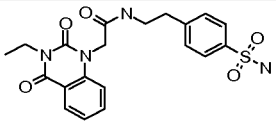
24		454.5	N-(4-Diethylsulfamoyl-phenyl)-2-(4-oxo-4H-benzo[4,5]furo[3,2-d]pyrimidin-3-yl)-acetamide	C
25		487.6	N-(5-Diethylsulfamoyl-2-isopropoxy-phenyl)-3-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-propionamide	C
26		428.5	N-(4-Diethylsulfamoyl-phenyl)-2-(8-methyl-4-oxo-4H-quinazolin-3-yl)-acetamide	C
27		459.5	N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-3-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-propionamide	C
28		460.6	N-[4-(2,6-Dimethyl-piperidine-1-sulfonyl)-phenyl]-2-(4-oxo-4H-thieno[2,3-d]pyrimidin-3-yl)-acetamide	C
29		471.6	N-(4-Diethylsulfamoyl-phenyl)-2-[ethyl-(4-oxo-3,4-dihydro-quinazolin-2-ylmethyl)-amino]-acetamide	C
30		440.4	2-(4-Oxo-4H-quinazolin-3-yl)-N-[4-(2,2,2-trifluoro-ethylsulfamoyl)-phenyl]-acetamide	C
31		412.5	2-(4-Oxo-4H-quinazolin-3-yl)-N-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetamide	D
32		441.5	2-(4-Oxo-4H-quinazolin-3-yl)-N-[4-(thiazol-2-ylsulfamoyl)-phenyl]-acetamide	D
33		464.5	N-[4-(4,6-Dimethyl-pyrimidin-2-ylsulfamoyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
34		428.5	N-[4-(Morpholine-4-sulfonyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
35		428.5	N-[4-(Butyl-methyl-sulfamoyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
36		462.5	N-[4-(Benzyl-methyl-sulfamoyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D

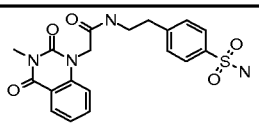
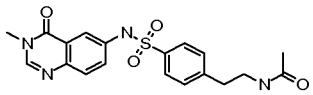
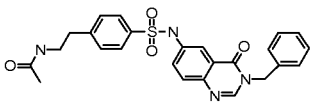
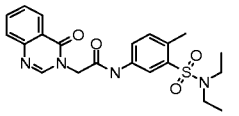
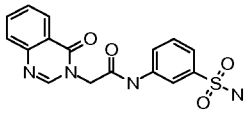
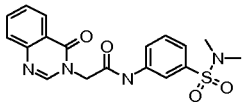
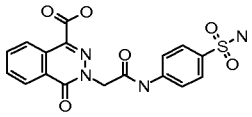
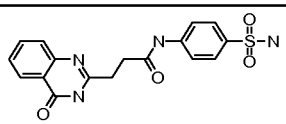
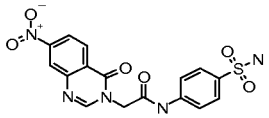
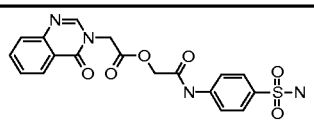
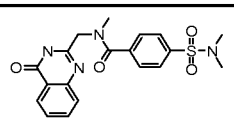
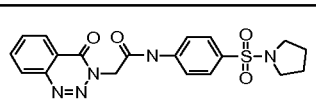
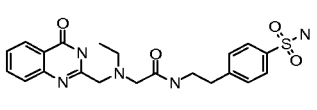
37		440.5	N-[4-(2-Methyl-piperidine-1-sulfonyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
38		358.4	2-(4-Oxo-4H-quinazolin-3-yl)-N-(4-sulfamoyl-phenyl)-acetamide	D
39		436.5	2-(4-Oxo-4H-quinazolin-3-yl)-N-[4-(pyrimidin-2-ylsulfamoyl)-phenyl]-acetamide	D
40		485.6	N-[4-(3-Morpholin-4-yl-propylsulfamoyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
41		438.5	N-{4-[(Furan-2-ylmethyl)-sulfamoyl]-phenyl}-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
42		414.5	N-[4-(Isopropyl-methyl-sulfamoyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
43		480.6	N-[4-(1-Bicyclo[2.2.1]hept-2-yl-ethylsulfamoyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
44		400.5	N-(4-Isopropylsulfamoyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
45		441.5	N-[4-(4-Methyl-piperazine-1-sulfonyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
46		372.4	N-(4-Methylsulfamoyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
47		440.5	N-[4-(4-Methyl-piperidine-1-sulfonyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
48		476.5	N-[4-(1,1-Dioxo-tetrahydro-1lambda*6*-thiophen-3-ylsulfamoyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
49		454.5	N-[4-(Cyclohexyl-methyl-sulfamoyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D

