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(54) **Title**: SIGMA 1 RECEPTOR INHIBITION AS A NOVEL THERAPEUTICAL APPROACH AGAINST HEPATITIS C VIRUS INFECTION

(57) **Abstract**: A method for treating or ameliorating the symptoms of a Hepatitis C virus infection comprising administering a Sigma 1 receptor binding compound or an interfering RNA is provided. Methods for identifying a compound that inhibits a Hepatitis C virus infection are also provided. The Sigma 1 receptor binding compound or interfering RNA is believed to act by reducing the susceptibility of uninfected human cells to infection by Hepatitis C virus, inhibiting viral spread in a cellular population.

SIGMA 1 RECEPTOR INHIBITION AS A NOVEL THERAPEUTICAL APPROACH AGAINST HEPATITIS C VIRUS INFECTION

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the priority of U.S. Ser. No. 61/157,587, filed March 5, 2009, which is incorporated by reference herein in its entirety.

STATEMENT OF GOVERNMENT SUPPORT

This invention was made with government support under Grant No. R01CA108304, awarded by the National Institutes of Health. The U.S. government has certain rights in the invention.

BACKGROUND

Hepatitis C virus (HCV) is a major human pathogen, infecting an estimated 170 million persons worldwide-roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma.

Currently, the most effective HCV therapy employs a combination of α-interferon and ribavirin, leading to sustained efficacy in 40% of patients. Clinical results demonstrate that pegylated α-interferon is superior to unmodified α-interferon as monotherapy. However, even with experimental therapeutic regimens involving combinations of pegylated α-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load.

HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the *Flaviviridae* family. All members of the *Flaviviridae* family have enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins via translation of a single, uninterrupted, open reading frame.

A great deal of heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome. At least six major genotypes have been characterized, and more than 50 subtypes have been described. The

major genotypes of HCV differ in their distribution worldwide, and the clinical significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the possible effect of genotypes on pathogenesis and therapy.

The sigma-1 receptor is a protein, a transmembrane receptor that is expressed in many different types of tissue. See to http://en.wikipedia.org/wiki/Sigma-1_receptor. It is particularly concentrated in certain regions of the central nervous system and in the liver. Weissman AD, Su TP, Hedreen JC, London ED (1988). "Sigma receptors in post-mortem human brains". *J. Pharmacol. Exp. Ther.* **247** (1): 29–33. Although the receptor is a transmembrane protein, it is believed to be widely distributed intracellularly, although it may also be present on the cell surface. The functioning of this receptor is believed to be involved in a wide variety of different metabolic phenomena in humans, including cardiovascular function, schizophrenia, clinical depression, cocaine abuse, and cancer. For example, see Guitart X, Codony X, Monroy X (2004). "Sigma receptors: biology and therapeutic potential". *Psychopharmacology (Berl.)* **174** (3): 301–19; Zhang H, Cuevas J (2005). "Sigma Receptor activation blocks potassium channels and depresses neuroexcitability in rat intracardiac neurons". *J. Pharmacol. Exp. Ther.* **313** (3): 1387–96. The Sigma 1 receptor has also been implicated in various metabolic syndromes, such as hyperlipidemias. See for example WO2007/098939, "Use of compounds binding to the Sigma receptor for the treatment of metabolic syndrome." The protein has no apparent homology to any other known mammalian protein. The binding affinities of large numbers of organic compounds to the sigma-1 receptor are known, but no endogenous ligand has yet been identified. It has been postulated that N,N-dimethyltryptamine may be an endogenous Sigma-1 ligand. Fontanella et al., (PMID: 19213917).

A variety of specific physiological functions have been attributed to Sigma 1 receptor. These functions include, for example, modulation of Ca^{2+} release, modulation of cardiac myocyte contractility, and inhibition of voltage gated potassium ion channels. The effects are not well understood, even though Sigma 1 receptors have been linked circumstantially to a wide variety of signal transduction pathways. The Sigma 1 receptor has been shown to appear in a complex with voltage gated K^+ channels (K_v 1.4 and K_v 1.5). The wide scope

and effect of ligand binding on Sigma 1 receptors suggests that Sigma 1 receptors are intracellular signal transduction amplifiers. Sigma receptors have recently been reviewed (Guitart et al., Psychopharmacology, 174, 301-319 (2004)). Pharmacological data based on ligand binding studies, anatomical distribution and biochemical features distinguish between the Sigma 1 and Sigma 2 receptors (Quiron et al., Trends Pharmacol. Sci,. 13, 85-86 (1992); Leitner et al., Eur. J. Pharmacol. 259, 65-69 (1994); Hellewell et al., Brain Res., 527, 244-253 (1990); Ronsisvalle et al., Pure Appl. Chem., 73, 1499-1509 (2001).

Interfering RNAs (RNAi), also known as "small interfering RNAs" (siRNA) are relatively short segments of RNA or an analog thereof that interfere with transcription of a gene into messenger RNA (mRNA), or interfere with mRNA processing and/or the translation of that mRNA into a functional protein on the ribosome. The "interfering RNAs" can be formal RNA molecules, i.e., poly(3',5'-ribonucleoside)phosphates, or can be structural analogs of the polymer, for example wherein a nuclease-resistant linkage replaces the 3',5'-phosphodiester linking moiety. See, for example, http://www.alnylam.com/Leadership-in-RNAi/Publications.php?pub=19 and references cited therein.

SUMMARY

The present invention is directed to methods of treating mammals infected with Hepatitis C virus (HCV), and methods of blocking HCV infections or the spread of HCV infections in mammals exposed to the Hepatitis C virus. It has been unexpectedly discovered by the inventors herein that blockage or deactivation of the Sigma 1 receptor, such as by use of compounds binding to the Sigma 1 receptor ("Sigma 1 receptor binding compounds"), or by use of RNAi or siRNA ("interfering RNAs or analogs thereof") can inhibit HCV infection of mammalian cells and/or viral spread in populations of mammalian cells. This can in turn serve to prevent or limit HCV infections in mammals and to ameliorate the symptoms of HCV infections in mammals. This action can take place through blocking the HCV infection from spreading within a population of cells by disabling the Sigma 1 receptor with small molecule antagonists or with interfering RNA or analogs thereof.

Furthermore, the high degree of correlation of Sigma 1 binding activity of a candidate small molecule compound with the bioactivity that compound exhibits in inhibiting the spread of viral infections within a population of cells in an organism allows Sigma 1 binding activity to be used for pre-screening a set of compounds for anti-HCV bioactivity.

In various embodiments, the invention provides a method of reducing the susceptibility of a population of mammalian cells in a mammal to infection by HCV comprising blocking or deactivating the Sigma 1 receptor expressed in the population of cells, wherein the blocking or deactivating takes place *in vivo*.

In various embodiments, the invention provides a method of reducing the susceptibility of the population of mammalian cells by inhibiting the viral spread of Hepatitis C virus in a population of cells in a mammal exposed to an infectious inoculum of a Hepatitis C virus.

For example, blocking or deactivating can comprise administering an effective amount of a Sigma 1 receptor binding compound to the mammalian cells. Alternatively, blocking or deactivating can comprise administering an effective amount of an interfering RNA or analog thereof to the mammalian cells wherein the interfering RNA or analog blocks or decreases expression of a gene coding for a protein comprising the Sigma 1 receptor. Or, both a Sigma 1 receptor binding compound and an interfering RNA or analog thereof can be administered in effective amounts.

In various embodiments, the invention provides a method of treating a Hepatitis C viral infection in a mammal, or of ameliorating symptoms of a Hepatitis C viral infection in a mammal, or of preventing viral spread of Hepatitis C virus among mammalian cells therein, or any combination thereof, comprising administering to the mammal an amount of a Sigma 1 receptor binding compound, or an interfering RNA or analog thereof wherein the interfering RNA or analog blocks or decreases expression of a gene coding for the Sigma 1 receptor, or both; in a dose, at a frequency, and for a duration sufficient to provide a beneficial effect to the mammal.

In various embodiments, the invention provides a method of screening each compound of a set of compounds for anti-HCV activity, comprising determining a binding constant for each compound of the set of compounds with respect to the Sigma 1 receptor; then, selecting a subset of the set wherein the

compounds each have a binding constant with respect to the Sigma 1 receptor of less than about 1 μM; then, testing each of the subset of compounds for anti-HCV activity, wherein a percentage of active anti-HCV compounds among the subset is greater than a percentage of active anti-HCV compounds among the set.

In various embodiments, the invention provides a use of a Sigma 1 receptor binding compound or of an interfering RNA or analog thereof to the mammalian cells wherein the interfering RNA or analog blocks or decreases expression of a gene coding for a protein comprising the Sigma 1 receptor, or both, for the manufacture of a medicament for the treatment of a Hepatitis C virus infection.

DETAILED DESCRIPTION

Definitions

Reference will now be made in detail to certain embodiments of the disclosed subject matter, examples of which are illustrated in the accompanying structures and formulas. While the disclosed subject matter will be described in conjunction with the enumerated embodiments, it will be understood that there is no intention to limit the disclosure to those embodiments. References in the specification to "one embodiment" indicate that the embodiment described may include a particular feature, structure, or characteristic, but every embodiment may not necessarily include the particular feature, structure, or characteristic. Moreover, such phrases are not necessarily referring to the same embodiment. Further, when a particular feature, structure, or characteristic is described in connection with an embodiment, it is submitted that it is within the knowledge of one skilled in the art to affect such feature, structure, or characteristic in connection with other embodiments whether or not explicitly described.

The presently disclosed subject matter relates to a method of treating one or more cells inflicted with a Hepatitis C virus infection by administering to one or more cells inflicted with a Hepatitis C virus infection an effective amount of at least one compound that binds to the Sigma 1 receptor and protects the one or more cells from Hepatitis C virus infection. When describing the methods described herein, the following terms have the following meanings, unless otherwise indicated.

Unless otherwise indicated, the words and phrases presented in this document have their ordinary meanings to one of skill in the art. Such ordinary meanings can be obtained by reference to their use in the art and by reference to general and scientific dictionaries, for example, Webster's Third New International Dictionary, Merriam-Webster Inc, Springfield, MA, 1993, The American Heritage Dictionary of the English Language, Houghton Mifflin, Boston MA, 1981, and Hawley's Condensed Chemical Dictionary, 14th edition, Wiley Europe, 2002.

One of ordinary skill in the art would readily appreciate that the pharmaceutical formulations and methods described herein can be prepared and practiced by applying known procedures in the pharmaceutical arts. These include, for example, conventional techniques of pharmaceutical sciences including pharmaceutical dosage form design, drug development, pharmacology, of organic chemistry, and polymer sciences. See generally, for example, Remington: The Science and Practice of Pharmacy, 19th Ed., Mack Publishing Co., Easton, Pa. (1995).

The following explanations of certain terms are meant to be illustrative rather than exhaustive. These terms have their ordinary meanings given by usage in the art and in addition include the following explanations.

As used herein, the term "about" refers to a variation of 10 percent of the value specified; for example about 50 percent carries a variation from 45 to 55 percent.

As used herein, the term "and/or" refers to any one of the items, any combination of the items, or all of the items with which this term is associated.

As used herein, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

As used herein, the term "administration" refers to a providing a compound that binds to the Sigma 1 receptor to an animal, for example, a human or a one or more cells or cell cultures.

As used herein, the phrase "compounds of the disclosure" refer to compounds that bind to the Sigma 1 receptor, and pharmaceutically acceptable enantiomers, diastereomers, and salts thereof.

As used herein, the phrase "compound that binds to the Sigma 1 receptor" or "Sigma 1 receptor binding compound" refers to a compound that

has an IC_{50} value of less than about 1000 nM. Further, as used herein, a compound that binds to the Sigma 1 receptor causes at least greater than 50% displacement using 10 mM radioligand specific for the Sigma 1 receptor in a standard receptor binding assay.

An "interfering RNA or analog thereof", as the term is used herein, refers to an RNAi or siRNA that interferes with expression of a gene coding for a protein comprising the Sigma 1 receptor. Interfering RNAs (RNAi), also known as "small interfering RNAs" (siRNA) are relatively short segments of RNA or an analog thereof that interfere with transcription of a gene into messenger RNA (mRNA), or interfere with the translation of that mRNA into a functional protein on the ribosome. The molecules can be formal RNA molecules, i.e., poly(3',5'-ribonucleoside)phosphates, or can be structural analogs of the polymer, for example wherein a nuclease-resistant linkage replaces the 3',5'-phosphodiester linking moiety. Accordingly, an "analog thereof" with respect to an interfering RNA refers to a molecule that mimics the effect of an interfering RNA on gene expression. When the term "RNA" or "interfering RNA" or "siRNA" is used in the context of an interfering RNA, the term is understood to include RNA analogs as well.

As used herein, the term "contacting" refers to the act of touching, making contact, or of bringing into immediate proximity.

As used herein, the term "infection" refers to the invasion of the host by germs that reproduce and multiply, causing disease by local cell injury, release of poisons, or germ-antibody reaction in the cells. The infection can be in a mammal (e.g., human).

As used herein, the terms "individual," "host," "subject," and "patient" are used interchangeably, and refer to a mammal, including, but not limited to, primates, including simians and humans.

As used herein, the term "animal" refers to mammals, which is class of warm-blooded higher vertebrates that nourish their young with milk secreted by mammary glands and have skin typically more or less covered with hair, and non- exclusively includes humans and non-human primates, their children, including neonates and adolescents, both male and female, livestock species, such as horses, cattle, sheep, and goats, and research and domestic species, including dogs, cats, mice, rats, guinea pigs, and rabbits.

As used herein, the term "metabolite" refers to any compound that binds to the Sigma 1 receptor produced *in vivo* or *in vitro* from the parent drug, or its prodrugs.

As used herein, the term "patient" refers to a warm-blooded animal, and preferably a mammal, such as, for example, a cat, dog, horse, cow, pig, mouse, rat, or primate, including a human.

As used herein, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

As used herein, the term "pharmaceutically acceptable salts" refers to ionic compounds, wherein a parent non–ionic compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include conventional non–toxic salts and quaternary ammonium salts of the parent compound formed, for example, from non–toxic inorganic or organic acids. Non–toxic salts can include those derived from inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfamic, phosphoric, nitric and the like. Salts prepared from organic acids can include those such as acetic, 2–acetoxybenzoic, ascorbic, benzenesulfonic, benzoic, citric, ethanesulfonic, ethane disulfonic, formic, fumaric, gentisinic, glucaronic, gluconic, glutamic, glycolic, hydroxymaleic, isethionic, isonicotinic, lactic, maleic, malic, mesylate or methanesulfonic, oxalic, pamoic (1,1'–methylene–bis–(2–hydroxy–3–naphthoate)), pantothenic, phenylacetic, propionic, salicylic, sulfanilic, toluenesulfonic, stearic, succinic, tartaric, bitartaric, and the like. Certain compounds can form pharmaceutically acceptable salts with various amino acids. For a review on pharmaceutically acceptable salts, *see*, e.g., Berge et al., *J. Pharm. Sci.* 1977, *66*(1), 1–19, which is incorporated herein by reference.

The pharmaceutically acceptable salts of the compounds described herein can be synthesized from the parent compound that binds to the Sigma 1 receptor,

which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of many suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, (1985), 1418, and the disclosure of which is incorporated herein by reference.

It should be appreciated by those skilled in the art that compounds useful in the disclosed subject matter having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the presently disclosed subject matter encompasses any racemic, optically–active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the presently disclosed subject matter, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically–active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine anti–HCV activity using the standard tests described herein, or using other similar tests which are well known in the art.

One diastereomer of a compound disclosed herein may display superior activity compared with the other. When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Tucker et al., J. Med. Chem., 37, 2437 (1994). A chiral compound described herein may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g., Huffman et al., J. Org. Chem., 60:1590 (1995).

As used herein, the terms "prevent," "preventative," "prevention," "protect," and "protection" refer to medical procedures that keep the malcondition from occurring in the first place. The terms mean that there is no or a lessened development of disease or disorder where none had previously occurred, or no further disorder or disease development if there had already been development of the disorder or disease.

As used herein, the term "prodrug" refers to any pharmaceutically acceptable form of a compound that binds to the Sigma 1 receptor which, upon administration to a patient, provides a compound that binds to the Sigma 1 receptor. Pharmaceutically acceptable prodrugs refer to a compound that is metabolized, for example hydrolyzed or oxidized, in the host to form a compound that binds to the Sigma 1 receptor. Typical examples of prodrugs include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated to produce the active compound.

