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(54) Title: HETEROCYCLIC COMPOUNDS HAVING AN OXADIAZOLE MOIETY AND HYDRO ISOMERS THEREOF

(57) Abstract: The present invention relates to substituted diphenyl heterocycle compounds having an oxadiazole moiety and pharmaceutical compositions thereof that inhibit replication of HCV virus. The present invention also relates to the use of the compounds and/or compositions to inhibit HCV replication and/or proliferation and to treat or prevent HCV infections.



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HETEROCYCLIC COMPOUNDS HAVING AN OXADIAZOLE MOIETY AND HYDRO ISOMERS THEREOF

1. CROSS REFERENCE TO RELATED APPLICATION

This application claims benefit under 35 U.S.C. § 119(e) to application Serial No. 60/547,009, filed February 23, 2004 (attorney docket No. 28817/US).

2. FIELD OF INVENTION

The present invention relates to substituted diphenyl heterocycles having an oxadiazole side chain and compositions thereof useful for treating or preventing Hepatitis C virus (HCV) infections. In particular, the present invention relates to substituted diphenyl heterocycles having oxadiazole side chains and hydro isomers thereof, compositions comprising the compounds and the use of such compounds and compositions to inhibit HCV replication and/or proliferation as a therapeutic approach towards the treatment and/or prevention of HCV infections in humans and animals.

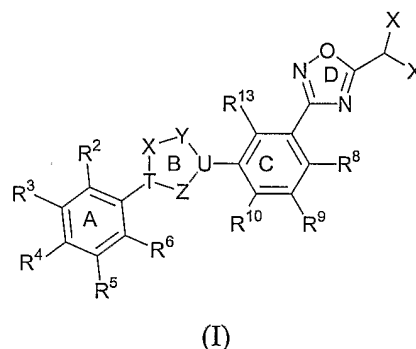
3. BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) infection is a global human health problem with approximately 150,000 new reported cases each year in the United States alone. HCV is a single stranded RNA virus, which is the etiological agent identified in most cases of non-A, non-B post-transfusion and post-transplant hepatitis and is a common cause of acute sporadic hepatitis (Choo *et al.*, *Science* 244:359, 1989; Kuo *et al.*, *Science* 244:362, 1989; and Alter *et al.*, in *Current Perspective in Hepatology*, p. 83, 1989). It is estimated that more than 50% of patients infected with HCV become chronically infected and 20% of those develop cirrhosis of the liver within 20 years (Davis *et al.*, *New Engl. J. Med.* 321:1501, 1989; Alter *et al.*, in *Current Perspective in Hepatology*, p. 83, 1989; Alter *et al.*, *New Engl. J. Med.* 327:1899, 1992; and Dienstag *Gastroenterology* 85:430, 1983). Moreover, the only therapy available for treatment of HCV infection is interferon- α (INTRON[®] A, PEG-INTRON[®] A, Schering-Plough; ROFERON-A[®], PEGASys[®], Roche). Most patients are unresponsive, however, and among the responders, there is a high recurrence rate within 6-12 months after cessation of treatment (Liang *et al.*, *J. Med. Virol.* 40:69, 1993). Ribavirin, a guanosine analog with broad spectrum activity against many RNA and DNA viruses,

has been shown in clinical trials to be effective against chronic HCV infection when used in combination with interferon- α (*see, e.g.,* Poynard *et al.*, *Lancet* 352:1426-1432, 1998; Reichard *et al.*, *Lancet* 351:83-87, 1998), and this combination therapy has been recently approved (REBETRON, Schering-Plough; *see also* Fried *et al.*, 2002, *N. Engl. J. Med.* 347:975-982). However, the response rate is still at or below 50%. Therefore, additional compounds for treatment and prevention of HCV infection are needed.

4. SUMMARY OF THE INVENTION

In one aspect, the present invention provides substituted diphenyl heterocycles having an oxadiazole moiety (i.e., the "D" ring) that are potent inhibitors of Hepatitis C virus ("HCV") replication and/or proliferation. In one embodiment, the compounds are substituted diphenyl heterocycles having an oxadiazole moiety and B-ring hydro isomers thereof according to structural formula (I):



where the B ring is an aromatic or nonaromatic ring that includes from one to four heteroatoms. X, Y, Z of the heterocyclic ring are each, independently of one another selected from C, CH, N, NR¹⁶, NR¹⁸, S or O and U and T are each, independently of one another, selected from C, CH or N, provided that two oxygen atoms are not adjacent to each other in the B ring. Each X of the -CHX₂ group, independently, is a leaving group, such as a halogen atom. In certain embodiments, T and U, each independently, are C or CH.

The "A" phenyl ring includes at least one, and in many instances two, substituents positioned *ortho* to the point of attachment (R² and/or R⁶) and optionally from 1 to 4 additional substituents, which may be the same or different. Although the

“A” ring may include a single *ortho* (R^2 or R^6) substituent, compounds which include two *ortho* substituents (R^2 and R^6) are particularly active and useful. It is preferable that at least one of the substituent groups at positions R^2 and/or R^6 provides some steric bulk. For example, it is preferable that the R^2 and/or R^6 substituent be larger than a fluoro group.