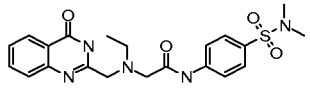
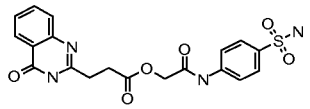
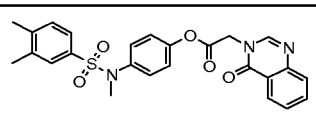
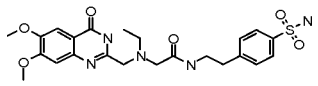
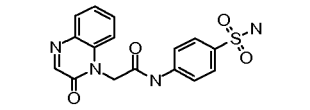
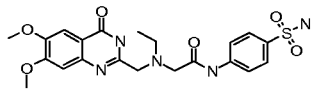
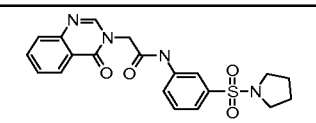
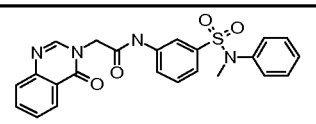
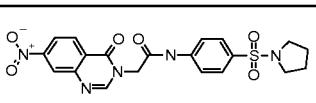
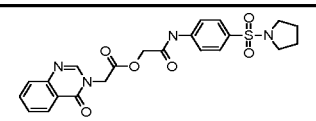
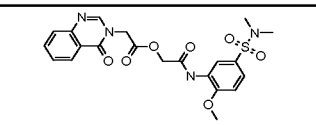
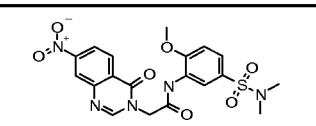
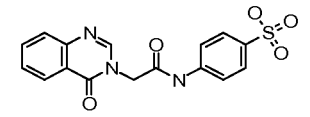
50		386.4	N-(4-Dimethylsulfamoyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
51		440.5	N-[4-(Azepane-1-sulfonyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
52		426.5	2-(4-Oxo-4H-quinazolin-3-yl)-N-[4-(piperidine-1-sulfonyl)-phenyl]-acetamide	D
53		440.5	N-[4-(3-Methyl-piperidine-1-sulfonyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
54		430.4	{4-[2-(4-Oxo-4H-quinazolin-3-yl)-acetylamino]-benzenesulfonylamino}-acetic acid methyl ester	D
55		414.5	N-(3-tert-Butylsulfamoyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
56		496.6	N-(4-Diethylsulfamoyl-phenyl)-2-(4-oxo-6-phenyl-4H-thieno[2,3-d]pyrimidin-3-yl)-acetamide	D
57		432.5	N-(4-Diethylsulfamoyl-phenyl)-2-(7-fluoro-4-oxo-4H-quinazolin-3-yl)-acetamide	D
58		474.5	N-(4-Diethylsulfamoyl-phenyl)-2-(6,7-dimethoxy-4-oxo-4H-quinazolin-3-yl)-acetamide	D
59		496.6	N-(4-Diethylsulfamoyl-phenyl)-2-(4-oxo-5-phenyl-4H-thieno[2,3-d]pyrimidin-3-yl)-acetamide	D
60		488.5	N-(4-Diethylsulfamoyl-phenyl)-2-(7-methylamino-6-nitro-4-oxo-4H-quinazolin-3-yl)-acetamide	D
61		526.6	N-(4-Diethylsulfamoyl-phenyl)-2-[6-(4-methoxy-phenyl)-4-oxo-4H-thieno[3,2-d]pyrimidin-3-yl]-acetamide	D
62		400.5	N-(4-Dimethylsulfamoyl-phenyl)-2-(8-methyl-4-oxo-4H-quinazolin-3-yl)-acetamide	D