As used herein, the term "therapeutic agent" refers any agent which serves to repair damage to a living organism to heal the organism, to cure a malcondition, to combat an infection by a microorganism or a virus, to assist the body of the living mammal to return to a healthy state.

As used herein, the term "therapeutic composition" refers to an admixture with an organic or inorganic carrier or excipient, and can be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, or other form suitable for use.

As used herein, the term "therapeutically effective amount" is intended to include an amount of a compound described herein, or an amount of the combination of compounds described herein, e.g., to treat or prevent the disease or disorder, or to treat the symptoms of the disease or disorder, in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, Adv. Enzyme Regul., 22:27 (1984), occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased activity, or some other beneficial effect of the combination compared with the individual components.

As used herein, the terms "treating" or "treat" includes (i) preventing a pathologic condition from occurring (e.g., prophylaxis); (ii) inhibiting the

pathologic condition or arresting its development; (iii) relieving the pathologic condition; and/or (iv) diminishing symptoms associated with the pathologic condition. As used herein, "ameliorate" means to diminish symptoms associated with the pathologic condition.

As used herein, "μg" denotes microgram, "mg" denotes milligram, "g" denotes gram, "μL" denotes microliter, "mL" denotes milliliter, "L" denotes liter, "nM" denotes nanomolar, "μM" denotes micromolar, "mM" denotes millimolar, "M" denotes molar, and "nm" denotes nanometer.

Concentrations, amounts, etc., of various components are often presented in a range format throughout this disclosure. The description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the claimed invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub ranges as well as individual numerical values within that range. For example, description of a range such as 1% to 8% should be considered to have specifically disclosed sub ranges such as 1% to 7%, 2% to 8%, 2% to 6%, 3% to 6%, 4% to 8%, 3% to 8% etc., as well as individual numbers within that range, such as, 2%, 5%, 7% etc. This construction applies regardless of the breadth of the range and in all contexts throughout this disclosure.

In the claims provided herein, the steps specified to be taken in a claimed method or process may be carried out in any order without departing from the principles of the invention, except when a temporal or operational sequence is explicitly defined by claim language. Recitation in a claim to the effect that first a step is performed then several other steps are performed shall be taken to mean that the first step is performed before any of the other steps, but the other steps may be performed in any sequence unless a sequence is further specified within the other steps. For example, claim elements that recite "first A, then B, C, and D, and lastly E" shall be construed to mean step A should be first, step E should be last, but steps B, C, and D may be carried out in any sequence between steps A and E and the process of that sequence will still fall within the four corners of the claim.

Furthermore, in the claims provided herein, specified steps may be carried out concurrently unless explicit claim language requires that they be carried out separately or as parts of different processing operations. For

example, a claimed step of doing X and a claimed step of doing Y may be conducted simultaneously within a single operation, and the resulting process will be covered by the claim. Thus, a step of doing X, a step of doing Y, and a step of doing Z may be conducted simultaneously within a single process step, or in two separate process steps, or in three separate process steps, and that process will still fall within the four corners of a claim that recites those three steps.

Similarly, except as explicitly required by claim language, a single substance or component may meet more than a single functional requirement, provided that the single substance fulfills the more than one functional requirement as specified by claim language.

Description

In various embodiments, the invention provides a method of reducing the susceptibility of a population of mammalian cells in a mammal to infection by HCV comprising blocking or deactivating the Sigma 1 receptor expressed in the population of cells, wherein the blocking or deactivating takes place *in vivo*.

In various embodiments, the invention provides a method of reducing the susceptibility of the population of mammalian cells by inhibiting the viral spread of Hepatitis C virus in a population of cells in a mammal exposed to an infectious inoculum of a Hepatitis C virus.

For example, blocking or deactivating can comprise administering an effective amount of a Sigma 1 receptor binding compound to the mammalian cells. Alternatively, blocking or deactivating can comprise administering an effective amount of an interfering RNA or analog thereof to the mammalian cells wherein the interfering RNA or analog blocks or decreases expression of a gene coding for a protein comprising the Sigma 1 receptor. Or, both a Sigma 1 receptor binding compound and an interfering RNA or analog thereof can be administered in effective amounts.

In various embodiments, the invention provides a method of treating a Hepatitis C viral infection in a mammal, or of ameliorating symptoms of a Hepatitis C viral infection in a mammal, or of preventing viral spread of Hepatitis C virus among mammalian cells therein, or any combination thereof, comprising administering to the mammal an amount of a Sigma 1 receptor

binding compound, or an interfering RNA or analog thereof wherein the interfering RNA or analog blocks or decreases expression of a gene coding for the Sigma 1 receptor, or both; in a dose, at a frequency, and for a duration sufficient to provide a beneficial effect to the mammal.

The Sigma 1 receptor, also known as the "opioid receptor sigma 1". "SIGMAR1", or "OPRS1", has previously been associated with a variety of mental malconditions in humans, such as schizophrenia, clinical depression, cocaine abuse, as well as with physical malconditions such as cardiovascular malfunction and cancer. It has not previously, to the knowledge of the inventors herein, been implicated in viral infections. It has surprisingly been found by the inventors and is disclosed herein that the anti-HCV bioactivity of a subset of compounds identified by screening of a random library of a set of compounds is highly correlated with Sigma 1 receptor binding bioactivity of that subset of compounds.

The anti-HCV bioactivity can be apparent at very low doses of the Sigma 1 binding compound, such as at sub-micromolar levels. Many of the Sigma 1 binding compounds disclosed herein are already in medicinal use for the treatment of conditions unrelated to viral infections. Certain of the compounds that bind to the Sigma 1 receptor are used at much higher doses in therapeutic applications, for example as anti-psychotics; however, the present disclosure includes compositions and methods for protection of cells, tissues and patients against the effects of a Hepatitis C virus infection at doses of the compounds that can be well below the doses in which the compounds are administered for treatment of conditions not associated with HCV infection. The Sigma 1 receptor binding compounds, which can be provided in low-dosage forms, can be used for administration to a patient in need of protection from a Hepatitis C virus infection, or a patient in need of amelioration of the symptoms of an HCV infection. Due to their long history of usage, approval and known dosages and side-effects, such known compounds that bind to the Sigma 1 receptor have a heightened potential for regulatory approval for use in Hepatitis C virus infected individuals. It has been found by the inventors herein that the known Sigma 1 receptor antagonist BD1047 (N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino)ethylamine), having an IC_{50} value of about 850 nM, exhibits a

profound inhibitory effect on the infection of mammalian cells in culture by HCV.

It has also been found by the inventors herein that an interfering RNA targeting the Sigma 1 receptor also exhibits a profound inhibitory effect on the infection of mammalian cells in culture by HCV. An interfering RNA is a relatively short antisense strand complementary to a coding region of a gene that encodes a protein comprising the Sigma 1 receptor. To the extent that post-translational modification of the gene product may occur to provide the mature Sigma 1 receptor protein, a 223 amino acid sequence, the interfering RNA (siRNA) can be complementary to a portion of the coding sequence for the mature receptor, or can be complementary to a portion of the coding sequence for protein fragments removed in any post-translational modification that occurs, provided that the interfering RNA or analog thereof blocks or decreases the level of expression of the gene to provide the mature, functional receptor in mammalian cells.

In various embodiments of the invention, the mammal can be a human and the mammalian cells can be human cells.

In various embodiments of the invention wherein cells are contacted with a Sigma 1 receptor binding compound or the compound is administered to a mammal, the cells can be contacted with the compound or the compound administered to the mammal prior to or substantially concurrently with the exposure of the cells to the infectious inoculum of the Hepatitis C virus. In other embodiments, the cells can be contacted with the compound or the compound administered to the mammal after exposure of the cells or the mammal with an infectious inoculum of Hepatitis C virus.

In various embodiments with an interfering RNA or analog thereof, the cells can be contacted with or the mammal administered the RNA or analog prior to or substantially concurrently with the exposure of the cells to the infectious inoculum of the Hepatitis C virus. In other embodiments, the cells can be contacted with or the mammal administered the RNA or the RNA analog after exposure of the cells or the mammal to an infectious inoculum of Hepatitis C virus.

In various embodiments of the invention wherein a Sigma 1 receptor binding compound or interfering RNA or analog thereof is administered to a

mammal to prevent or treat an HCV infection, the compound or the RNA can be administered to the mammal either prior to Hepatitis C infection or in the early stages of a Hepatitis C infection. In various embodiments, the Sigma 1 receptor binding compound or the interfering RNA inhibits the viral spread within a population of potential viral host cells in the mammal, thus at least ameliorating the symptoms of HCV even if a low degree of infection occurs.

In various embodiments of the invention, the Sigma 1 receptor binding compound can have a high affinity binding constant with respect to the Sigma 1 receptor, for example of less than about 1 μM. A subset of compounds having a high affinity binding constant with respect to the Sigma 1 receptor, selected from among a set of compounds screened for Sigma 1 receptor binding activity, can be used as a pre-screened subset of compounds for testing against HCV virus. The high degree of correlation unexpectedly found by the inventors herein between anti-HCV bioactivity and Sigma 1 receptor binding activity provides for a higher "hit" rate of compounds in this subset of high affinity Sigma 1 binding compounds for potential medicinal compounds for treatment of HCV infections in humans.

In various embodiments of the invention, the compound that binds to the Sigma 1 receptor can be in a neutral form, in an acid or base form, or in a salt form. For example, a Sigma 1 receptor binding compound can be a free acid, or a salt thereof; or the compound can be a basic amine, or a salt thereof.

In various embodiments of the invention, the Sigma 1 receptor binding compound can comprise a pharmaceutically acceptable salt, a prodrug, a metabolite thereof, or a combination thereof. For example, a compound that is a basic amine can be provided as a hydrochloride salt, a sulfate salt, a tartrate salt, or a salt of an acid that is not itself toxic or detrimental to a human upon ingestion. A prodrug of a Sigma 1 receptor binding compound can be a compound, as are well known in the art, that is metabolically transformed by enzymes endogenous to human tissue into the active form. For example, a prodrug can be an ester, such as an acetate ester, of a compound bearing a hydroxyl group, wherein the acetate ester is hydrolyzed to the hydroxyl-bearing active compound by an endogenous non-specific esterase. Other examples of prodrugs are well known to those of ordinary skill in the art. A metabolite of a Sigma 1 receptor binding compound, as is well known in the art, is a chemical

compound that is the product of a metabolic reaction of a compound within the organism. For example, a Sigma 1 receptor binding compound that is endogenously deacetylated by an endogenous non-specific esterase, wherein the deacetylated metabolite has anti-HCV activity, can be used according to an inventive method herein.

In various embodiments of the invention, the Sigma 1 receptor binding compound can comprise a solvate, a polymorph, a racemate, a pure stereoisomer, or a combination thereof. A solvate is a molecular composition comprising the compound and a certain percentage of a solvent, such as an organic solvent, or such as water (a special example of a solvate termed a hydrate). A polymorph, as is well known in the art, is one of several crystalline forms that a particular Sigma 1 receptor binding compound can crystallize in. Different polymorphs can, for example, possess different bioavailability, but provided the polymorph has some bioavailability, it can serve as an anti-HCV treatment according to an inventive method herein. A racemate, as is well known in the art, is a 1:1 mixture of two enantiomers (optical isomers) of a compound. A racemate of a Sigma 1 receptor binding compound can be used for treatment of HCV as disclosed and claimed herein, even if only one stereoisomer of the racemate possesses the Sigma 1 receptor binding bioactivity, provided that the other stereoisomer is not toxic or otherwise detrimental to the organism. In various embodiments of the invention, the Sigma 1 receptor binding compound can comprise an enantiomer, a diasteromer, or a combination thereof. Alternatively, a pure stereoisomer, free of an inactive enantiomeric or diastereomeric form, having Sigma 1 receptor binding bioactivity, can be used in the treatment of an HCV infection.

In various embodiments of the invention, the Sigma 1 receptor binding compound can act on the Sigma 1 receptor as an antagonist, an agonist, or an allosteric regulator. It is believed by the inventors herein that the exemplary compounds are almost entirely antagonists of the Sigma 1 receptor; however, it may be that an agonist or an allosteric regulator of the Sigma 1 receptor can interfere with the Sigma 1 receptor in such a manner as to provide anti-HCV bioactivity.

In various embodiments of the invention, the Sigma 1 receptor binding compound can be azelastine, (-)-cyanopindolol hemifumarate, (2-ibutylamino-

ethyl)-carbamic acid 2-(4-benzofuran-2-yl)methyl-piperazin-1-yl)-ethyl ester, (4-[1,2,3]thiadiazol-4-yl-benzyl)-carbamic acid 1-(3-methoxy-2-nitro-benzyl)-piperidin-3-yl)methyl ester, (S)-methamphetamine HCl, [1-(9-ethyl-9H-carbazol-3-yl)methyl)-pyrrolidin-3-yl]-carbamic acid 1-(3-benzyloxy-4-methoxy-benzyl)-piperidin-3-yl)methyl ester, [1-(9-ethyl-9H-carbazol-3-yl)methyl)-pyrrolidin-3-yl]-carbamic acid 2-(tert-butoxycarbonyl-naphthalen-1-yl)methyl-amino)-ethyl ester, [4-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-phenyl]-[4-(3-phenyl-allyl)-piperazin-1-yl]-methanone, 1-(1,2-diphenylethyl)piperidine aleate, (+/-) 1-(1-naphthyl)piperazine HCl, 1-(3-chlorophenyl)piperazine HCl, 1-(4-bromo-benzenesulfonyl)-4-(2-tert-butylsulfanyl-benzyl)-piperazine, 2-(2-{[1-(3-chloro-benzyl)-pyrrolidin-3-yl]-methyl-carbamoyl}-2-methyl-propyl)-4,6-dimethyl-benzoic acid, 2-chloro-11-(4-methylpiperazino)dibenz[B, F]oxepin maleate, 3,3'-diethylthiacarbocyanine iodide, 3-mercapto-2-methylpropanoic acid 1,2-diphenylethylamine, 3-quinuclidinyl benzilate, 3-tropanyl-3,5-dichlorobenzoate, 3-tropanyl-indole-3-carboxylate HCl, 4-(1H-indol-4-yl)-piperazine-1-carboxylic acid 2-(5-bromo-2-ethoxy-, 4-(2-tert-butylsulfanyl-benzyl)-piperazine-1-carboxylic acid-2-phenylamino)-cyclohexylmethyl ester, thiophen-2-yl-ethyl ester, 4-(3,5-dimethoxy-phenyl)-piperazine-1-carboxylic acid 1-(2-fluoro-benzyl)-piperidin-2-yl)methyl ester, 4-(3-nitro-5-sulfamoyl-thiophen-2-yl)-piperazine-1-carboxylic acid 1-(2-fluoro-5-methoxy-benzyl)-piperidin-3-yl)methyl ester, 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)piperidine oxalate, 4-(5-trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid pent-2-ynyl ester, 4,4'-bis[4-(P-chlorophenyl)-4-hydroxypiperidino]butyrophenone, 4-[1-(4-chlorobenzyl)-4-(benzylpiperidin-4-yl]-2-hydroxy-4-oxobut-2-enoic acid 4-bromo-N-[1-(9-ethyl-9H-carbazol-3-yl)methyl)-pyrrolidin-3-yl)]-2-trifluoromethoxy-benzenesulfonamide, cardevilol, clobenprobit, 4'-chloro-3-α-(diphenylmethoxy)tropane HCl, 4-furan-2-yl)methyl-piperazine-1-carboxylic acid 2-{4-[3-(2-trifluoromethyl-phenothiazin-10-yl)-propyl]-piperazin-1-yl)}-ethyl ester, 4-methoxy-N-[1-(7-methoxy-benzo[1,3]dioxol-5-yl)methyl)-pyrrolidin-3-yl)]-benzenesulfonamide, 5-(N-ethyl-N-isopropyl)-amiloride, 7-hydroxy-DPAT HBr, (R)-(+)-, 8-Hydroxy-DPAT HBr, S(-)-9-[4-({[4'-(trifluoromethyl)-1,1'-biphenyl-2-yl]carbonyl}amino)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, acepromazine maleate, acetophenazine maleate, acrinol ajmaline, alaproclate HCl, aloe-emodin,