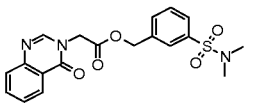
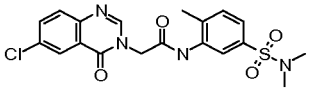
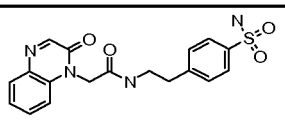
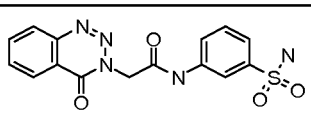
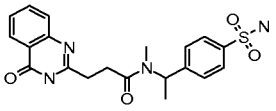
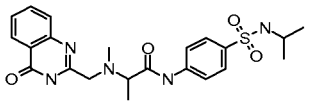
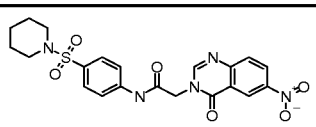
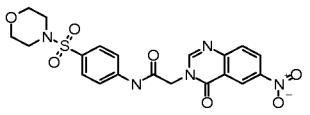
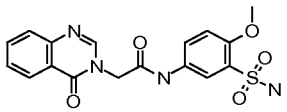
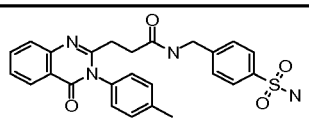
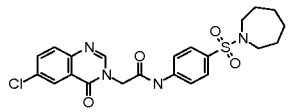
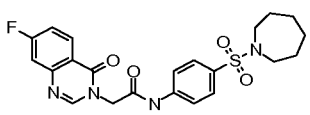
63		417.5	N-[(4-Diethylsulfamoyl-phenylcarbamoyl)-methyl]-3,5-dimethyl-benzamide	D
64		474.6	N-(4-Diethylsulfamoyl-phenyl)-2-(3-ethyl-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetamide	D
65		414.5	N-(3-Diethylsulfamoyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
66		472.5	4-Diethylsulfamoyl-benzoic acid 3-carbamoylmethyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethyl ester	D
67		400.5	4-Diethylsulfamoyl-N-(4-oxo-4H-quinazolin-3-yl)-benzamide	D
68		457.6	N-[1-(4-Diethylsulfamoyl-phenyl)-ethyl]-3-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-propionamide	D
69		428.5	N-(4-Diethylsulfamoyl-benzyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
70		496.6	N-[(4-Diethylsulfamoyl-phenylcarbamoyl)-methyl]-3-dimethylsulfamoyl-benzamide	D
71		460.6	N-(4-Diethylsulfamoyl-phenyl)-2-(3-methyl-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetamide	D
72		403.5	N-[(4-Diethylsulfamoyl-phenylcarbamoyl)-methyl]-4-methyl-benzamide	D
73		510.6	N-[(4-Diethylsulfamoyl-phenylcarbamoyl)-methyl]-4-isopropylsulfamoyl-benzamide	D
74		439.5	Naphthalene-2-carboxylic acid [(4-diethylsulfamoyl-phenylcarbamoyl)-methyl]-amide	D
75		506.0	2-[(7-Chloro-4-oxo-3,4-dihydro-quinazolin-2-ylmethyl)-ethyl-amino]-N-(4-diethylsulfamoyl-phenyl)-acetamide	D

76		460.6	4-{[(4-Diethylsulfamoyl-phenylcarbamoyl)-methyl]-amino}-N,N-diethyl-benzamide	D
77		429.5	N-(4-Diethylsulfamoyl-phenyl)-3-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-propionamide	D
78		458.5	N-(4-Diethylsulfamoyl-phenyl)-2-(3-ethyl-2,4-dioxo-3,4-dihydro-2H-quinazolin-1-yl)-acetamide	D
79		449.5	N-[(4-Diethylsulfamoyl-phenylcarbamoyl)-methyl]-3,4-dimethoxy-benzamide	D
80		465.6	Biphenyl-4-carboxylic acid [(4-diethylsulfamoyl-phenylcarbamoyl)-methyl]-amide	D
81		473.5	(4-Oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetic acid (4-diethylsulfamoyl-phenylcarbamoyl)-methyl ester	D
82		429.5	N-[4-(Morpholine-4-sulfonyl)-phenyl]-2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetamide	D
83		481.6	N-[4-(1-Bicyclo[2.2.1]hept-2-yl-ethylsulfamoyl)-phenyl]-2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetamide	D
84		403.4	N-[4-(Methoxy-methyl-sulfamoyl)-phenyl]-2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetamide	D
85		387.4	N-(4-Dimethylsulfamoyl-phenyl)-2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetamide	D
86		415.5	N-[4-(Isopropyl-methyl-sulfamoyl)-phenyl]-2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetamide	D
87		427.5	2-(4-Oxo-4H-benzo[d][1,2,3]triazin-3-yl)-N-[4-(piperidine-1-sulfonyl)-phenyl]-acetamide	D
88		457.6	N-(5-Diethylsulfamoyl-2-dimethylamino-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D

89		428.5	N-(5-Diethylsulfamoyl-2-methyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
90		442.5	N-(5-Diethylsulfamoyl-2,3-dimethyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
91		444.5	N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
92		458.5	N-(5-Diethylsulfamoyl-2-ethoxy-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
93		448.9	N-(2-Chloro-5-diethylsulfamoyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
94		431.5	N-(5-Diethylsulfamoyl-2-hydroxy-phenyl)-2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetamide	D
95		429.5	N-(5-Diethylsulfamoyl-2-methyl-phenyl)-2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetamide	D
96		426.5	1-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethyl)-2,3-dihydro-1H-indole-5-sulfonic acid diethylamide	D
97		468.6	1-[2-(8-Methyl-4-oxo-4H-quinazolin-3-yl)-acetyl]-1,2,3,4-tetrahydro-quinoline-6-sulfonic acid diethylamide	D
98		476.6	N-[4-(Benzyl-methyl-sulfamoyl)-phenyl]-3-(4-oxo-4H-quinazolin-3-yl)-propionamide	D
99		405.5	N-(3-Benzyl-4-oxo-3,4-dihydro-quinazolin-6-yl)-4-methyl-benzenesulfonamide	D
100		372.4	2-(4-Methyl-1-oxo-1H-phthalazin-2-yl)-N-(4-sulfamoyl-phenyl)-acetamide	D
101		430.5	2-(3-Ethyl-2,4-dioxo-3,4-dihydro-2H-quinazolin-1-yl)-N-[2-(4-sulfamoyl-phenyl)-ethyl]-acetamide	D

102		416.5	2-(3-Methyl-2,4-dioxo-3,4-dihydro-2H-quinazolin-1-yl)-N-[2-(4-sulfamoyl-phenyl)-ethyl]-acetamide	D
103		400.5	N-{2-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-6-ylsulfamoyl)-phenyl]-ethyl}-acetamide	D
104		476.6	N-{2-[4-(3-Benzyl-4-oxo-3,4-dihydro-quinazolin-6-ylsulfamoyl)-phenyl]-ethyl}-acetamide	D
105		428.5	N-(3-Diethylsulfamoyl-4-methyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
106		358.4	2-(4-Oxo-4H-quinazolin-3-yl)-N-(3-sulfamoyl-phenyl)-acetamide	D
107		386.4	N-(3-Dimethylsulfamoyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
108		402.4	4-Oxo-3-[(4-sulfamoyl-phenylcarbamoyl)-methyl]-3,4-dihydro-phthalazine-1-carboxylic acid	D
109		372.4	3-(4-Oxo-3,4-dihydro-quinazolin-2-yl)-N-(4-sulfamoyl-phenyl)-propionamide	D
110		403.4	2-(7-Nitro-4-oxo-4H-quinazolin-3-yl)-N-(4-sulfamoyl-phenyl)-acetamide	D
111		416.4	(4-Oxo-4H-quinazolin-3-yl)-acetic acid (4-sulfamoyl-phenylcarbamoyl)-methyl ester	D
112		400.5	4-Dimethylsulfamoyl-N-methyl-N-(4-oxo-3,4-dihydro-quinazolin-2-ylmethyl)-benzamide	D
113		413.5	2-(4-Oxo-4H-benzo[d][1,2,3]triazin-3-yl)-N-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetamide	D
114		443.5	2-[Ethyl-(4-oxo-3,4-dihydro-quinazolin-2-ylmethyl)-amino]-N-[2-(4-sulfamoyl-phenyl)-ethyl]-acetamide	D

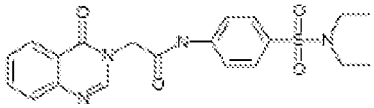
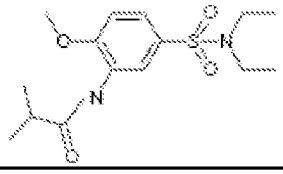
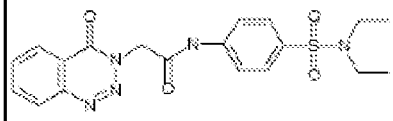
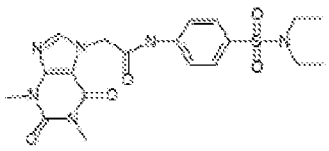
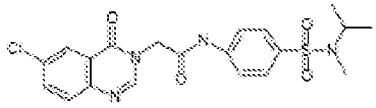
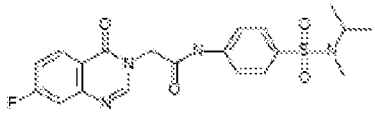
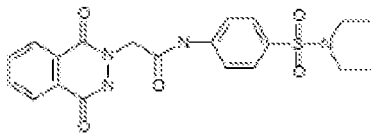
115		443.5	N-(4-Dimethylsulfamoyl-phenyl)-2-[ethyl-(4-oxo-3,4-dihydro-quinazolin-2-ylmethyl)-amino]-acetamide	D
116		430.4	3-(4-Oxo-3,4-dihydro-quinazolin-2-yl)-propionic acid (4-sulfamoyl-phenylcarbamoyl)-methyl ester	D
117		477.5	(4-Oxo-4H-quinazolin-3-yl)-acetic acid 4-[(3,4-dimethyl-benzenesulfonyl)-methyl-amino]-phenyl ester	D
118		503.6	2-[(6,7-Dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-ylmethyl)-ethyl-amino]-N-[2-(4-sulfamoyl-phenyl)-ethyl]-acetamide	D
119		358.4	2-(2-Oxo-2H-quinoxalin-1-yl)-N-(4-sulfamoyl-phenyl)-acetamide	D
120		475.5	2-[(6,7-Dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-ylmethyl)-ethyl-amino]-N-(4-sulfamoyl-phenyl)-acetamide	D
121		412.5	2-(4-Oxo-4H-quinazolin-3-yl)-N-[3-(pyrrolidine-1-sulfonyl)-phenyl]-acetamide	D
122		448.5	N-[3-(Methyl-phenyl-sulfamoyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
123		457.5	2-(7-Nitro-4-oxo-4H-quinazolin-3-yl)-N-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetamide	D
124		470.5	(4-Oxo-4H-quinazolin-3-yl)-acetic acid [4-(pyrrolidine-1-sulfonyl)-phenylcarbamoyl]-methyl ester	D
125		474.5	(4-Oxo-4H-quinazolin-3-yl)-acetic acid (5-dimethylsulfamoyl-2-methoxy-phenylcarbamoyl)-methyl ester	D
126		461.5	N-(5-Dimethylsulfamoyl-2-methoxy-phenyl)-2-(7-nitro-4-oxo-4H-quinazolin-3-yl)-acetamide	D
127		359.4	4-[2-(4-Oxo-4H-quinazolin-3-yl)-acetylamino]-benzenesulfonic acid	D