alprenolol D-tartrate hydrate, alprenolol HCl, AMI-193, aminobenztropine, amiodarone HCl, amodiaquine HCl, amorolfine HCl, amoxapine, anileridine HCl, anisotropine methylbromide, anpirtoline ARC 239·2HCl, astemizole auramine O HCl, azaperone, azatadine maleate, azelastine HCl, bamethan sulfate, BD 1008·2HBr, BD-1047, BD-1063, benextramine·4HCl, benfluorex HCl, benidipine HCl, benoxathian HCl, benoxinate HCl, benperidol, benproperine phosphate, benzododecinium bromide, benzphetamine HCl, benztropine mesylate, benzydamine HCl, bephenium hydroxynaphthoate, bepridil HCl, berberine chloride, betaxolol HCl, bifemelane, BMY 7378·2HCl, bopindolol malonate, BP 554, maleate, bromhexine HCl, bromodiphenhydramine HCl, bromperidol, brompheniramine maleate, BTCP HCl, buclizine HCl, buflomedil HCl, bupropion HCl, buspirone HCl, butacaine sulfate, butaclamol HCl, (±)-butenafine HCl, butoconazole nitrate, BW 723C86 HCl, carbetapentane citrate, carbinoxamine maleate, carpipramine·2HCl, DiH2O, carvedilol, cephapirin benzathine CGS-12066A maleate, chloroprocaine HCl, chloroquine phosphate, chlorpheniramine maleate, chlorphenoxamine HCl, chlorpromazine HCl, chlorprothixene, cinanserin HCl, cinnarizine, cirazoline HCl, cis-(+/-)-N-Methyl-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexamine·2HBr, cis(Z)-flupentixol·2HCl, cisapride hydrate, citalopram HBr clebopride maleate, clemastine fumarate, clemizole HCl, clenbuterol HCl, clidinium bromide, CSG 12066B, clobenpropit·2HBr clofazimine, clofilium tosylate, clomiphene citrate, clomiphene A, clomipramine, cloperastine HCl, clorgyline HCl, clozapine, cyclizine, cyclobenzaprine HCl, cycloheximide, cyproheptadine HCl, demecarium bromide, denatonium benzoate, deptropine citrate, desloratadine, dexbrompheniramine maleate, dexchlorpheniramine maleate, dexfenfluramine HCl, dibucaine HCl, dicyclomine HCl, diethylpropion HCl, dimethisoquin HCl, dimetindene maleate, diphemanil methylsulfate, diphenidol HCl, diphenoxylate HCl, diphenylpyraline HCl, dipropyldopamine HBr, dobutamine HCl, donepezil HCl, doxepin HCl, droperidol, duloxetine, dyclonine HCl, ebastine, econazole nitrate, epinastine HCl, ethaverine HCl, ethopropazine HCl, eticlopride HCl, S(-)-etofenamate, etonitazenyl esothiocyanate, femoxetine HCl, fenfluramine HCl, fentanyl citrate, fenticonazole nitrate, fipexide HCl, flavoxate HCl, flunarizine·2HCl, fluoxetine B, fluperlapine, fluphenazine decanoate·2HCl,

fluphenazine enanthate·2HCl, fluphenazine HCl, fluphenazine N-mustard·2HCl, flurazepam C, fluspirilene fluvoxamine maleate, GBR 12783·2HCl, GBR 12909·2HCl, GBR 13069·2HCl, GBR-12935·2HCl, GR 89696, fumarate guanabenz acetate, guanadrel sulfate, guanethidine sulfate, halofantrine HCl, haloperidol, hexylcaine HCl, hycanthone hydroxychloroquine sulfate, hydroxyzine HCl, hyoscyamine sulfate, IBZM, S(-)-ICI-199,441 HCl, ifenprodil tartrate, imipramine HCl, indatraline HCl, llofetamine HCl, irinotecan HCl, isamoltane hemifumarate, isopromethazine HCl, isoxsuprine HCl, ketanserin L-tartrate, ketoconazole, ketotifen fumarate, L-693,403 maleate, L-741,626, L-741,742 HCl, L-745,870·3HCl, labetalol HCl, levetimide HCl, R(-) levobunolol HCl, lidoflazine, lisuride hydrogen maleate, R(+)-lobeline HCl, lomerizine·2HCl, lofepramine, loperamide HCl, loxapine succinate, LY-53,857, maleate maprotiline HCl, mazindol, MDL 12,330A HCl, mebhydroline 1,5-naphthalendisulfonate, meclizine HCl, mefloquine HCl, meprylcaine HCl, mesoridazine besylate, metaphit methanesulfonate, metergoline methantheline bromide, methdilazine, methiothepin mesylate, methixene HCl, methoctramine, methotrimeprazine maleate, methylene violet 3 HCl, metipranolol mexiletine HCl, mianserin HCl, miconazole, ML-9 HCl, morantel hydrogen L-tartrate, MR 16728 HCl, N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine HCl, N'-[2-(benzo[1,2,5]thiadiazole-4-sulfonylamino)-acetyl]-hydrazinecarboxylic acid 2-(2-{4-[(4-chloro-phenyl)-phenyl-methyl]-piperazin-1-yl)}-ethoxy)-ethyl ester, nafronyl oxalate, naftifine, naftopidil·2HCl, naltriben mesylate, NAN-190 HBr, NE-100, nefazodone, nefopam HCl, nicardipine HCl, nicergoline, niguldipine HCl, (+/-)-nisoxetine HCl, nortriptyline HCl, nylidrin HCl, octoclothepin maleate, (±) orphenadrine citrate, oxamniquine, oxamniquine A, oxamniquine B, oxatomide, oxiconazole nitrate, oxybutynin HCl, panaxatriol, PAPP methyl triparoxetine, paxilline, p-chlorobenzhydrylpiperazine, penbutolol sulfate, pentamidine isethionate, entazocine, (±)-pergolide methanesulfonate, perhexiline maleate, perospirone, perphenazine, perphenazine sulfoxide, phenamil methanesulfonate, phencyclidine HCl, phenosafranin HCl, phenoxybenzamine HCl, phenyltoloxamine citrate, piboserod, pimozide, pinacyanol chloride, pindobind, (+/-)-piperacetazine, piperazine-1,4-dicarboxylic acid benzyl ester, 2-[4-(4-dimethylamino-benzyl)-piperazin-1-yl)]-ethyl ester, piperidolate HCl, pirenperone, PPHT HCl, (±)-pramoxine HCl, prenylamine lactate, pridinol

methanesulfonate, prochlorperazine maleate, procyclidine HCl, proflavine hemisulfate, progesterone, promazine HCl, promethazine HCl, propafenone HCl, proparacaine HCl, propericyazine, propiomazine propranolol HCl, protokylol protriptyline HCl, pyrilamine maleate, pyrimethamine, pyrrolidine-1,2-dicarboxylic acid 1-[1-(4-allyloxy-benzyl)-piperidin-2-yl)methyl] ester, 2-benzyl ester pyrvinium pamoate, quetiapine fumarate, quinacrine HCl, quinaldine red, quipazine dimaleate, quipazine, raloxifene, rimantadine HCl, rimcazole, risperidone, ritanserin ritodrine HCl, RS 23597-190 HCl, RS 67333 HCl, RS 67506 HCl, safranin O HCl, salmeterol, SB203186, SCH-23390 HCl, R(+)-sertaconazole nitrate, sertindole sertraline, sibutramine HCl, SKF-525A HCl, SKF-96365 HCl, SNC 121, spiperone HCl, sufentanil, T-226296, tamoxifen citrate, tamsulosin HCl, tegaserod maleate, terbinafine HCl, terconazole, terfenadine, terfenadine A, tetracaine HCl, tetrindole mesylate, thiethylperazine malate, thioperamide maleate, thioproperazine, thioridazine, thiothixene thiothixene, (E)-thonzonium bromide tioconazole A, TMB-8 HCl, tolterodine L-tartrate, toremifene citrate, tramazoline HCl, trans-U-50488 methanesulfonate, (±)-trazodone HCl, tridihexethyl chloride, trifluoperazine HCl, trifluperidol HCl, triflupromazine HCl, trihexyphenidyl HCl, trimebutine, trimeprazine hemi-L-tartrate, trimipramine maleate, tripelennamine HCl, triprolidine HCl, triprolidine HCl, tropanyl 3,5-dimethylbenzoate, tropine 2-(4-chlorophenoxy)butanoate, maleate, U-50488 HCl, U-62066, UH 232 maleate, (+)-vecuronium bromide, verapamil HCl, verapamil B vesamicol HCl, vinpocetine W-7 HCl, WB-4101 HCl, xylazine, xylometazoline HCl; or a combination thereof.

In various embodiments of the invention, the Sigma 1 receptor binding compound can be amiodarone HCl, azelastine HCl, benproperine phosphate, carvedilol, cyproheptadine HCl, desloratadine, fluphenazine HCl, haloperidol, lofepramine, methyl paroxetine, prochlorpromazine, rimcazole, salmeterol, trifluoperazine·2HCl; or a combination thereof.

When the inventive method involves a step of contacting cells, the contacting can be *in vitro* or *in vivo*. When administering a Sigma 1 binding compound or an interfering RNA to a patient, it is understood that the method is directed to an *in vivo* use.

In various embodiments of the invention, a medicament having anti-Hepatitis C virus activity, other than a Sigma 1 receptor binding compound or

interfering RNA, can be additionally administered. For example, a medicament having anti-Hepatitis C virus activity can be an interferon, ribavirin, or a combination thereof. More specifically, the interferon can comprise interferon α2b, pegylated interferon α, consensus interferon, interferon α2a, lymphoblastoid interferon τ, or a combination thereof. Or, the medicament having anti-Hepatitis C virus activity can be interleukin 2, interleukin 6, interleukin 12, interfering RNA, anti-sense RNA, imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, a viral protease inhibitor, a viral nuclease inhibitor, amantadine, rimantadine, or a combination thereof.

In various embodiments, the invention provides a method of screening each compound of a set of compounds for anti-HCV activity, comprising determining a binding constant for each compound of the set of compounds with respect to the Sigma 1 receptor; then, selecting a subset of the set wherein the compounds each have a binding constant with respect to the Sigma 1 receptor of less than about 1 μM; then, testing each of the subset of compounds for anti-HCV activity, wherein a percentage of active anti-HCV compounds among the subset is greater than a percentage of active anti-HCV compounds among the set.

In various embodiments, the invention provides a use of a Sigma 1 receptor binding compound or of an interfering RNA or analog thereof to the mammalian cells wherein the interfering RNA or analog blocks or decreases expression of a gene coding for a protein comprising the Sigma 1 receptor, or both, for the manufacture of a medicament for the treatment of a Hepatitis C virus infection.

The compound used for the manufacture of the medicament for the treatment of a Hepatitis C virus infection can be azelastine, (-)-cyanopindolol hemifumarate, (2-ibutylamino-ethyl)-carbamic acid 2-(4-benzofuran-2-yl)methyl-piperazin-1-yl)-ethyl ester, (4-[1,2,3]thiadiazol-4-yl-benzyl)-carbamic acid 1-(3-methoxy-2-nitro-benzyl)-piperidin-3-yl)methyl ester, (S)-methamphetamine HCl, [1-(9-ethyl-9H-carbazol-3-yl)methyl)-pyrrolidin-3-yl]-carbamic acid 1-(3-benzyloxy-4-methoxy-benzyl)-piperidin-3-yl)methyl ester, [1-(9-ethyl-9H-carbazol-3-yl)methyl)-pyrrolidin-3-yl]-carbamic acid 2-(tert-butoxycarbonyl-naphthalen-1-yl)methyl-amino)-ethyl ester, [4-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-phenyl]-[4-(3-phenyl-allyl)-piperazin-1-yl]-methanone, 1-(1,2-diphenylethyl)piperidine aleate, (+/-) 1-(1-naphthyl)piperazine HCl, 1-(3-

chlorophenyl)piperazine HCl, 1-(4-bromo-benzenesulfonyl)-4-(2-tert-butylsulfanyl-benzyl)-piperazine, 2-(2-{[1-(3-chloro-benzyl)-pyrrolidin-3-yl]-methyl-carbamoyl}-2-methyl-propyl)-4,6-dimethyl-benzoic acid, 2-chloro-11-(4-methylpiperazino)dibenz[B, F]oxepin maleate, 3,3'-diethylthiacarbocyanine iodide, 3-mercapto-2-methylpropanoic acid 1,2-diphenylethylamine, 3-quinuclidinyl benzilate, 3-tropanyl-3,5-dichlorobenzoate, 3-tropanyl-indole-3-carboxylate HCl, 4-(1H-indol-4-yl)-piperazine-1-carboxylic acid 2-(5-bromo-2-ethoxy-, 4-(2-tert-butylsulfanyl-benzyl)-piperazine-1-carboxylic acid-2-phenylamino)-cyclohexylmethyl ester, thiophen-2-yl-ethyl ester, 4-(3,5-dimethoxy-phenyl)-piperazine-1-carboxylic acid 1-(2-fluoro-benzyl)-piperidin-2-yl)methyl ester, 4-(3-nitro-5-sulfamoyl-thiophen-2-yl)-piperazine-1-carboxylic acid 1-(2-fluoro-5-methoxy-benzyl)-piperidin-3-yl)methyl ester, 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)piperidine oxalate, 4-(5-trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid pent-2-ynyl ester, 4,4'-bis[4-(P-chlorophenyl)-4-hydroxypiperidino]butyrophenone, 4-[1-(4-chlorobenzyl)-4-(benzylpiperidin-4-yl]-2-hydroxy-4-oxobut-2-enoic acid 4-bromo-N-[1-(9-ethyl-9H-carbazol-3-yl)methyl)-pyrrolidin-3-yl)]-2-trifluoromethoxy-benzenesulfonamide, cardevilol, clobenprobit, 4'-chloro-3-α-(diphenylmethoxy)tropane HCl, 4-furan-2-yl)methyl-piperazine-1-carboxylic acid 2-{4-[3-(2-trifluoromethyl-phenothiazin-10-yl)-propyl]-piperazin-1-yl)}-ethyl ester, 4-methoxy-N-[1-(7-methoxy-benzo[1,3]dioxol-5-yl)methyl)-pyrrolidin-3-yl)]-benzenesulfonamide, 5-(N-ethyl-N-isopropyl)-amiloride, 7-hydroxy-DPAT HBr, (R)-(+)-, 8-Hydroxy-DPAT HBr, S(-)-9-[4-({[4'-(trifluoromethyl)-1,1'-biphenyl-2-yl]carbonyl}amino)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, acepromazine maleate, acetophenazine maleate, acrinol ajmaline, alaproclate HCl, aloe-emodin, alprenolol D-tartrate hydrate, alprenolol HCl, AMI-193, aminobenztropine, amiodarone HCl, amodiaquine HCl, amorolfine HCl, amoxapine, anileridine HCl, anisotropine methylbromide, anpirtoline ARC 239·2HCl, astemizole auramine O HCl, azaperone, azatadine maleate, azelastine HCl, bamethan sulfate, BD 1008·2HBr, BD-1047, BD-1063, benextramine·4HCl, benfluorex HCl, benidipine HCl, benoxathian HCl, benoxinate HCl, benperidol, benproperine phosphate, benzododecinium bromide, benzphetamine HCl, benztropine mesylate, benzydamine HCl, bephenium hydroxynaphthoate,