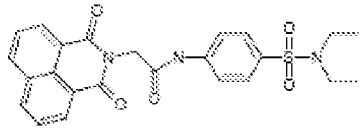
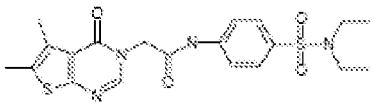
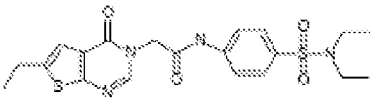
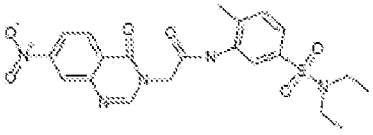
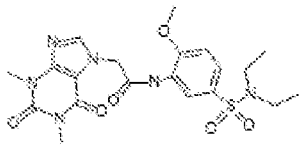
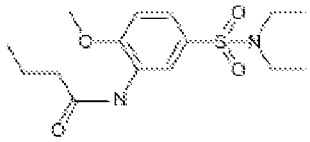
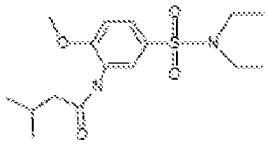
128		401.4	(4-Oxo-4H-quinazolin-3-yl)-acetic acid 3-dimethylsulfamoyl-benzyl ester	D
129		434.9	2-(6-Chloro-4-oxo-4H-quinazolin-3-yl)-N-(5-dimethylsulfamoyl-2-methyl-phenyl)-acetamide	D
130		386.4	2-(2-Oxo-2H-quinoxalin-1-yl)-N-[2-(4-sulfamoyl-phenyl)-ethyl]-acetamide	D
131		359.4	2-(4-Oxo-4H-benzo[d][1,2,3]triazin-3-yl)-N-(3-sulfamoyl-phenyl)-acetamide	D
132		414.5	N-Methyl-3-(4-oxo-3,4-dihydro-quinazolin-2-yl)-N-[1-(4-sulfamoyl-phenyl)-ethyl]-propionamide	D
133		457.6	N-(4-Isopropylsulfamoyl-phenyl)-2-[methyl-(4-oxo-3,4-dihydro-quinazolin-2-ylmethyl)-amino]-propionamide	D
134		471.5	2-(6-Nitro-4-oxo-4H-quinazolin-3-yl)-N-[4-(piperidine-1-sulfonyl)-phenyl]-acetamide	D
135		473.5	N-[4-(Morpholine-4-sulfonyl)-phenyl]-2-(6-nitro-4-oxo-4H-quinazolin-3-yl)-acetamide	D
136		388.4	N-(4-Methoxy-3-sulfamoyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	D
137		476.6	3-(4-Oxo-3-p-tolyl-3,4-dihydro-quinazolin-2-yl)-N-(4-sulfamoyl-benzyl)-propionamide	D
138		475.0	N-[4-(Azepane-1-sulfonyl)-phenyl]-2-(6-chloro-4-oxo-4H-quinazolin-3-yl)-acetamide	D
139		458.5	N-[4-(Azepane-1-sulfonyl)-phenyl]-2-(7-fluoro-4-oxo-4H-quinazolin-3-yl)-acetamide	D

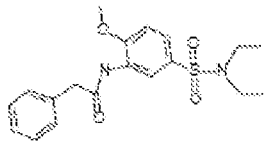
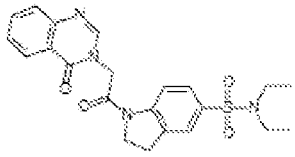
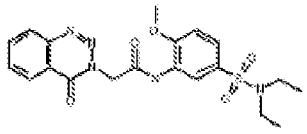
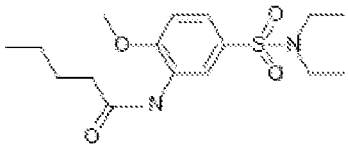
Example 2 – Determining Selectivity or Specificity of Compounds of the Present Invention

[000080] Those compounds with activity against dengue-2 at effective concentrations of less than 10 μM as identified in Example 1 above were tested for activity against each serotype of dengue in a viral yield assay to generate EC50 values (Table 2). Select compounds were also tested for more broad spectrum activity against other members of the Flaviviridae family including Modoc, which is a murine flavivirus, as well as Bovine Viral Diarrhea Virus (BVDV), which is a Pestivirus. Since dengue virus is able to replicate in multiple cell lines and to ensure that the activity seen in vero cells is consistent, select compounds were also tested for their effective concentration in a viral yield assay against dengue-2 in C6/36 mosquito cells.

Table 2 – Select Compounds activities against Den-1, Den-2, Den-3, Den-4, Modoc and BVDV.

Compound	MW	Structure	EC50/90 (μM) Yield	Specificity (μM)
1	414.48 MW		4.3 / 10.7 Den-1 0.3 / 5.2 Den-2 1.0 / 8.2 Den-3 1.7 / 4.1 Den-4	1.2 Modoc >50 BVDV 0.3 C6/36
2	328.43 MW		7.6 /8.9 Den-1 0.3 / 4.1 Den-2 5.5 /13.3 Den-3 2.1 / 12.5 Den-4	6.2 Modoc >50 BVDV 0.7 C6/36
3	415.47 MW		1.3 / 5.1Den-1 4.0 / 10.0 Den-2 1.0 / 12.1 Den-3 2.3 / 10.0 Den-4	3.1 Modoc >50 BVDV
4	448.50 MW		7.6 / 8.9 Den-2 13.5 /22.6 Den-3 4.3 / 22.7 Den-4	>25 Modoc >50 BVDV
6	448.93 MW		1.8 /43.2 Den-2	64 BVDV
7	432.42 MW		4.6 />50 Den-2	>50 BVDV
8	430.48 MW		2.8 /25.6 Den-2	>50 BVDV

Compound	MW	Structure	EC50/90 (μM) Yield	Specificity (μM)
9	465.52 MW		1.3 / 7.3 Den-2	>50 BVDV
10	448.5 MW		1.25/>50 Den-2	
11	448.5 MW		4.9 />50 Den-2	
12	473.51 MW		>25 / >25 Den-1 11.1 / >25 Den-2 2.9 / >25Den-3 5.2 / 14.6 Den-4	>25 Modoc >50 BVDV
13	478.53 MW		7.1 / 8.5 Den-1 2.4 / 10.3 Den-2 4.1 / 9.4 Den-3 1.9 / 9.2 Den-4	>25 Modoc 47.7 BVDV 2.1 C8/36
14	328.43 MW		>25 />25 Den-1 3.6 /27.5 Den-2 4.2 /14.9 Den-3 4.8 /11.1 Den-4	>25 Modoc >50 BVDV
15	342.46 MW		2.4 />100 Den-2 1.2 / 37.2 Den-4	10.1 Modoc >50 BVDV

Compound	MW	Structure	EC50/90 (μM) Yield	Specificity (μM)
16	378.47 MW		Den-1 5.6 / 10.3 Den-2 Den-3 2.1 / 6.4 Den-4	3.6 Modoc >50 BVDV
17			Den-1 5.1 / 12.1 Den-2 Den-3 Den-4	
20	449.94 MW		Den-1 1.3 / 20 Den-2 Den-3 Den-4	
21	342.46 MW		Den-1 14.2 /24.1 Den-2 Den-3 6.2 / 12.0 Den-4	6 Modoc >50 BVDV

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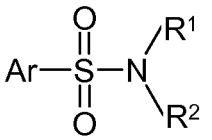
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[000081] All references cited herein are herein incorporated by reference in their entirety for all purposes.

[000082] The invention has been described in terms of preferred embodiments thereof, but is more broadly applicable as will be understood by those skilled in the art. The scope of the invention is only limited by the following claims.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the following general formula I or a pharmaceutically acceptable salt thereof:



wherein R^1 and R^2 are independently hydrogen, alkyl, alkenyl, alkynyl, or unsubstituted or substituted cycloalkyl, arylalkyl, aryl, or R^1 and R^2 together may form a substituted or unsubstituted ring, which may include one or more heteroatoms in the ring; and

Ar is substituted or unsubstituted aryl or heteroaryl;

said cycloalkyl, arylalkyl, and aryl group substituents being one or more radical(s) independently selected from the group consisting of a straight- or branched chain alkyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, halogen, polyfluoroalkyl, polyfluoroalkoxy, carboxy, cyano, nitro, amido, amidoalkyl, carboxamide, alkylthio, alkylsulfinyl, alkylsulfonyl, sulfonamide, and mercapto.