bepridil HCl, berberine chloride, betaxolol HCl, bifemelane, BMY 7378·2HCl, bopindolol malonate, BP 554, maleate, bromhexine HCl, bromodiphenhydramine HCl, bromperidol, brompheniramine maleate, BTCP HCl, buclizine HCl, buflomedil HCl, bupropion HCl, buspirone HCl, butacaine sulfate, butaclamol HCl, (±)-butenafine HCl, butoconazole nitrate, BW 723C86 HCl, carbetapentane citrate, carbinoxamine maleate, carpipramine·2HCl, DiH2O, carvedilol, cephapirin benzathine CGS-12066A maleate, chloroprocaine HCl, chloroquine phosphate, chlorpheniramine maleate, chlorphenoxamine HCl, chlorpromazine HCl, chlorprothixene, cinanserin HCl, cinnarizine, cirazoline HCl, cis-(+/-)-N-Methyl-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexamine·2HBr, cis(Z)-flupentixol·2HCl, cisapride hydrate, citalopram HBr clebopride maleate, clemastine fumarate, clemizole HCl, clenbuterol HCl, clidinium bromide, CSG 12066B, clobenpropit·2HBr clofazimine, clofilium tosylate, clomiphene citrate, clomiphene A, clomipramine, cloperastine HCl, clorgyline HCl, clozapine, cyclizine, cyclobenzaprine HCl, cycloheximide, cyproheptadine HCl, demecarium bromide, denatonium benzoate, deptropine citrate, desloratadine, dexbrompheniramine maleate, dexchlorpheniramine maleate, dexfenfluramine HCl, dibucaine HCl, dicyclomine HCl, diethylpropion HCl, dimethisoquin HCl, dimetindene maleate, diphemanil methylsulfate, diphenidol HCl, diphenoxylate HCl, diphenylpyraline HCl, dipropyldopamine HBr, dobutamine HCl, donepezil HCl, doxepin HCl, droperidol, duloxetine, dyclonine HCl, ebastine, econazole nitrate, epinastine HCl, ethaverine HCl, ethopropazine HCl, eticlopride HCl, S(-)-etofenamate, etonitazenyl esothiocyanate, femoxetine HCl, fenfluramine HCl, fentanyl citrate, fenticonazole nitrate, fipexide HCl, flavoxate HCl, flunarizine·2HCl, fluoxetine B, fluperlapine, fluphenazine decanoate·2HCl, fluphenazine enanthate·2HCl, fluphenazine HCl, fluphenazine N-mustard·2HCl, flurazepam C, fluspirilene fluvoxamine maleate, GBR 12783·2HCl, GBR 12909·2HCl, GBR 13069·2HCl, GBR-12935·2HCl, GR 89696, fumarate guanabenz acetate, guanadrel sulfate, guanethidine sulfate, halofantrine HCl, haloperidol, hexylcaine HCl, hycanthone hydroxychloroquine sulfate, hydroxyzine HCl, hyoscyamine sulfate, IBZM, S(-)-ICI-199,441 HCl, ifenprodil tartrate, imipramine HCl, indatraline HCl, llofetamine HCl, irinotecan HCl, isamoltane hemifumarate, isopromethazine HCl, isoxsuprine HCl, ketanserin L-

tartrate, ketoconazole, ketotifen fumarate, L-693,403 maleate, L-741,626, L-741,742 HCl, L-745,870·3HCl, labetalol HCl, levetimide HCl, R(-) levobunolol HCl, lidoflazine, lisuride hydrogen maleate, R(+)-lobeline HCl, lomerizine·2HCl, lofepramine, loperamide HCl, loxapine succinate, LY-53,857, maleate maprotiline HCl, mazindol, MDL 12,330A HCl, mebhydroline 1,5-naphthalendisulfonate, meclizine HCl, mefloquine HCl, meprylcaine HCl, mesoridazine besylate, metaphit methanesulfonate, metergoline methantheline bromide, methdilazine, methiothepin mesylate, methixene HCl, methoctramine, methotrimeprazine maleate, methylene violet 3 HCl, metipranolol mexiletine HCl, mianserin HCl, miconazole, ML-9 HCl, morantel hydrogen L-tartrate, MR 16728 HCl, N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine HCl, N'-[2-(benzo[1,2,5]thiadiazole-4-sulfonylamino)-acetyl]-hydrazinecarboxylic acid 2-(2-{4-[(4-chloro-phenyl)-phenyl-methyl]-piperazin-1-yl)}-ethoxy)-ethyl ester, nafronyl oxalate, naftifine, naftopidil·2HCl, naltriben mesylate, NAN-190 HBr, NE-100, nefazodone, nefopam HCl, nicardipine HCl, nicergoline, niguldipine HCl, (+/-)-nisoxetine HCl, nortriptyline HCl, nylidrin HCl, octoclothepin maleate, (±) orphenadrine citrate, oxamniquine, oxamniquine A, oxamniquine B, oxatomide, oxiconazole nitrate, oxybutynin HCl, panaxatriol, PAPP methyl triparoxetine, paxilline, p-chlorobenzhydrylpiperazine, penbutolol sulfate, pentamidine isethionate, entazocine, (±)-pergolide methanesulfonate, perhexiline maleate, perospirone, perphenazine, perphenazine sulfoxide, phenamil methanesulfonate, phencyclidine HCl, phenosafranin HCl, phenoxybenzamine HCl, phenyltoloxamine citrate, piboserod, pimozide, pinacyanol chloride, pindobind, (+/-)-piperacetazine, piperazine-1,4-dicarboxylic acid benzyl ester, 2-[4-(4-dimethylamino-benzyl)-piperazin-1-yl)]-ethyl ester, piperidolate HCl, pirenperone, PPHT HCl, (±)-pramoxine HCl, prenylamine lactate, pridinol methanesulfonate, prochlorperazine maleate, procyclidine HCl, proflavine hemisulfate, progesterone, promazine HCl, promethazine HCl, propafenone HCl, proparacaine HCl, propericyazine, propiomazine propranolol HCl, protokylol protriptyline HCl, pyrilamine maleate, pyrimethamine, pyrrolidine-1,2-dicarboxylic acid 1-[1-(4-allyloxy-benzyl)-piperidin-2-yl)methyl] ester, 2-benzyl ester pyrvinium pamoate, quetiapine fumarate, quinacrine HCl, quinaldine red, quipazine dimaleate, quipazine, raloxifene, rimantadine HCl, rimcazole, risperidone, ritanserin ritodrine HCl, RS 23597-190 HCl, RS 67333 HCl, RS

67506 HCl, safranin O HCl, salmeterol, SB203186, SCH-23390 HCl, R(+)-sertaconazole nitrate, sertindole sertraline, sibutramine HCl, SKF-525A HCl, SKF-96365 HCl, SNC 121, spiperone HCl, sufentanil, T-226296, tamoxifen citrate, tamsulosin HCl, tegaserod maleate, terbinafine HCl, terconazole, terfenadine, terfenadine A, tetracaine HCl, tetrindole mesylate, thiethylperazine malate, thioperamide maleate, thioproperazine, thioridazine, thiothixene thiothixene, (E)-thonzonium bromide tioconazole A, TMB-8 HCl, tolterodine L-tartrate, toremifene citrate, tramazoline HCl, trans-U-50488 methanesulfonate, (±)-trazodone HCl, tridihexethyl chloride, trifluoperazine HCl, trifluperidol HCl, triflupromazine HCl, trihexyphenidyl HCl, trimebutine, trimeprazine hemi-L-tartrate, trimipramine maleate, tripelennamine HCl, triprolidine HCl, triprolidine HCl, tropanyl 3,5-dimethylbenzoate, tropine 2-(4-chlorophenoxy)butanoate, maleate, U-50488 HCl, U-62066, UH 232 maleate, (+)-vecuronium bromide, verapamil HCl, verapamil B vesamicol HCl, vinpocetine W-7 HCl, WB-4101 HCl, xylazine, xylometazoline HCl; or a combination thereof.

Compounds binding to the Sigma 1 receptor typically are known as Sigma 1 receptor ligands and are well known in the art. Ligands can include antagonists (binding to but not activating the receptor, and blocking the effects of agonists), agonists (binding to and activating the receptor), and allosteric regulators (binding to the receptor at a site other than the agonist-binding site, and altering the receptor's affinity for binding compounds at the agonist-binding site). It is believed that the majority of above-listed exemplary compounds are Sigma 1 receptor antagonists, or inhibitors. It is believed that interfering RNAs are antagonists insomuch as they block but do not activate the receptor.

There are many uses known for Sigma 1 receptor ligands such as antipsychotic drugs, anxiolytics, antidepressants, the treatment of stroke, antiepileptic drugs and many other indications; however, until the discovery by the inventors herein, there has not been any indication that these compounds are useful against Hepatitis C virus infection.

Unless otherwise stated, the compounds that bind to the Sigma 1 receptor include, for example, compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by a deuterium or tritium, or

the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon or ^{15}N-enriched nitrogen are within the scope of this invention.

Combination Therapy

The compounds that bind to the Sigma 1 receptor or the interfering RNAs can also be used in combination with other active ingredients. Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmacologic properties of the combination.

It is also possible to combine any compound or RNA of the invention with one or more other active ingredients in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

The combination therapy may provide "synergy" and "synergistic effect," *i.e.*, the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, *e.g.*, in separate tablets, pills, or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e.*, serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

Treating a Hepatitis Virus Infection

The methods described herein are useful in treatment of an of HCV infection in a human. Whether a subject method is effective in treating an HCV infection can be determined by a reduction in viral load, a reduction in time to seroconversion (virus undetectable in patient serum), an increase in the rate of sustained viral response to therapy, a reduction of morbidity or mortality in clinical outcomes, or the prevalence or severity of disease symptoms, or other indicators of disease response.

In general, an effective amount of a compound that binds to the Sigma 1 receptor or of an interfering RNA, and optionally one or more additional antiviral agents, is an amount that is effective to reduce viral load or achieve a sustained viral response to therapy, or to reduce the rate or severity of the progression of an HCV infection following inoculation from an infectious source.

Whether a subject method is effective in treating an HCV infection can be determined by measuring viral load, or by measuring a parameter associated with HCV infection, including, but not limited to, liver fibrosis, elevations in serum transaminase levels, and necroinflammatory activity in the liver.

Various embodiments of the inventive method involve administering an effective amount of a compound that binds to the Sigma 1 receptor or of an interfering RNA, optionally in combination with an effective amount of one or more additional antiviral agents, to a patient who has been exposed to, or may be exposed to in the near future, an infectious source of HCV. In one embodiment, an effective amount of a compound that binds to the Sigma 1 receptor or of an interfering RNA, and optionally one or more additional antiviral agents, is an amount that is effective to reduce viral titers to undetectable levels, e.g., to about 1000 to about 5000, to about 500 to about 1000, or to about 100 to about 500 genome copies/mL serum. In one embodiment, an effective amount of a compound that binds to the Sigma 1 receptor or of an interfering RNA, and optionally one or more additional antiviral agents, is an amount that is effective to reduce viral load to lower than 100 genome copies/mL serum.

In one embodiment, an effective amount of a compound that binds to the Sigma 1 receptor or of an interfering RNA, and optionally one or more additional antiviral agents, is an amount that is effective to achieve a 1.5-log, a 2-log, a 2.5-log, a 3-log, a 3.5-log, a 4-log, a 4.5-log, or a 5-log reduction in viral titer in the serum of the individual.

Generally, the choice and regimen for administration of an effective amount of compound that binds to the Sigma 1 receptor or of an interfering RNA, and optionally one or more additional antiviral agents, should be within the discretion and wisdom of the patient's attending physician. Guidelines for administration include, for example, dose ranges of from about 0.001 mg to about 100 mg/kg of patient body weight of a compound that binds to the Sigma

1 receptor or of an interfering RNA, preferably a dose range of about 5 μg to about 50 mg/kg of patient bodyweight of a compound that binds to the Sigma 1 receptor or of an interfering RNA, and optionally one or more additional antiviral agents, preferably from about 0.001 mg to about 100 mg/kg of patient body weight, more preferably from about 5 μg to about 50 mg/kg of patient body weight, depending upon the identity of the additional antiviral agent used.

In one embodiment, an effective amount of a compound that binds to the Sigma 1 receptor or of an interfering RNA, and optionally one or more additional antiviral agents, is an amount that is effective to achieve a sustained viral response, e.g., non-detectable or substantially non-detectable HCV RNA (e.g., less than about 500, less than about 400, less than about 200, or less than about 100 genome copies per milliliter serum) is found in the patient's serum for a period of at least about one month, at least about two months, at least about three months, at least about four months, at least about five months, or at least about six months following cessation of therapy.

As noted above, whether a subject method is effective in treating an HCV infection can be determined by measuring a parameter associated with HCV infection, such as liver fibrosis. Methods of determining the extent of liver fibrosis are well known to one of skill in the art. In one embodiment, the level of a serum marker of liver fibrosis indicates the degree of liver fibrosis.

As one non-limiting example, levels of serum alanine aminotransferase (ALT) are measured, using standard assays. In general, an ALT level of less than about 45 international units is considered normal. In one embodiment, an effective amount of a compound that binds to the Sigma 1 receptor or of an interfering RNA, and optionally one or more additional antiviral agents, is an amount effective to reduce ALT levels to less than about 45 IU/ml serum.

A therapeutically effective amount of a compound that binds to the Sigma 1 receptor or of an interfering RNA, and optionally one or more additional antiviral agents, is an amount that is effective to reduce a serum level of a marker of liver fibrosis by at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, or at least about 80%, or more, compared to the level of the marker in an untreated individual, or to a

placebo-treated individual. Methods of measuring serum markers include immunological-based methods, e.g., enzyme-linked immunosorbent assays (ELISA), radioimmunoassays, and the like, using antibody specific for a given serum marker.

In one embodiment, an effective amount of a compound that binds to the Sigma 1 receptor or of an interfering RNA, and an additional antiviral agent is a synergistic amount. As used herein, a "synergistic combination" or a "synergistic amount" of a compound that binds to the Sigma 1 receptor or of an interfering RNA, and an additional antiviral agent is a combined dosage that is more effective in the therapeutic or prophylactic treatment of an HCV infection than the incremental improvement in treatment outcome that could be predicted or expected from a merely additive combination of (i) the therapeutic or prophylactic benefit of the compound that binds to the Sigma 1 receptor when administered at that same dosage as a monotherapy and (ii) the therapeutic or prophylactic benefit of the additional antiviral agent when administered at the same dosage as a monotherapy.

In one embodiment, a selected amount of a compound that binds to the Sigma 1 receptor or of an interfering RNA, and a selected amount of an additional antiviral agent are effective when used in combination therapy for a disease, but the selected amount of the compound that binds to the Sigma 1 receptor or of an interfering RNA, and/or the selected amount of the additional antiviral agent is ineffective when used in monotherapy for the disease. Thus, the embodiments encompass (1) regimens in which a selected amount of the additional antiviral agent enhances the therapeutic benefit of a selected amount of the compound that binds to the Sigma 1 receptor or of an interfering RNA when used in combination therapy for a disease, where the selected amount of the additional antiviral agent provides no therapeutic benefit when used in monotherapy for the disease (2) regimens in which a selected amount of the compound that binds to the Sigma 1 receptor or of an interfering RNA enhances the therapeutic benefit of a selected amount of the additional antiviral agent when used in combination therapy for a disease, where the selected amount of the compound that binds to the Sigma 1 receptor or of an interfering RNA provides no therapeutic benefit when used in monotherapy for the disease and (3) regimens in which a selected amount of the compound that binds to the

Sigma 1 receptor or of an interfering RNA and a selected amount of the additional antiviral agent provide a therapeutic benefit when used in combination therapy for a disease, where each of the selected amounts of the compound that binds to the Sigma 1 receptor or of an interfering RNA, and the additional antiviral agent, respectively, provides no therapeutic benefit when used in monotherapy for the disease. As used herein, a "synergistically effective amount" of a compound that binds to the Sigma 1 receptor or of an interfering RNA, and an additional antiviral agent, and its grammatical equivalents, shall be understood to include any regimen encompassed by any of (1)-(3) above.

Other Antiviral Agents

As discussed above, a subject method will in some embodiments be carried out by administering a compound that binds to the Sigma 1 receptor or of an interfering RNA, and optionally one or more additional antiviral agent(s).

In one embodiment, the method further includes administration of one or more interferon receptor agonist(s). Interferon receptor agonists are described herein.

In one embodiment, the method further includes administration of pirfenidone or a pirfenidone analog. Pirfenidone and pirfenidone analogs are described herein.

Additional antiviral agents that are suitable for use in combination therapy include, but are not limited to, nucleotide and nucleoside analogs. Non-limiting examples include azidothymidine (AZT) (zidovudine), and analogs and derivatives thereof; 2',3'-dideoxyinosine (DDI) (didanosine), and analogs and derivatives thereof; 2',3'-dideoxycytidine (DDC) (dideoxycytidine), and analogs and derivatives thereof; 2'3,'-didehydro-2',3'-dideoxythymidine (D4T) (stavudine), and analogs and derivatives thereof; combivir; abacavir; adefovir dipoxil; cidofovir; ribavirin; ribavirin analogs; and the like.

In one embodiment, the method further includes administration of ribavirin. Ribavirin, 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide, available from ICN Pharmaceuticals, Inc., Costa Mesa, Calif., is described in The Merck Index, 11th Edition, Rahway, NJ. Some embodiments also involve use of derivatives of ribavirin. The ribavirin may be administered orally in capsule or tablet form, or in the same or different administration form and in the same or different route as the compound that binds to the Sigma 1 receptor. Of

course, other types of administration of both medicaments, as they become available are contemplated, such as by nasal spray, transdermally, intravenously, by suppository, by sustained release dosage form, etc. Any form of administration should work so long as the proper dosages are delivered without destroying the active ingredient.