2. The composition of claim 1, wherein R^1 is ethyl.

3. The composition of claim 1, wherein R^2 is ethyl.

4. The composition of claim 1, wherein Ar is mono-substituted phenyl.

5. The composition of claim 4, wherein said mono-substituted phenyl is amido-phenyl.

6. The composition of claim 5, wherein said amido-phenyl is selected from the group consisting of isobutyramidophenyl, *p*-[2-(4-oxo-4H-quinazolin-3-yl)-acetamido]-phenyl and *p*-[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetamido]-phenyl.

7. The composition of claim 1, wherein Ar is a di-substituted phenyl.

8. The composition of claim 7, wherein said di-substituted phenyl has one substituent as amido and the other one as methoxy.

9. The composition of claim 8, wherein said di-substituted phenyl is *m*-phenyl-acetamido-*p*-methoxy-phenyl.

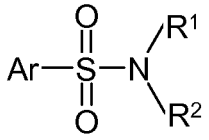
10. The composition of claim 8, wherein di-substituted phenyl is *m*-(3-methyl-butyramido)-*p*-methoxy-phenyl.

11. The compound of claim 1, wherein the compound of Formula I is selected from the group consisting of N-(4-Diethylsulfamoyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide; N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-isobutyramide; N-(4-Diethylsulfamoyl-phenyl)-2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetamide; N-(4-Diethylsulfamoyl-phenyl)-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-yl)-acetamide; N-(4-Diethylsulfamoyl-phenyl)-2-(4-oxo-4H-thieno[2,3-d]pyrimidin-3-yl)-acetamide; 2-(6-Chloro-4-oxo-4H-quinazolin-3-yl)-N-[4-(isopropyl-methyl-sulfamoyl)-phenyl]-acetamide; 2-(7-Fluoro-4-oxo-4H-quinazolin-3-yl)-

N-[4-(isopropyl-methyl-sulfamoyl)-phenyl]-acetamide; N-(4-Diethylsulfamoyl-phenyl)-2-(1,4-dioxo-3,4-dihydro-1H-phthalazin-2-yl)-acetamide; N-(4-Diethylsulfamoyl-phenyl)-2-(1,3-dioxo-1H,3H-benzo[de]isoquinolin-2-yl)-acetamide; N-(4-Diethylsulfamoyl-phenyl)-2-(5,6-dimethyl-4-oxo-4H-thieno[2,3-d]pyrimidin-3-yl)-acetamide; N-(4-Diethylsulfamoyl-phenyl)-2-(6-ethyl-4-oxo-4H-thieno[2,3-d]pyrimidin-3-yl)-acetamide; N-(5-Diethylsulfamoyl-2-methyl-phenyl)-2-(7-nitro-4-oxo-4H-quinazolin-3-yl)-acetamide; N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-yl)-acetamide; N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-butyramide; N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-3-methyl-butyramide; N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-2-phenyl-acetamide; 1-[2-(4-Oxo-4H-quinazolin-3-yl)-acetyl]-2,3-dihydro-1H-indole-5-sulfonic acid diethylamide; N-[4-(2,6-Dimethyl-piperidine-1-sulfonyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide; N-[4-(3,5-Dimethyl-piperidine-1-sulfonyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide; N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetamide; and Pentanoic acid (5-diethylsulfamoyl-2-methoxy-phenyl)-amide.

12. The composition of claim 1, wherein the compound of Formula I is N-(4-Diethylsulfamoyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide.

13. A method for the treatment or prophylaxis of a viral infection or disease associated therewith, comprising administering in a therapeutically effective amount to a mammal in need thereof, a compound of Formula I below or a pharmaceutically acceptable salt thereof:



wherein R^1 and R^2 are independently hydrogen, alkyl, alkenyl, alkynyl, or unsubstituted or substituted cycloalkyl, arylalkyl, aryl, or R^1 and R^2 together may form a substituted or unsubstituted ring, which may include one or more heteroatoms in the ring; and

Ar is substituted or unsubstituted aryl or heteroaryl;

said cycloalkyl, arylalkyl, and aryl group substituents being one or more radical(s) independently selected from the group consisting of a straight- or branched chain alkyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, halogen, polyfluoroalkyl, polyfluoroalkoxy, carboxy, cyano, nitro, amido, amidoalkyl, carboxamide, alkylthio, alkylsulfinyl, alkylsulfonyl, sulfonamide, and mercapto.

14. The method of claim 13, wherein R^1 is ethyl.

15. The method of claim 13, wherein R^2 is ethyl.

16. The method of claim 13, wherein Ar is mono-substituted phenyl.

17. The method of claim 16, wherein said mono-substituted phenyl is amido-phenyl.

18. The method of claim 17, wherein said amido-phenyl is selected from the group consisting of isobutyramidophenyl, *p*-[2-(4-oxo-4H-quinazolin-3-yl)-acetamido]-phenyl and *p*-

[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetamido]-phenyl.

19. The method of claim 13, wherein Ar is a di-substituted phenyl.

20. The method of claim 19, wherein said di-substituted phenyl has one substituent as amido and the other one as methoxy.

21. The method of claim 20, wherein said di-substituted phenyl is *m*-phenyl-acetamido-*p*-methoxy-phenyl.

22. The composition of claim 20, wherein di-substituted phenyl is *m*-(3-methyl-butyramido)-*p*-methoxy-phenyl.

23. The method of claim 13, wherein the compound of Formula I is selected from the group consisting of N-(4-Diethylsulfamoyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide; N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-isobutyramide; N-(4-Diethylsulfamoyl-phenyl)-2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetamide; N-(4-Diethylsulfamoyl-phenyl)-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-yl)-acetamide; N-(4-Diethylsulfamoyl-phenyl)-2-(4-oxo-4H-thieno[2,3-d]pyrimidin-3-yl)-acetamide; 2-(6-Chloro-4-oxo-4H-quinazolin-3-yl)-N-[4-(isopropyl-methyl-sulfamoyl)-phenyl]-acetamide; 2-(7-Fluoro-4-oxo-4H-quinazolin-3-yl)-N-[4-(isopropyl-methyl-sulfamoyl)-phenyl]-acetamide; N-(4-Diethylsulfamoyl-phenyl)-2-(1,4-dioxo-3,4-dihydro-1H-phthalazin-2-yl)-acetamide; N-(4-Diethylsulfamoyl-phenyl)-2-(1,3-dioxo-1H,3H-benzo[de]isoquinolin-2-yl)-acetamide; N-(4-Diethylsulfamoyl-phenyl)-2-(5,6-dimethyl-4-oxo-4H-thieno[2,3-d]pyrimidin-3-yl)-acetamide; N-(4-

Diethylsulfamoyl-phenyl)-2-(6-ethyl-4-oxo-4H-thieno[2,3-d]pyrimidin-3-yl)-acetamide; N-(5-Diethylsulfamoyl-2-methyl-phenyl)-2-(7-nitro-4-oxo-4H-quinazolin-3-yl)-acetamide; N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-yl)-acetamide; N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-butyramide; N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-3-methyl-butyramide; N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-2-phenyl-acetamide; 1-[2-(4-Oxo-4H-quinazolin-3-yl)-acetyl]-2,3-dihydro-1H-indole-5-sulfonic acid diethylamide; N-[4-(2,6-Dimethyl-piperidine-1-sulfonyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide; N-[4-(3,5-Dimethyl-piperidine-1-sulfonyl)-phenyl]-2-(4-oxo-4H-quinazolin-3-yl)-acetamide; N-(5-Diethylsulfamoyl-2-methoxy-phenyl)-2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-acetamide; and Pentanoic acid (5-diethylsulfamoyl-2-methoxy-phenyl)-amide.

24. The method of claim 13, wherein the compound of Formula I is N-(4-Diethylsulfamoyl-phenyl)-2-(4-oxo-4H-quinazolin-3-yl)-acetamide.

25. The method of claim 13, wherein the mammal is a human.

26. The method of claim 13, wherein the viral infection is a flavivirus infection.

27. The method of claim 26, wherein the flavivirus virus is selected from the group consisting of Dengue virus, West Nile virus, yellow fever virus, Japanese encephalitis virus, and tick-borne encephalitis virus.

28. The method of claim 26, wherein said viral infection is associated with a condition selected from the group consisting of Dengue fever, Yellow fever, West Nile, St.

Louis encephalitis, Hepatitis C, Murray Valley encephalitis, and Japanese encephalitis.

29. The method of claim 27, wherein said virus is a Dengue virus.

30. The method of claim 29, wherein said Dengue virus is selected from the group consisting of DEN-1, DEN-2, DEN-3, and DEN-4.

31. The method of claim 26, wherein said viral infection is associated with Dengue fever.

32. The method of claim 31, wherein said Dengue fever is selected from the group consisting of classical dengue fever, dengue hemorrhagic fever syndrome, and dengue shock syndrome.

33. The method of claim 13, which further comprises co-administration of at least one agent selected from the group consisting of antiviral agent, vaccine, and interferon.

34. The method of claim 33, wherein said antiviral agent is Ribavirin.

35. The method of claim 33, wherein said antiviral agent is cidofovir.

36. The method of claim 33, wherein said interferon is pegylated.