In one embodiment, the method further includes administration of ritonavir. Ritonavir, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester [5S-(5R*,8R*,10R*,11R*)], available from Abbott Laboratories, is an inhibitor of the protease of the human immunodeficiency virus and also of the cytochrome P450 3A and P450 2D6 liver enzymes frequently involved in hepatic metabolism of therapeutic molecules in man. Because of its strong inhibitory effect on cytochrome P450 3A and the inhibitory effect on cytochrome P450 2D6, ritonavir at doses below the normal therapeutic dosage may be combined with other protease inhibitors to achieve therapeutic levels of the second protease inhibitor while reducing the number of dosage units required, the dosing frequency, or both.

Coadministration of low-dose ritonavir may also be used to compensate for drug interactions that tend to decrease levels of a protease inhibitor metabolized by CYP3A. The ritonavir may be administered orally in capsule or tablet or oral solution form, or in the same or different administration form and in the same or different route as the compound that binds to the Sigma 1 receptor. Of course, other types of administration of both medicaments, as they become available are contemplated, such as by nasal spray, transdermally, intravenously, by suppository, by sustained release dosage form, etc. Any form of administration should work so long as the proper dosages are delivered without destroying the active ingredient.

As are well known in the art, various compounds that inhibit a viral protease or a viral nuclease can be used in treatment of an infection of a mammal by that virus. Inhibition of a viral protease interferes with the production of mature viral proteins, necessary for self-assembly of a viral infectious particle, for the single polyprotein that many viral genomes encode. Inhibition of a viral nuclease interferes with the replication of viral RNA (for RNA-coded viruses such as HCV), and consequently inhibit the expansion of viral populations

within a host system. Compounds having one of the other of these bioactivities can be used in treatment of viral infections in conjunction with a Sigma 1 receptor binding compound using an inventive method disclosed and claimed herein.

In one embodiment, an additional antiviral agent is administered during the entire course of the compound that binds to the Sigma 1 receptor or of an interfering RNA treatment. In one embodiment, an additional antiviral agent is administered for a period of time that is overlapping with that of the compound that binds to the Sigma 1 receptor or of an interfering RNA treatment, e.g., the additional antiviral agent treatment can begin before the compound that binds to the Sigma 1 receptor or of an interfering RNA treatment begins and end before the compound that binds to the Sigma 1 receptor or of an interfering RNA treatment ends; the additional antiviral agent treatment can begin after the compound that binds to the Sigma 1 receptor or of an interfering RNA treatment begins and end after the compound that binds to the Sigma 1 receptor or of an interfering RNA treatment ends; the additional antiviral agent treatment can begin after the compound that binds to the Sigma 1 receptor or of an interfering RNA treatment begins and end before the compound that binds to the Sigma 1 receptor or of an interfering RNA treatment ends; or the additional antiviral agent treatment can begin before the compound that binds to the Sigma 1 receptor or of an interfering RNA treatment begins and end after the compound that binds to the Sigma 1 receptor or of an interfering RNA treatment ends.

Certain illustrative HCV inhibitor compounds which can be administered with the compounds of the present disclosure include those disclosed in the following PCT Patent Application Publications Nos. WO 02/04425, WO 03/007945, WO 03/010141, WO 03/010142, WO 03/010143, WO 03/000254, WO 01/32153, WO 00/06529, WO 00/18231, WO 00/10573, WO 00/13708, WO 01/85172, WO 03/037893, WO 03/037894, WO 03/037895, WO 02/100851, WO 02/100846, WO 99/01582, and WO 00/09543.

The following lists some illustrative examples of compounds that can be administered with the compounds of this disclosure. The compounds of the disclosure can be administered with other anti-HCV activity or anti-Hepatitis C virus activity compounds in combination therapy, either jointly or separately, or by combining the compounds into a composition. These illustrative examples

include: NIM811 (Novartis), Zadaxin (Sciclone), Suvus (Bioenvision), Actilon (CPG10101) (Coley), Batabulin (T67) (Tularik Inc., South San Francisco, CA), ISIS 14803 (ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., New York, NY), Boceprevir (Schering-Plough Corporation, Kenilworth, NJ), IC41 (Intercell Novartis), Summetrel (Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA), GS-9132 (ACH-806) (Achillion/Gilead), Levovirin (Ribapharm Inc., Costa Mesa, CA), Merimepodib (Vertex Pharmaceuticals Inc., Cambridge, MA), XTL-6865 (Biopharmaceuticals Ltd., Rehovot, Israel), Telaprevir (Vertex Pharmaceuticals Inc., Cambridge, MA), HCV-796 (Wyeth), NM-283 (Idenix), GL-59728 (Gene Labs), GL-60667(Gene Labs), 2'C MeA (Gilead), PSI 6130 (Roche), R1626 (Roche), 2'C Methyl adenosine (Merck), JTK-003 (Japan Tobacco Inc., Tokyo, Japan), Ribavirin (Schering-Plough Corporation, Kenilworth, NJ), Viramidine (Ribapharm Inc., Costa Mesa, CA), Heptazyme (Ribozyme Pharmaceuticals Inc., Boulder, CO), BILN-2061dervitives (Boehringer Ingelheim Pharma KG, Ingelheim, Germany), SCH 503034 (Schering Plough), Zadazim (SciClone Pharmaceuticals Inc., San Mateo, CA), Ceplene (Maxim Pharmaceuticals Inc., San Diego, CA), CellCept (Hoffmann-La Roche LTD, Basel, Switzerland), Civacir (Nabi Biopharmaceuticals Inc., Boca Raton, FL), Albuferon-α (Human Genome Sciences Inc., Rockville, MD), Infergen A (InterMune Pharmaceuticals Inc., Brisbane, CA), Omega IFN (Intarcia Therapeutics) IFN-β and EMZ701 (Therapeutics Inc., Ontario, Canada), Rebif (Serono, Geneva, Switzerland), Roferon A (Hoffmann-La Roche LTD, Basel, Switzerland), Intron A (Schering-Plough Corporation, Kenilworth, NJ), Intron A (RegeneRx Biopharmiceuticals Inc., Bethesda, MD), Rebetron (Schering-Plough Corporation, Kenilworth, NJ), Actimmune (InterMune Inc., Brisbane, CA), Interferon-β (Serono), Multiferon (Viragen Valentis), Wellferon (GlaxoSmithKline plc, Uxbridge, UK), Omniferon (Viragen Inc., Plantation, FL), Pegasys (Hoffmann-La Roche LTD, Basel, Switzerland), Pegasys and Ceplene (Maxim Pharmaceuticals Inc., San Diego, CA), Pegasys and Ribavirin (Hoffmann-La Roche LTD, Basel, Switzerland), PEG-Intron (Schering-Plough Corporation, Kenilworth, NJ), PEG-Intron/Ribavirin (Schering-Plough Corporation, Kenilworth, NJ), IP-501 (Indevus Pharmaceuticals Inc., Lexington, MA), IDN-6556 (Idun Pharmaceuticals Inc., San Diego, CA), ITMN-191 (R-7227) (InterMune

inhibitor Pharmaceuticals Inc., Brisbane, CA), GL-59728 (Genelabs), MK0608 (Merck), VX-500 and VX-813 (Vertex Pharmaceuticals Inc., Cambridge, MA), CSL-123 (Chiron/CSL), ANA-971 (Anadys), and the like.

The compounds that bind to the Sigma 1 receptor or an interfering RNA may also be combined with one or more additional compounds having anti-Hepatitis C virus activity that are effective to inhibit the function of a target including Hepatitis C virus metalloprotease, Hepatitis C virus serine protease, Hepatitis C virus polymerase, Hepatitis C virus helicase, Hepatitis C virus NS4B protein, Hepatitis C virus entry, Hepatitis C virus binding to a target cell and fusion of its membrane to the target cell and other undefined acts, Hepatitis C virus genome transport including inhibitors o Hepatitis C virus translation/replication, NS2 protein, Hepatitis C virus pVII protein, Hepatitis C virus assembly, Hepatitis C virus egress, Hepatitis C virus NS5A protein, IMPDH for the treatment of a Hepatitis C virus infection, and viracidal molecules.

Pharmaceutical Formulations

The compounds that bind to the Sigma 1 receptor described herein may be formulated with conventional carriers and excipients, which should be selected in accord with ordinary practice. Tablets should contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally should be isotonic. All formulations should optionally contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients, 5th Ed.; Rowe, Sheskey, and Owen, Eds.; American Pharmacists Association; Pharmaceutical Press: Washington, DC, 2006. Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, for human use, of the disclosed subject matter include at least one active ingredient, as above defined, together with one or more acceptable carriers thereof and optionally other therapeutic ingredients. The carrier(s) should be

"acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, (1985). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers, finely divided solid carriers, or both, and then, if needed, shaping the product.

Formulations of the presently disclosed subject matter suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary, or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free–flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

Pharmaceutical formulations according to the presently disclosed subject matter include one or more compounds of the disclosed subject matter together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or

soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non–toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions of the disclosed subject matter contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate). The aqueous

suspension may also contain one or more preservatives such as ethyl or n–propyl p–hydroxy–benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil, or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin, or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the disclosed subject matter suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the disclosed subject matter may also be in the form of oil–in–water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally–occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol, or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the disclosed subject matter may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation

may also be a sterile injectable solution or suspension in a non–toxic parenterally acceptable diluent or solvent, such as a solution in 1,3–butane–diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono– or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form should vary depending upon the host treated and the particular mode of administration. For example, a time–release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges including the active ingredient in a flavored basis, typically sucrose and acacia or tragacanth; pastilles including the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes including the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base including for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5,

1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of a given condition.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non–aqueous sterile injection solutions which may contain anti–oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non–aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit–dose or multi–dose containers, for example sealed ampoules and vials, and may be stored in a freeze–dried (lyophilized) condition requiring the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub–dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this disclosed subject matter may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Compounds of the disclosed subject matter can also be formulated to provide controlled release of the active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient. Accordingly, the disclosed subject matter also provided compositions including

one or more compounds of the disclosed subject matter formulated for sustained or controlled release.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses), the method of delivery, and the pharmaceutical formulation, and should be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day, typically, from about 0.01 to about 10 mg/kg body weight per day, more typically, from about 0.01 to about 5 mg/kg body weight per day, and more typically, from about 0.05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight should range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

If desired, the compounds of the invention may be applied in conjunction with one or more inert or active ingredients.

Routes of Administration

One or more compounds of the disclosed subject matter (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It should be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of some of the compounds of this disclosed subject matter is that they are orally bioavailable and can be dosed orally.

Methods of Treatment

Monotherapies

The compounds that bind to the Sigma 1 receptor or an interfering RNA described herein may be used in acute or chronic therapy for HCV disease. In one embodiment, the compound that binds to the Sigma 1 receptor is administered for a period of about 1 day to about 7 days, or about 1 week to about 2 weeks, or about 2 weeks to about 3 weeks, or about 3 weeks to about 4 weeks, or about 1 month to about 2 months, or about 3 months to about 4 months, or about 4 months to about 6 months, or about 6 months to about 8

months, or about 8 months to about 12 months, or at least one year, and may be administered over longer periods of time. The compound that binds to the Sigma 1 receptor can be administered 5 times per day, 4 times per day, tid, bid, qd, qod, biw, tiw, qw, qow, three times per month, or once monthly. In one embodiment, the compound that binds to the Sigma 1 receptor is administered as a continuous infusion.

In one embodiment, a compound that binds to the Sigma 1 receptor is administered orally.

In connection with the above-described methods for the treatment of HCV disease in a patient, a compound that binds to the Sigma 1 receptor as described herein may be administered to the patient at a dosage from about 0.001 mg to about 100 mg/kg patient bodyweight per day, in 1 to 5 divided doses per day. In one embodiment, the compound that binds to the Sigma 1 receptor is administered at a dosage of about 5 μg to about 50 mg/kg patient bodyweight per day, in 1 to 5 divided doses per day.

The amount of active ingredient that may be combined with carrier materials to produce a dosage form can vary depending on the host to be treated and the particular mode of administration. A typical pharmaceutical preparation can contain from about 5% to about 95% active ingredient (w/w). In one embodiment, the pharmaceutical preparation can contain from about 20% to about 80% active ingredient.

Those of skill should readily appreciate that dose levels can vary as a function of the specific compound that binds to the Sigma 1 receptor, the severity of the symptoms and the susceptibility of the subject to side effects. Preferred dosages for a given compound that binds to the Sigma 1 receptor are readily determinable by those of skill in the art by a variety of means. A preferred means is to measure the physiological potency of a given interferon receptor agonist.

In one embodiment, multiple doses of a compound that binds to the Sigma 1 receptor are administered. For example, a compound that binds to the Sigma 1 receptor is administered once per month, twice per month, three times per month, every other week (qow), once per week (qw), twice per week (biw), three times per week (tiw), four times per week, five times per week, six times per week, every other day (qod), daily (qd), twice a day (qid), or three times a

day (tid), over a period of time ranging from about one day to about one week, from about two weeks to about four weeks, from about one month to about two months, from about two months to about four months, from about four months to about six months, from about six months to about eight months, from about eight months to about 1 year, from about 1 year to about 2 years, or from about 2 years to about 4 years, or more.

Combination Therapies

In one embodiment, the methods provide for combination therapy including administering a compound that binds to the Sigma 1 receptor or an interfering RNA, as described above, and an effective amount of ribavirin.

In one embodiment, the methods provide for combination therapy including administering a compound that binds to the Sigma 1 receptor or an interfering RNA, as described above, and an effective amount of levovirin.

In one embodiment, the methods provide for combination therapy including administering a compound that binds to the Sigma 1 receptor or an interfering RNA, as described above, and an effective amount of viramidine.

In one embodiment, the methods provide for combination therapy including administering a compound that binds to the Sigma 1 receptor or an interfering RNA as described above, and an effective amount of ritonavir.

In one embodiment, the methods provide for combination therapy including administering a compound that binds to the Sigma 1 receptor or an interfering RNA as described above, and an effective amount of an inhibitor of an HCV protease.

In one embodiment, the methods provide for combination therapy including administering a compound that binds to the Sigma 1 receptor or an interfering RNA as described above, and an effective amount of an inhibitor of an HCV nuclease.

In one embodiment, the methods provide for combination therapy including administering a compound that binds to the Sigma 1 receptor or an interfering RNA as described above, and an effective amount of an Alpha-Glucosidase Inhibitor. Suitable α-glucosidase inhibitors include any of the above-described imino-sugars, including long-alkyl chain derivatives of imino sugars as disclosed in U.S. Patent Application Publication No. 20040110795; inhibitors of endoplasmic reticulum-associated α-glucosidases; inhibitors of

membrane bound α-glucosidase; miglitol (GLYSET), and active derivatives, and analogs thereof; and acarbose (PRECOSE), and active derivatives, and analogs thereof.

In one embodiment, the methods provide for combination therapy including administering a compound that binds to the Sigma 1 receptor or an interfering RNA as described above, and an effective amount of thymosin-α.

In one embodiment, the methods provide for combination therapy including administering a compound that binds to the Sigma 1 receptor or an interfering RNA as described above, and an effective amount of an interferon receptor agonist. In one embodiment, a compound that binds to the Sigma 1 receptor or an interfering RNA and a Type I or III interferon receptor agonist are co-administered in the treatment methods described herein. Type I interferon receptor agonists suitable for use herein include any interferon-α (IFN-α). In certain embodiments, the interferon-α is a PEGylated interferon-α. In one embodiment, the interferon-α is a consensus interferon, such as INFERGEN interferon alfacon-1. In still other embodiments, the interferon-α is a monoPEG (30 kD, linear)-ylated consensus interferon.

In one embodiment, a compound that binds to the Sigma 1 receptor or an interfering RNA and a Type II interferon receptor agonist are co-administered in the treatment methods of the embodiments. Type II interferon receptor agonists suitable for use herein include any interferon-γ (IFN-γ).

In one embodiment, a Type I or a Type III interferon receptor agonist is administered in a first dosing regimen, followed by a second dosing regimen. The first dosing regimen of Type I or a Type III interferon receptor agonist (also referred to as "the induction regimen") generally involves administration of a higher dosage of the Type I or Type III interferon receptor agonist The second dosing regimen of the Type I or Type III interferon receptor agonist (also referred to as "the maintenance dose") generally involves administration of a lower amount of the Type I or Type III interferon receptor agonist.

In one embodiment, the invention provides methods using an amount of a Type I or Type III interferon receptor agonist, a Type II interferon receptor agonist, and a compound that binds to the Sigma 1 receptor or an interfering RNA, effective for the treatment of HCV infection in a patient. Some embodiments provide methods using an effective amount of an IFN-α, IFN-γ,

and an NS3 inhibitor compound in the treatment of HCV infection in a patient. One embodiment provides a method using an effective amount of a consensus IFN-α α, IFN-γ and a compound that binds to the Sigma 1 receptor or an interfering RNA in the treatment of HCV infection in a patient. In general, an effective amount of a consensus interferon (CIFN) and IFN-γ suitable for use in the methods of the embodiments is provided by a dosage ratio of 1 μg CIFN: 10 μg IFN-γ, where both CIFN and IFN-γ are unPEGylated and unglycosylated species.

In one embodiment, the methods provide for combination therapy including administering a compound that binds to the Sigma 1 receptor or an interfering RNA as described above, and an effective amount of pirfenidone or a pirfenidone analog.

In one embodiment, the methods provide for combination therapy including administering an effective amount of a compound that binds to the Sigma 1 receptor or an interfering RNA as described above, and an effective amount of TNF-α antagonist, in combination therapy for treatment of an HCV infection.

In one embodiment, the methods provide for combination therapy including administering an effective amount of a compound that binds to the Sigma 1 receptor or an interfering RNA as described above, and an effective amount of thymosin-α, in combination therapy for treatment of an HCV infection.

Some embodiments provide a method of treating an HCV infection in an individual having an HCV infection, the method including administering an effective amount of a compound that binds to the Sigma 1 receptor or an interfering RNA, and effective amount of a TNF-α antagonist, and an effective amount of one or more interferons.

Other agents such as inhibitors of HCV NS3 helicase are also attractive drugs for combinational therapy, and are contemplated for use in combination therapies described herein. Ribozymes such as HEPTAZYME and phosphorothioate oligonucleotides which are complementary to HCV protein sequences and which inhibit the expression of viral core proteins are also suitable for use in combination therapies described herein.

Patient Identification

In certain embodiments, the specific regimen of drug therapy used in treatment of the HCV patient is selected according to certain disease parameters exhibited by the patient, such as the initial viral load, genotype of the HCV infection in the patient, liver histology and/or stage of liver fibrosis in the patient. Thus, some embodiments provide any of the above-described methods for the treatment of HCV infection in which the subject method is modified to treat a treatment failure patient for a duration of, for example, 48 weeks.

Subjects Suitable for Treatment

Any of the above treatment regimens can be administered to individuals who have been diagnosed with an HCV infection. Any of the above treatment regimens can be administered to individuals who have failed previous treatment for HCV infection ("treatment failure patients," including non-responders and relapsers).

Individuals who have been clinically diagnosed as infected with HCV are of particular interest. Individuals who are infected with HCV are identified as having HCV RNA in their blood, and/or having anti-HCV antibody in their serum. Such individuals include anti-HCV ELISA-positive individuals, and individuals with a positive recombinant immunoblot assay (RIBA). Such individuals may also, but need not, have elevated serum ALT levels.

Individuals who are clinically diagnosed as infected with HCV include naive individuals (e.g., individuals not previously treated for HCV, particularly those who have not previously received IFN-α-based and/or ribavirin-based therapy) and individuals who have failed prior treatment for HCV ("treatment failure" patients). Treatment failure patients include non-responders (i.e., individuals in whom the HCV titer was not significantly or sufficiently reduced by a previous treatment for HCV, e.g., a previous IFN-α monotherapy, a previous IFN-α and ribavirin combination therapy, or a previous pegylated IFN-α and ribavirin combination therapy); and relapsers (i.e., individuals who were previously treated for HCV, e.g., who received a previous IFN-α monotherapy, a previous IFN-α and ribavirin combination therapy, or a previous pegylated IFN-α and ribavirin combination therapy, whose HCV titer decreased, and subsequently increased).

In particular embodiments of interest, individuals have an HCV titer of at least about 10^5, at least about 5×10^5, or at least about 10^6, or at least about $2 \times$

10^6, genome copies of HCV per milliliter of serum. The patient may be infected with any HCV genotype (genotype 1, including 1a and 1b, 2, 3, 4, 6, etc. and subtypes (e.g., 2a, 2b, 3a, etc.), particularly a difficult to treat genotype such as HCV genotype 1 and particular HCV subtypes and quasispecies.

Also of interest are HCV-positive individuals (as described above) who exhibit severe fibrosis or early cirrhosis (non-decompensated, Child's-Pugh class A or less), or more advanced cirrhosis (decompensated, Child's-Pugh class B or C) due to chronic HCV infection and who are viremic despite prior anti-viral treatment with IFN-α-based therapies or who cannot tolerate IFN-α-based therapies, or who have a contraindication to such therapies. In particular embodiments of interest, HCV-positive individuals with stage 3 or 4 liver fibrosis according to the METAVIR scoring system are suitable for treatment with the methods described herein. In one embodiment, individuals suitable for treatment with the methods of the embodiments are patients with decompensated cirrhosis with clinical manifestations, including patients with far-advanced liver cirrhosis, including those awaiting liver transplantation. In still other embodiments, individuals suitable for treatment with the methods described herein include patients with milder degrees of fibrosis including those with early fibrosis (stages 1 and 2 in the METAVIR, Ludwig, and Scheuer scoring systems; or stages 1, 2, or 3 in the Ishak scoring system).

Pharmaceutical Kits

The present disclosure also includes pharmaceutical kits useful, for example, for the treatment of a Hepatitis C virus infection, which comprise one or more containers containing a pharmaceutical composition including a therapeutically effective amount of a compound that binds to the Sigma 1 receptor or of an interfering RNA. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Printed instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit. It should be understood that although the specified materials and conditions are important in practicing the disclosed subject matter, unspecified materials and conditions are

not excluded so long as they do not prevent the benefits of the invention from being realized.

Background Documents

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All patents, patent applications, publications, scientific articles, web sites, and other documents and materials referenced or mentioned herein are indicative of the levels of skill of those skilled in the art to which the invention pertains, and each such referenced document and material is hereby incorporated by reference to the same extent as if it had been incorporated by reference in its entirety individually or set forth herein in its entirety. Additionally, all claims in this application, and all priority applications, including but not limited to original claims, are hereby incorporated in their entirety into, and form a part of, the written description of the invention. Applicants reserve the right to physically incorporate into this specification any and all materials and information from any such patents, applications, publications, scientific articles, web sites, electronically available information, and other referenced materials or documents. Applicants reserve the right to physically incorporate into any part of this document, including any part of the written description, the claims referred to above including but not limited to any original claims.

The following Examples are intended to illustrate the above invention and should not be construed as to narrow its scope. One skilled in the art should readily recognize that the Examples suggest many other ways in which the invention could be practiced. It should be understood that numerous variations and modifications may be made while remaining within the scope of the invention.

EXAMPLES

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

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

Example 1: Compound Library Screening

Target cells were seeded the day before (10^4 cells/well/ 96-well). The chemical library used was the NIH Clinical Collection. See the following URL for a description: http://www.nihclinicalcollection.com/. This collection was provided in a 96-well format in DMSO solutions at 10mM concentration. The compounds were diluted to a final concentration of 20μM in complete medium (DMEM+10%FCS). A virus dilution containing ~8.10^3 HCV infectious units per ml (FFU/ml) of a cell culture adapted strain (D183, Zhong et al., J. Virology, 80, 11082-93 (2006)) was prepared in complete medium. Compound and virus dilutions were mixed 1:1 and added to clone 2 cells, which were incubated in the presence of the virus (400 FFU/well) and compound (10μM) for 72 hours at 37°C. After this incubation period, the cells were fixed at room temperature (RT) with a 4% paraformaldehide solution in phosphate buffered saline (PBS, pH 7) for 20 minutes. The fixed cells were processed for colorimetric analysis as follows.

The procedure is a modification of the infectivity titration assay described in Zhong et al., Proc. Natl. Acad. Sci. USA, 102, 9294-9 (2005).

Paraformaldehyde-fixed test wells are washed twice with 100 µl of PBS and incubated with 50 µl of blocking buffer (0.3% TritonX100, 3% bovine serum albumin –BSA-, 10% fetal calf serum-FCS and 5% hydrogen peroxide in PBS) for 1 hour at room temperature. A dilution (1µg/ml) of a recombinant human IgG anti-E2 is added in incubation buffer (0.3% TritonX100, 3% bovine serum albumin (BSA) in PBS) for 1 hour at room temperature. The cells are washed four times with 200 µl of PBS and incubated with the appropriate dilution (1:15000) of the secondary antibody conjugated to horseradish peroxidase (HRP, Goat anti-human IgG-HRP; Jackson Immunoresearch, Stanford, CA) for 1 hour at room temperature. The cells are washed again four times with 200 µl of PBS and the remaining peroxidase activity is evaluated by adding 3,3',5,5'-tetramethylbenzidine (TMB; Pierce, Rockford, IL) to the cells in the presence of hydrogen peroxide. The oxidation of TMB leads to the generation of a blue product that absorbs light at 650 nm. Before this colorimetric reaction reaches saturation levels, the reaction can be stopped by the addition of 1 volume of 1N H_2SO_4, which generates a yellow product with an optimal absorbance of 450 nm. Each plate includes a standard curve with serial 2-fold dilutions of the virus to ensure appropriate colorimetric value transformation and negative controls (uninfected cells) to determine the background of the assay. Compounds with known antiviral capacity have been included in the process as quality controls of the assay and, as expected, their antiviral activity was also demonstrated using this technology. The signals above the background in each well are expressed as percentage of the control after data transformation using the standard curve. Values below 20% of the control should be considered positive hits.

The screening technology described above does not discriminate between an antiviral compound and a false-positive result, as both should be associated with a reduced $O.D._{450nm}$ signal. As for many cell-based assays, the readout relies on viable, proliferating cells. Since the virus requires actively dividing cells for efficient replication and viral antigen quantitation relies on the presence of similar amounts of cells in the well, a non-specific toxic effect of a given compound should lead to a false-positive readout. To avoid problem, the impact of the compounds on cell viability was evaluated. During the screening process, false-positive results were identified by measuring the cell biomass per well by staining the cells with crystal violet (1% solution in 50% ethanol-water) (*see*,

e.g., Bernhardt et al. J. Cancer Res. Clin. Oncology, 118, 35-43 (1992)). The excess dye was extensively washed off with water and the bound dye was solubilized in 50 ml of a 1% SDS solution in water. The optical density was determined at 570 nm (biomass) and 690 nm (plate background). The difference between the $O.D._{570\text{-}690nm}$ was used to calculate the relative biomass present in each well using vehicle-treated wells as a reference. This staining reflects the number of live cells in the well at the moment of fixation. Using this approach, it was possible to discriminate a positive hit from a false-positive for compounds that are toxic and whose antiviral activity cannot be evaluated using this system. The wells with biomass values below 75% of the positive control were considered false-positive and discarded for further analysis. Compounds for which antiviral activity in the absence of toxic effects was confirmed, were considered for further evaluation.

The candidate molecules selected after this primary screening were tested in a second round (counterscreening) using the same screening concentration. During this process, molecules with similar chemical structures were added to the collection in order to identify common structural features that confer antiviral activity against HCV. The hits obtained in this second round were tested in a third round of counterscreening to clearly identify the compounds that binds to the Sigma 1 receptor.

Potency and Toxicity

It was desirable to define the measurable parameters to be used to evaluate the significance of the antiviral activity of a given compound. Compounds were generally ranked based on their potency, a parameter that is defined by the inhibitory concentration 50 (IC_{50}). The IC_{50} is the concentration at which the compound inhibits the maximum value of the assay by 50%. This parameter is generally accompanied by the toxicity of the compound, provided as the lethal dose 50 (LD_{50}). The LD_{50} is the concentration of compound that reduces cell viability by 50%. In general, candidates with a low IC_{50} and a high LD_{50} receive high priority, since the likelihood of the specificity of the observed antiviral effect increases as these two indices differ.

Potency (IC_{50})

In order to determine the IC_{50}, serial dilutions of the different antiviral compounds were assayed using the colorimetric assay. Serial 2-fold dilutions of

the compound were prepared. These solutions (50 µl) were mixed with 50 µl of an 8.10^3 FFU/ml virus dilution in complete medium containing final compound concentrations starting at 50µM. The mixture was transferred into a 96-well plate containing 10^4 clone 2 cells per well seeded the day prior to the experiment. The cultures were incubated for a period of 72 hours at 37°C, after which the cells were fixed and processed for colorimetric analysis as described above. IC_{50} is defined as the compound concentration that should reduce HCV by 50%, based on the values obtained after O.D. transformation with the standard curve. This analysis was applied to antiviral compounds obtaining the results described in the Table 1.

Table 1

Generic Name	Chemical Name	IC_{50} (μM)	LD_{90} (μM)	LD_{50} (μM)	Clinical Indication	Cellular Target/Mode of Action
Haloperidol	4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidyl]-1-(4-fluorophenyl)-butan-1-one	2.25	6.0	32	Schizophrenia, Psychosis	Sigma 1 Receptors/D2-like Dopamine receptors
Rimcazole	9-[3-[(3S,5R)-3,5-dimethylpiperazin-1-yl] propyl] carbazole	1.3	5.0	30	Psychosis, Cocaine Antagonist	Sigma 1 Receptors/Dopamine Transporter
Lofepramine	N-methyl-N-[4-Chlorobenzoyl-methyl-3-(10,11-dihydro-5H-dibenz (b, t)azepin-5-yl]-propylamine	1.5	4.0	40	Antidepressant	Serotonin and noradrenalin Reuptake Inhibitor-Liver Tryptophan Pyrrolase (in vitro)/Sigma 1 Ligand
Methyl Paroxetine	(3S-trans)-3-((1,3-Benzodioxol-5-yloxy)methyl)-4-(4-fluorophenyl)-piperidine	2.0	6.0	30	Antidepressant	Serotonin Reuptake Inhibitor/Sigma 1 Ligand

Prochlorpromazine	2-chloro-10-[3-(4-methylpiperazin-1-yl)propyl]phenothiazine	0.5	2.5	40	Antipsychotic, Antiemetic	Sigma 1 Ligand
Fluphenazine HCl	2-[4-[3-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]propyl]-piperazin-1-yl]ethanol	0.3	0.8	20	Antipsychotic	Sigma 1 Ligand
Cyproheptadine HCl	4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-methylpiperidine hydrochloride (as the hydrochloride salt)	0.5	3.0	35	Antihistaminic, Antiserotonergic; Treatment of Allergy and Anorexia Nervosa	5-HT2 Receptor Antagonist; Calcium channel blocker; Sigma 1 Ligand
Trifluoperazine 2HCl	10-[3-(4-methylpiperazin-1-yl)propyl]-2-(trifluoromethyl)-10H-phenothiazine (as the dihydrochloride salt)	0.3	1.2	15	Schizophrenia	Sigma 1 Ligand
Azelastine HCl	4-[(4-chlorophenyl)methyl]-2- (1-methylazepan-4-yl)-phthalazin-1-one (as the hydrochloride salt)	1.6	3.5	30	Allergies	Anithistamine; Sigma 1 Ligand
Desloratadine	8-chloro-6,11-dihydro-11-(4-piperdinylidene)- 5H-	2.5	7.0	30	Allergies	Mast Cell Stabilizer: Sigma 1 Ligand

	benzo[5,6]cyclohepta[1,2-b]pyridine					
Salmeterol	2-(hydroxymethyl)-4-{1-hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl}phenol	3.3	11.0	50	Asthma	Beta 2-Adrenergic Receptor Agonist; Sigma 1 Ligand
Carvedilol	1-(9H-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)ethylamino]propan-2-ol	3.5	6.0	15	Cogestive Heart Failure; Control of Blood Pressure	Alpha-1, Beta -1 and -2 Adrenergic Receptors; Sigma 1 Receptor
Amiodarone HCl	(2-butylbenzofuran-3-yl)- [4-(2-diethylaminoethoxy)- 3,5-diiodo-phenyl]-methanone (as the hydrochloride salt)	0.7	5.0	30	Treatment of Acute life-Threatening Arrhythmias, Chronic Suppression of Arrhythmias	Beta Blocker-Like and Potassium Channel Blocker-like Actions on the SA and AV Nodes; potential Thyroid receptor Binding; Sigma 1 Ligand
Benproperine Phosphate	1-[1-(2-benzylphenoxy)propan-2-yl]piperidine	3.0	6.0	20	Cough Suppressant	Sigma 1 Ligand
Doxepin	(E0-3-(dibenzo[b,e]oxepin-11(6H)-ylidene)-N,N-dimethylpropan-1-amine	0.8	4.0	50	Antidepressant	Serotonin and Noradrenalin Reuptake

						Inhibitor/Sigma 1 Ligand
Ketotifen Fumarate	4,9-dihydro-4-(1-methyl-4-piperidnylidene)-10H-benzocyclohepta{1,2-b]thiophen-10-one	10	50	50	Antihistamic	Non-competitive H1 Receptor Antagonist
Clobenpropit	N'-[(4-chlorophenyl)methyl]-1-[3-(3H-imidazol-4-yl)propylthio]formamidine	3.0	6.0	35		Histamine H3 Antagonist
Toremifene Citrate	2-[4-(4-chloro-1,2-diphenyl-but-1-enyl)phenoxy]-N,N-dimethyl-ethanamine	0.8	4.0	20	Cancer	Estrogen Receptor Modulator
BD1047	N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino)ethylamine dihydrochloride	0.7	4.0	35.0		Sigma 1 Ligand

Toxicity (LD_{50})

Our preliminary toxicity results ensure that the selected compounds are non-toxic at the screening concentration (10μM). However, in order to measure precisely the toxicity (LD_{50}) of the selected compounds, cell viability was measured in the presence of increasing concentrations of the antiviral compounds. Cell viability may be determined by measuring the mitochondrial metabolic capacity of the cells at any given time point. This may be achieved by culturing metabolically active cells with a modified soluble tetrazolium salt Thiazolyl Blue Tetrazolium Bromide also called MTT (Sigma-Aldrich, St.Louis, MO), which transforms MTT into formazan, a purple precipitate. This transformation, dependent on mitochondrial dehydrogenases, was quantified within 2-4 hours using a colorimetric assay that is read at 570 nm. The LD_{50} of a particular compound was determined similarly to the IC_{50}. Serial dilutions of the compound (typically from 100 μM to 100 nanoM) in complete medium were added to the cells and incubated for 72 hours. Cell viability was analyzed by adding MTT (5μg/ml final concentration) and measuring the resulting formazan content, after resuspension in 100% DMSO, at 570 nm in a microplate spectrophotometer. LD_{50} values were obtained by plotting the colorimetric values ($O.D._{570nm}$) versus the compound concentration and determining the concentration that rendered 50% of the activity observed in the control. This procedure is widely used for determination of cell viability because it is rapid, simple and yields highly reproducible results.

CLAIMS

What is claimed is:

1. A method of reducing the susceptibility of a population of mammalian cells in a mammal to infection by HCV comprising blocking or deactivating the Sigma 1 receptor expressed in the population of cells, wherein the blocking or deactivating takes place *in vivo*.

2. The method of claim 1 wherein reducing the susceptibility of a population of mammalian cells comprises inhibiting the viral spread of Hepatitis C virus in a population of cells in a mammal exposed to an infectious inoculum of a Hepatitis C virus.

3. The method of claim 1 wherein blocking or deactivating comprises administering an effective amount of a Sigma 1 receptor binding compound to the mammalian cells.

4. The method of claim 1 wherein blocking or deactivating comprises administering an effective amount of an interfering RNA or analog thereof to the mammalian cells wherein the interfering RNA or analog blocks or decreases expression of a gene coding for a protein comprising the Sigma 1 receptor.

5. A method of treating a Hepatitis C viral infection in a mammal, or of ameliorating symptoms of a Hepatitis C viral infection in a mammal, or of preventing viral spread of Hepatitis C virus among mammalian cells therein, or any combination thereof, comprising administering to the mammal an amount of a Sigma 1 receptor binding compound, or an interfering RNA or analog thereof wherein the interfering RNA or analog blocks or decreases expression of a gene coding for the Sigma 1 receptor, or both; in a dose, at a frequency, and for a duration sufficient to provide a beneficial effect to the mammal.

6. The method of any one of claims 1-5 wherein the mammal is a human and the mammalian cells are human cells.

7. The method of claim 5 wherein the Sigma 1 receptor binding compound, or interfering RNA or analog thereof, is administered to the mammal prior to or substantially concurrently with the exposure of the mammal to the infectious inoculum of the Hepatitis C virus.

8. The method of claim 5 wherein the Sigma 1 receptor binding compound, or interfering RNA or analog thereof, is administered to the mammal subsequent to the exposure of the mammal to the infectious inoculum of the Hepatitis C virus.

9. The method of claim 3 or 5 wherein the Sigma 1 receptor binding compound has a binding constant with respect to the Sigma 1 receptor of less than about 1 μM.

10. The method of claim 3 or 5 wherein the Sigma 1 receptor binding compound is in a neutral form, in an acid or base form, or in a salt form.

11. The method of claim 3 or 5, wherein the Sigma 1 receptor binding compound comprises a pharmaceutically acceptable salt, a prodrug, a metabolite thereof, or a combination thereof.

12. The method of claim 3 or 5, wherein the Sigma 1 receptor binding compound comprises a solvate, a polymorph, a racemate, a pure stereoisomer, or a combination thereof.

13. The method of claim 3 or 5, wherein the Sigma 1 receptor binding compound comprises an enantiomer, a diasteromer, or a combination thereof.

14. The method of claim 3 or 5 wherein the Sigma 1 receptor binding compound acts on the Sigma 1 receptor as an antagonist, an agonist, or an allosteric regulator.

15. The method of claim 3 or 5, wherein the Sigma 1 receptor binding compound is azelastine, (-)-cyanopindolol hemifumarate, (2-ibutylamino-ethyl)-

carbamic acid 2-(4-benzofuran-2-yl)methyl-piperazin-1-yl)-ethyl ester, (4-[1,2,3]thiadiazol-4-yl-benzyl)-carbamic acid 1-(3-methoxy-2-nitro-benzyl)-piperidin-3-yl)methyl ester, (S)-methamphetamine HCl, [1-(9-ethyl-9H-carbazol-3-yl)methyl)-pyrrolidin-3-yl]-carbamic acid 1-(3-benzyloxy-4-methoxy-benzyl)-piperidin-3-yl)methyl ester, [1-(9-ethyl-9H-carbazol-3-yl)methyl)-pyrrolidin-3-yl]-carbamic acid 2-(tert-butoxycarbonyl-naphthalen-1-yl)methyl-amino)-ethyl ester, [4-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-phenyl]-[4-(3-phenyl-allyl)-piperazin-1-yl]-methanone, 1-(1,2-diphenylethyl)piperidine aleate, (+/-) 1-(1-naphthyl)piperazine HCl, 1-(3-chlorophenyl)piperazine HCl, 1-(4-bromo-benzenesulfonyl)-4-(2-tert-butylsulfanyl-benzyl)-piperazine, 2-(2-{[1-(3-chloro-benzyl)-pyrrolidin-3-yl]-methyl-carbamoyl}-2-methyl-propyl)-4,6-dimethyl-benzoic acid, 2-chloro-11-(4-methylpiperazino)dibenz[B, F]oxepin maleate, 3,3'-diethylthiacarbocyanine iodide, 3-mercapto-2-methylpropanoic acid 1,2-diphenylethylamine, 3-quinuclidinyl benzilate, 3-tropanyl-3,5-dichlorobenzoate, 3-tropanyl-indole-3-carboxylate HCl, 4-(1H-indol-4-yl)-piperazine-1-carboxylic acid 2-(5-bromo-2-ethoxy-, 4-(2-tert-butylsulfanyl-benzyl)-piperazine-1-carboxylic acid-2-phenylamino)-cyclohexylmethyl ester, thiophen-2-yl-ethyl ester, 4-(3,5-dimethoxy-phenyl)-piperazine-1-carboxylic acid 1-(2-fluoro-benzyl)-piperidin-2-yl)methyl ester, 4-(3-nitro-5-sulfamoyl-thiophen-2-yl)-piperazine-1-carboxylic acid 1-(2-fluoro-5-methoxy-benzyl)-piperidin-3-yl)methyl ester, 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)piperidine oxalate, 4-(5-trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid pent-2-ynyl ester, 4,4'-bis[4-(P-chlorophenyl)-4-hydroxypiperidino]butyrophenone, 4-[1-(4-chlorobenzyl)-4-(benzylpiperidin-4-yl]-2-hydroxy-4-oxobut-2-enoic acid 4-bromo-N-[1-(9-ethyl-9H-carbazol-3-yl)methyl)-pyrrolidin-3-yl)]-2-trifluoromethoxy-benzenesulfonamide, cardevilol, clobenprobit, 4'-chloro-3-α-(diphenylmethoxy)tropane HCl, 4-furan-2-yl)methyl-piperazine-1-carboxylic acid 2-{4-[3-(2-trifluoromethyl-phenothiazin-10-yl)-propyl]-piperazin-1-yl)}-ethyl ester, 4-methoxy-N-[1-(7-methoxy-benzo[1,3]dioxol-5-yl)methyl)-pyrrolidin-3-yl)]-benzenesulfonamide, 5-(N-ethyl-N-isopropyl)-amiloride, 7-hydroxy-DPAT HBr, (R)-(+)-, 8-Hydroxy-DPAT HBr, S(-)-9-[4-({[4'-(trifluoromethyl)-1,1'-biphenyl-2-yl]carbonyl}amino)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, acepromazine maleate, acetophenazine maleate, acrinol ajmaline, alaproclate HCl, aloe-emodin,

alprenolol D-tartrate hydrate, alprenolol HCl, AMI-193, aminobenztropine, amiodarone HCl, amodiaquine HCl, amorolfine HCl, amoxapine, anileridine HCl, anisotropine methylbromide, anpirtoline ARC 239·2HCl, astemizole auramine O HCl, azaperone, azatadine maleate, azelastine HCl, bamethan sulfate, BD 1008·2HBr, BD-1047, BD-1063, benextramine·4HCl, benfluorex HCl, benidipine HCl, benoxathian HCl, benoxinate HCl, benperidol, benproperine phosphate, benzododecinium bromide, benzphetamine HCl, benztropine mesylate, benzydamine HCl, bephenium hydroxynaphthoate, bepridil HCl, berberine chloride, betaxolol HCl, bifemelane, BMY 7378·2HCl, bopindolol malonate, BP 554, maleate, bromhexine HCl, bromodiphenhydramine HCl, bromperidol, brompheniramine maleate, BTCP HCl, buclizine HCl, buflomedil HCl, bupropion HCl, buspirone HCl, butacaine sulfate, butaclamol HCl, (±)-butenafine HCl, butoconazole nitrate, BW 723C86 HCl, carbetapentane citrate, carbinoxamine maleate, carpipramine·2HCl, DiH2O, carvedilol, cephapirin benzathine CGS-12066A maleate, chloroprocaine HCl, chloroquine phosphate, chlorpheniramine maleate, chlorphenoxamine HCl, chlorpromazine HCl, chlorprothixene, cinanserin HCl, cinnarizine, cirazoline HCl, cis-(+/-)-N-Methyl-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexamine·2HBr, cis(Z)-flupentixol·2HCl, cisapride hydrate, citalopram HBr clebopride maleate, clemastine fumarate, clemizole HCl, clenbuterol HCl, clidinium bromide, CSG 12066B, clobenpropit·2HBr clofazimine, clofilium tosylate, clomiphene citrate, clomiphene A, clomipramine, cloperastine HCl, clorgyline HCl, clozapine, cyclizine, cyclobenzaprine HCl, cycloheximide, cyproheptadine HCl, demecarium bromide, denatonium benzoate, deptropine citrate, desloratadine, dexbrompheniramine maleate, dexchlorpheniramine maleate, dexfenfluramine HCl, dibucaine HCl, dicyclomine HCl, diethylpropion HCl, dimethisoquin HCl, dimetindene maleate, diphemanil methylsulfate, diphenidol HCl, diphenoxylate HCl, diphenylpyraline HCl, dipropyldopamine HBr, dobutamine HCl, donepezil HCl, doxepin HCl, droperidol, duloxetine, dyclonine HCl, ebastine, econazole nitrate, epinastine HCl, ethaverine HCl, ethopropazine HCl, eticlopride HCl, S(-)-etofenamate, etonitazenyl esothiocyanate, femoxetine HCl, fenfluramine HCl, fentanyl citrate, fenticonazole nitrate, fipexide HCl, flavoxate HCl, flunarizine·2HCl, fluoxetine B, fluperlapine, fluphenazine decanoate·2HCl,

fluphenazine enanthate·2HCl, fluphenazine HCl, fluphenazine N-mustard·2HCl, flurazepam C, fluspirilene fluvoxamine maleate, GBR 12783·2HCl, GBR 12909·2HCl, GBR 13069·2HCl, GBR-12935·2HCl, GR 89696, fumarate guanabenz acetate, guanadrel sulfate, guanethidine sulfate, halofantrine HCl, haloperidol, hexylcaine HCl, hycanthone hydroxychloroquine sulfate, hydroxyzine HCl, hyoscyamine sulfate, IBZM, S(-)-ICI-199,441 HCl, ifenprodil tartrate, imipramine HCl, indatraline HCl, llofetamine HCl, irinotecan HCl, isamoltane hemifumarate, isopromethazine HCl, isoxsuprine HCl, ketanserin L-tartrate, ketoconazole, ketotifen fumarate, L-693,403 maleate, L-741,626, L-741,742 HCl, L-745,870·3HCl, labetalol HCl, levetimide HCl, R(-) levobunolol HCl, lidoflazine, lisuride hydrogen maleate, R(+)-lobeline HCl, lomerizine·2HCl, lofepramine, loperamide HCl, loxapine succinate, LY-53,857, maleate maprotiline HCl, mazindol, MDL 12,330A HCl, mebhydroline 1,5-naphthalendisulfonate, meclizine HCl, mefloquine HCl, meprylcaine HCl, mesoridazine besylate, metaphit methanesulfonate, metergoline methantheline bromide, methdilazine, methiothepin mesylate, methixene HCl, methoctramine, methotrimeprazine maleate, methylene violet 3 HCl, metipranolol mexiletine HCl, mianserin HCl, miconazole, ML-9 HCl, morantel hydrogen L-tartrate, MR 16728 HCl, N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine HCl, N'-[2-(benzo[1,2,5]thiadiazole-4-sulfonylamino)-acetyl]-hydrazinecarboxylic acid 2-(2-{4-[(4-chloro-phenyl)-phenyl-methyl]-piperazin-1-yl)}-ethoxy)-ethyl ester, nafronyl oxalate, naftifine, naftopidil·2HCl, naltriben mesylate, NAN-190 HBr, NE-100, nefazodone, nefopam HCl, nicardipine HCl, nicergoline, niguldipine HCl, (+/-)-nisoxetine HCl, nortriptyline HCl, nylidrin HCl, octoclothepin maleate, (±) orphenadrine citrate, oxamniquine, oxamniquine A, oxamniquine B, oxatomide, oxiconazole nitrate, oxybutynin HCl, panaxatriol, PAPP methyl triparoxetine, paxilline, p-chlorobenzhydrylpiperazine, penbutolol sulfate, pentamidine isethionate, entazocine, (±)-pergolide methanesulfonate, perhexiline maleate, perospirone, perphenazine, perphenazine sulfoxide, phenamil methanesulfonate, phencyclidine HCl, phenosafranin HCl, phenoxybenzamine HCl, phenyltoloxamine citrate, piboserod, pimozide, pinacyanol chloride, pindobind, (+/-)-piperacetazine, piperazine-1,4-dicarboxylic acid benzyl ester, 2-[4-(4-dimethylamino-benzyl)-piperazin-1-yl)]-ethyl ester, piperidolate HCl, pirenperone, PPHT HCl, (±)-pramoxine HCl, prenylamine lactate, pridinol

methanesulfonate, prochlorperazine maleate, procyclidine HCl, proflavine hemisulfate, progesterone, promazine HCl, promethazine HCl, propafenone HCl, proparacaine HCl, propericyazine, propiomazine propranolol HCl, protokylol protriptyline HCl, pyrilamine maleate, pyrimethamine, pyrrolidine-1,2-dicarboxylic acid 1-[1-(4-allyloxy-benzyl)-piperidin-2-yl)methyl] ester, 2-benzyl ester pyrvinium pamoate, quetiapine fumarate, quinacrine HCl, quinaldine red, quipazine dimaleate, quipazine, raloxifene, rimantadine HCl, rimcazole, risperidone, ritanserin ritodrine HCl, RS 23597-190 HCl, RS 67333 HCl, RS 67506 HCl, safranin O HCl, salmeterol, SB203186, SCH-23390 HCl, R(+)-sertaconazole nitrate, sertindole sertraline, sibutramine HCl, SKF-525A HCl, SKF-96365 HCl, SNC 121, spiperone HCl, sufentanil, T-226296, tamoxifen citrate, tamsulosin HCl, tegaserod maleate, terbinafine HCl, terconazole, terfenadine, terfenadine A, tetracaine HCl, tetrindole mesylate, thiethylperazine malate, thioperamide maleate, thioproperazine, thioridazine, thiothixene thiothixene, (E)-thonzonium bromide tioconazole A, TMB-8 HCl, tolterodine L-tartrate, toremifene citrate, tramazoline HCl, trans-U-50488 methanesulfonate, (±)-trazodone HCl, tridihexethyl chloride, trifluoperazine HCl, trifluperidol HCl, triflupromazine HCl, trihexyphenidyl HCl, trimebutine, trimeprazine hemi-L-tartrate, trimipramine maleate, tripelennamine HCl, triprolidine HCl, triprolidine HCl, tropanyl 3,5-dimethylbenzoate, tropine 2-(4-chlorophenoxy)butanoate, maleate, U-50488 HCl, U-62066, UH 232 maleate, (+)-vecuronium bromide, verapamil HCl, verapamil B vesamicol HCl, vinpocetine W-7 HCl, WB-4101 HCl, xylazine, xylometazoline HCl; or a combination thereof.

16. The method of claim 3 or 5, wherein the Sigma 1 receptor binding compound is amiodarone HCl, azelastine HCl, benproperine phosphate, carvedilol, cyproheptadine HCl, desloratadine, fluphenazine HCl, haloperidol, lofepramine, methyl paroxetine, prochlorpromazine, rimcazole, salmeterol, trifluoperazine·2HCl; or a combination thereof.

17. The method of claim 4 or 5 wherein the RNA or analog thereof comprises RNA.

18. The method of claim 4 or 5 wherein the RNA or analog thereof

comprises an RNA analog.

19. The method of claim 5, further comprising administering a medicament having anti-Hepatitis C virus activity, other than a Sigma 1 receptor binding compound or an interfering RNA or analog thereof to the mammalian cells wherein the interfering RNA or analog blocks or decreases expression of a gene coding for a protein comprising the Sigma 1 receptor.

20. The method of claim 19, wherein the medicament is an interferon, ribavirin, or a combination thereof.

21. The method of claim 20, wherein the interferon comprises interferon α2b, pegylated interferon α, consensus interferon, interferon α2a, lymphoblastoid interferon τ, or a combination thereof.

22. The method of claim 19, wherein the medicament comprises interleukin 2, interleukin 6, interleukin 12, interfering RNA, anti-sense RNA, imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, a viral protease inhibitor, a viral nuclease inhibitor, amantadine, rimantadine, or a combination thereof.

23. A method of screening each compound of a set of compounds for anti-HCV activity, comprising

determining a binding constant for each compound of the set of compounds with respect to the Sigma 1 receptor; then,

selecting a subset of the set wherein the compounds each have a binding constant with respect to the Sigma 1 receptor of less than about 1 μM; then,

testing each of the subset of compounds for anti-HCV activity;

wherein a percentage of active anti-HCV compounds among the subset is greater than a percentage of active anti-HCV compounds among the set.

24. The use of a Sigma 1 receptor binding compound, or interfering RNA or analog thereof wherein the interfering RNA or analog blocks or decreases expression of a gene coding for a protein comprising the Sigma 1 receptor, or

both, for the manufacture of a medicament for the treatment of a Hepatitis C virus infection.

25. The use of claim 24, wherein the Sigma 1 receptor binding compound is azelastine, (-)-cyanopindolol hemifumarate, (2-ibutylamino-ethyl)-carbamic acid 2-(4-benzofuran-2-yl)methyl-piperazin-1-yl)-ethyl ester, (4-[1,2,3]thiadiazol-4-yl-benzyl)-carbamic acid 1-(3-methoxy-2-nitro-benzyl)-piperidin-3-yl)methyl ester, (S)-methamphetamine HCl, [1-(9-ethyl-9H-carbazol-3-yl)methyl)-pyrrolidin-3-yl]-carbamic acid 1-(3-benzyloxy-4-methoxy-benzyl)-piperidin-3-yl)methyl ester, [1-(9-ethyl-9H-carbazol-3-yl)methyl)-pyrrolidin-3-yl]-carbamic acid 2-(tert-butoxycarbonyl-naphthalen-1-yl)methyl-amino)-ethyl ester, [4-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-phenyl]-[4-(3-phenyl-allyl)-piperazin-1-yl]-methanone, 1-(1,2-diphenylethyl)piperidine aleate, (+/-) 1-(1-naphthyl)piperazine HCl, 1-(3-chlorophenyl)piperazine HCl, 1-(4-bromo-benzenesulfonyl)-4-(2-tert-butylsulfanyl-benzyl)-piperazine, 2-(2-{[1-(3-chloro-benzyl)-pyrrolidin-3-yl]-methyl-carbamoyl}-2-methyl-propyl)-4,6-dimethyl-benzoic acid, 2-chloro-11-(4-methylpiperazino)dibenz[B, F]oxepin maleate, 3,3'-diethylthiacarbocyanine iodide, 3-mercapto-2-methylpropanoic acid 1,2-diphenylethylamine, 3-quinuclidinyl benzilate, 3-tropanyl-3,5-dichlorobenzoate, 3-tropanyl-indole-3-carboxylate HCl, 4-(1H-indol-4-yl)-piperazine-1-carboxylic acid 2-(5-bromo-2-ethoxy-, 4-(2-tert-butylsulfanyl-benzyl)-piperazine-1-carboxylic acid-2-phenylamino)-cyclohexylmethyl ester, thiophen-2-yl-ethyl ester, 4-(3,5-dimethoxy-phenyl)-piperazine-1-carboxylic acid 1-(2-fluoro-benzyl)-piperidin-2-yl)methyl ester, 4-(3-nitro-5-sulfamoyl-thiophen-2-yl)-piperazine-1-carboxylic acid 1-(2-fluoro-5-methoxy-benzyl)-piperidin-3-yl)methyl ester, 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)piperidine oxalate, 4-(5-trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid pent-2-ynyl ester, 4,4'-bis[4-(P-chlorophenyl)-4-hydroxypiperidino]butyrophenone, 4-[1-(4-chlorobenzyl)-4-(benzylpiperidin-4-yl]-2-hydroxy-4-oxobut-2-enoic acid 4-bromo-N-[1-(9-ethyl-9H-carbazol-3-yl)methyl)-pyrrolidin-3-yl)]-2-trifluoromethoxy-benzenesulfonamide, cardevilol, clobenprobit, 4'-chloro-3-α-(diphenylmethoxy)tropane HCl, 4-furan-2-yl)methyl-piperazine-1-carboxylic acid 2-{4-[3-(2-trifluoromethyl-phenothiazin-10-yl)-propyl]-piperazin-1-yl)}-ethyl ester, 4-methoxy-N-[1-(7-methoxy-benzo[1,3]dioxol-5-yl)methyl)-

pyrrolidin-3-yl)]-benzenesulfonamide, 5-(N-ethyl-N-isopropyl)-amiloride, 7-hydroxy-DPAT HBr, (R)-(+)-, 8-Hydroxy-DPAT HBr, S(-)-9-[4-({[4'-(trifluoromethyl)-1,1'-biphenyl-2-yl]carbonyl}amino)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, acepromazine maleate, acetophenazine maleate, acrinol ajmaline, alaproclate HCl, aloe-emodin, alprenolol D-tartrate hydrate, alprenolol HCl, AMI-193, aminobenztropine, amiodarone HCl, amodiaquine HCl, amorolfine HCl, amoxapine, anileridine HCl, anisotropine methylbromide, anpirtoline ARC 239·2HCl, astemizole auramine O HCl, azaperone, azatadine maleate, azelastine HCl, bamethan sulfate, BD 1008·2HBr, BD-1047, BD-1063, benextramine·4HCl, benfluorex HCl, benidipine HCl, benoxathian HCl, benoxinate HCl, benperidol, benproperine phosphate, benzododecinium bromide, benzphetamine HCl, benztropine mesylate, benzydamine HCl, bephenium hydroxynaphthoate, bepridil HCl, berberine chloride, betaxolol HCl, bifemelane, BMY 7378·2HCl, bopindolol malonate, BP 554, maleate, bromhexine HCl, bromodiphenhydramine HCl, bromperidol, brompheniramine maleate, BTCP HCl, buclizine HCl, buflomedil HCl, bupropion HCl, buspirone HCl, butacaine sulfate, butaclamol HCl, (±)-butenafine HCl, butoconazole nitrate, BW 723C86 HCl, carbetapentane citrate, carbinoxamine maleate, carpipramine·2HCl, DiH2O, carvedilol, cephapirin benzathine CGS-12066A maleate, chloroprocaine HCl, chloroquine phosphate, chlorpheniramine maleate, chlorphenoxamine HCl, chlorpromazine HCl, chlorprothixene, cinanserin HCl, cinnarizine, cirazoline HCl, cis-(+/-)-N-Methyl-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexamine·2HBr, cis(Z)-flupentixol·2HCl, cisapride hydrate, citalopram HBr clebopride maleate, clemastine fumarate, clemizole HCl, clenbuterol HCl, clidinium bromide, CSG 12066B, clobenpropit·2HBr clofazimine, clofilium tosylate, clomiphene citrate, clomiphene A, clomipramine, cloperastine HCl, clorgyline HCl, clozapine, cyclizine, cyclobenzaprine HCl, cycloheximide, cyproheptadine HCl, demecarium bromide, denatonium benzoate, deptropine citrate, desloratadine, dexbrompheniramine maleate, dexchlorpheniramine maleate, dexfenfluramine HCl, dibucaine HCl, dicyclomine HCl, diethylpropion HCl, dimethisoquin HCl, dimetindene maleate, diphemanil methylsulfate, diphenidol HCl, diphenoxylate HCl, diphenylpyraline HCl, dipropyldopamine HBr, dobutamine HCl, donepezil

HCl, doxepin HCl, droperidol, duloxetine, dyclonine HCl, ebastine, econazole nitrate, epinastine HCl, ethaverine HCl, ethopropazine HCl, eticlopride HCl, S(-)-etofenamate, etonitazenyl esothiocyanate, femoxetine HCl, fenfluramine HCl, fentanyl citrate, fenticonazole nitrate, fipexide HCl, flavoxate HCl, flunarizine·2HCl, fluoxetine B, fluperlapine, fluphenazine decanoate·2HCl, fluphenazine enanthate·2HCl, fluphenazine HCl, fluphenazine N-mustard·2HCl, flurazepam C, fluspirilene fluvoxamine maleate, GBR 12783·2HCl, GBR 12909·2HCl, GBR 13069·2HCl, GBR-12935·2HCl, GR 89696, fumarate guanabenz acetate, guanadrel sulfate, guanethidine sulfate, halofantrine HCl, haloperidol, hexylcaine HCl, hycanthone hydroxychloroquine sulfate, hydroxyzine HCl, hyoscyamine sulfate, IBZM, S(-)-ICI-199,441 HCl, ifenprodil tartrate, imipramine HCl, indatraline HCl, llofetamine HCl, irinotecan HCl, isamoltane hemifumarate, isopromethazine HCl, isoxsuprine HCl, ketanserin L-tartrate, ketoconazole, ketotifen fumarate, L-693,403 maleate, L-741,626, L-741,742 HCl, L-745,870·3HCl, labetalol HCl, levetimide HCl, R(-) levobunolol HCl, lidoflazine, lisuride hydrogen maleate, R(+)-lobeline HCl, lomerizine·2HCl, lofepramine, loperamide HCl, loxapine succinate, LY-53,857, maleate maprotiline HCl, mazindol, MDL 12,330A HCl, mebhydroline 1,5-naphthalendisulfonate, meclizine HCl, mefloquine HCl, meprylcaine HCl, mesoridazine besylate, metaphit methanesulfonate, metergoline methantheline bromide, methdilazine, methiothepin mesylate, methixene HCl, methoctramine, methotrimeprazine maleate, methylene violet 3 HCl, metipranolol mexiletine HCl, mianserin HCl, miconazole, ML-9 HCl, morantel hydrogen L-tartrate, MR 16728 HCl, N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine HCl, N'-[2-(benzo[1,2,5]thiadiazole-4-sulfonylamino)-acetyl]-hydrazinecarboxylic acid 2-(2-{4-[(4-chloro-phenyl)-phenyl-methyl]-piperazin-1-yl)}-ethoxy)-ethyl ester, nafronyl oxalate, naftifine, naftopidil·2HCl, naltriben mesylate, NAN-190 HBr, NE-100, nefazodone, nefopam HCl, nicardipine HCl, nicergoline, niguldipine HCl, (+/-)-nisoxetine HCl, nortriptyline HCl, nylidrin HCl, octoclothepin maleate, (±) orphenadrine citrate, oxamniquine, oxamniquine A, oxamniquine B, oxatomide, oxiconazole nitrate, oxybutynin HCl, panaxatriol, PAPP methyl triparoxetine, paxilline, p-chlorobenzhydrylpiperazine, penbutolol sulfate, pentamidine isethionate, entazocine, (±)-pergolide methanesulfonate, perhexiline maleate, perospirone, perphenazine, perphenazine sulfoxide, phenamil

methanesulfonate, phencyclidine HCl, phenosafranin HCl, phenoxybenzamine HCl, phenyltoloxamine citrate, piboserod, pimozide, pinacyanol chloride, pindobind, (+/-)-piperacetazine, piperazine-1,4-dicarboxylic acid benzyl ester, 2-[4-(4-dimethylamino-benzyl)-piperazin-1-yl)]-ethyl ester, piperidolate HCl, pirenperone, PPHT HCl, (±)-pramoxine HCl, prenylamine lactate, pridinol methanesulfonate, prochlorperazine maleate, procyclidine HCl, proflavine hemisulfate, progesterone, promazine HCl, promethazine HCl, propafenone HCl, proparacaine HCl, propericyazine, propiomazine propranolol HCl, protokylol protriptyline HCl, pyrilamine maleate, pyrimethamine, pyrrolidine-1,2-dicarboxylic acid 1-[1-(4-allyloxy-benzyl)-piperidin-2-yl)methyl] ester, 2-benzyl ester pyrvinium pamoate, quetiapine fumarate, quinacrine HCl, quinaldine red, quipazine dimaleate, quipazine, raloxifene, rimantadine HCl, rimcazole, risperidone, ritanserin ritodrine HCl, RS 23597-190 HCl, RS 67333 HCl, RS 67506 HCl, safranin O HCl, salmeterol, SB203186, SCH-23390 HCl, R(+)-sertaconazole nitrate, sertindole sertraline, sibutramine HCl, SKF-525A HCl, SKF-96365 HCl, SNC 121, spiperone HCl, sufentanil, T-226296, tamoxifen citrate, tamsulosin HCl, tegaserod maleate, terbinafine HCl, terconazole, terfenadine, terfenadine A, tetracaine HCl, tetrindole mesylate, thiethylperazine malate, thioperamide maleate, thioproperazine, thioridazine, thiothixene thiothixene, (E)-thonzonium bromide tioconazole A, TMB-8 HCl, tolterodine L-tartrate, toremifene citrate, tramazoline HCl, trans-U-50488 methanesulfonate, (±)-trazodone HCl, tridihexethyl chloride, trifluoperazine HCl, trifluperidol HCl, triflupromazine HCl, trihexyphenidyl HCl, trimebutine, trimeprazine hemi-L-tartrate, trimipramine maleate, tripelennamine HCl, triprolidine HCl, triprolidine HCl, tropanyl 3,5-dimethylbenzoate, tropine 2-(4-chlorophenoxy)butanoate, maleate, U-50488 HCl, U-62066, UH 232 maleate, (+)-vecuronium bromide, verapamil HCl, verapamil B vesamicol HCl, vinpocetine W-7 HCl, WB-4101 HCl, xylazine, xylometazoline HCl; or a combination thereof.

26. The use of claim 24, wherein the Sigma 1 receptor binding compound is amiodarone HCl, azelastine HCl, benproperine phosphate, carvedilol, cyproheptadine HCl, desloratadine, fluphenazine HCl, haloperidol, lofepramine, methyl paroxetine, prochlorpromazine, rimcazole, salmeterol, trifluoperazine diHCl;or a combination thereof.