The nature of the R^2 and/or R^6 substituents, as well as the optional substituents at positions R^3 , R^4 and R^5 , can vary widely. As a consequence, the “A” phenyl ring may be substituted with virtually any substituent groups, provided that at least one of R^2 or R^6 is other than hydrogen. When the “A” phenyl ring includes more than one substituent, the substituents may be the same or different. Typical substituent groups useful for substituting the “A” ring include, but are not limited to, branched, straight-chain or cyclic alkyls, mono- or polycyclic aryls, branched, straight-chain or cyclic heteroalkyls, mono- or polycyclic heteroaryl, azos, halos, branched, straight-chain or cyclic haloalkyls, hydroxyls, oxos, thioxos, branched, straight-chain or cyclic alkoxys, branched, straight-chain or cyclic haloalkoxys, trifluoromethoxys, mono- or polycyclic aryloxys, mono- or polycyclic heteroaryloxys, ethers, alcohols, sulfides, thioethers, sulfanyls (thiols), imines, azos, azides, amines (primary, secondary and tertiary), nitriles (any isomer), cyanates (any isomer), thiocyanates (any isomer), nitrosos, nitros, diazos, sulfoxides, sulfonyls, sulfonic acids, sulfamides, sulfonamides, sulfamic esters, aldehydes, ketones, carboxylic acids, esters, amides, amidines, formadines, amino acids, acetylenes, carbamates, lactones, lactams, glucosides, gluconurides, sulfones, ketals, acetals, thioketals, oximes, oxamic acids, oxamic esters, etc., and combinations of these groups.

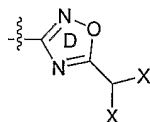
These substituent groups may be further substituted at one or more available carbon or heteroatoms with the same or different additional substituents, which may be selected from the substituents described above. Any reactive functionalities in the groups used to substituted the “A” phenyl ring may be masked with a protecting group or a progroup, as is well-known in the art.

The substituent groups may be attached directly to the phenyl ring, or they may be spaced away from the ring by way of a linker. The nature of the linker can vary widely, and can include virtually any combination of atoms or groups useful for spacing one molecular moiety from another. For example, the linker may be an acyclic hydrocarbon bridge (*e.g.*, a saturated or unsaturated alkylene such as methano,

ethano, etheno, propano, prop[1]eno, butano, but[1]eno, but[2]eno, buta[1,3]dieno, and the like), a monocyclic or polycyclic hydrocarbon bridge (*e.g.*, [1,2]benzeno, [2,3]naphthaleno, and the like), a simple acyclic heteroatomic or heteroalkyldiyl bridge (*e.g.*, -O-, -S-, -S-O-, -NH-, -C(O)-, -C(O)NH-, -NHC(O)O-, -S(O)-, -S(O)₂-, -S(O)NH-, -S(O)₂NH-, -O-CH₂-, -CH₂-O-CH₂-, -O-CH=CH-CH₂-, and the like), a monocyclic or polycyclic heteroaryl bridge (*e.g.*, [3,4]furano [2,3]furano, pyridino, thiopheno, piperidino, piperazino, pyrazidino, pyrrolidino, and the like) or combinations of such bridges.

In one embodiment, the “A” ring is substituted at both R² and R⁶ with the same or different halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, methoxy, haloalkyl, trifluoromethyl, 5-6 membered cycloheteroalkyl or substituted 5-6 membered cycloheteroalkyl group.

The “C” ring is substituted at the *meta* position with a group of the formula



as the “D” ring (an oxadiazole), wherein each X of the -CHX₂ group, independently, is a leaving group, such as a halogen atom (I, Br, Cl, F). The “C” ring may optionally include from 1 to 4 additional substituents (R⁸, R⁹, R¹⁰ and/or R¹³), which may be the same or different. As for the “A” phenyl ring, the nature of the optional R⁸, R⁹, R¹⁰ and R¹³ substituents can vary broadly. Groups useful for substituting the “C” phenyl ring are the same as those described for the “A” phenyl ring, *supra*. In one embodiment, the “C” ring does not include optional substituents, such that R⁸, R⁹, R¹⁰ and R¹³ are each hydrogen.

The “D” ring oxadiazole may be attached directly to the phenyl ring, or may be spaced away from the ring by way of a “tether” (“Q”). The nature of the “tether” can vary widely, and can include virtually any combination of atoms or groups useful for spacing one molecular moiety from another. For example, the tether may be an acyclic hydrocarbon bridge (*e.g.*, a saturated or unsaturated alkylene such as methano, ethano, etheno, propano, prop[1]eno, butano, but[1]eno, but[2]eno, buta[1,3]dieno, and the like), a monocyclic or polycyclic hydrocarbon bridge (*e.g.*, [1,2]benzeno, [2,3]naphthaleno, and the like), a simple acyclic heteroatomic or heteroalkyldiyl bridge (*e.g.*, -O-, -S-, -S-O-, -NH-, -C(O)-, -C(O)NH-, -NHC(O)O-, -S(O)-, -S(O)₂-, -

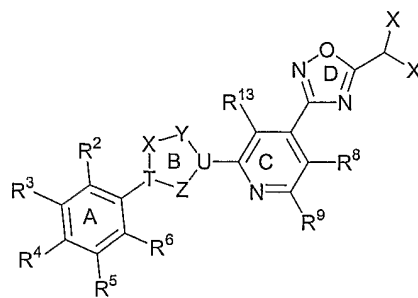
S(O)NH-, -S(O)₂NH-, -O-CH₂-, -CH₂-O-CH₂-, -O-CH=CH-CH₂-, and the like), a monocyclic or polycyclic heteroaryl bridge (*e.g.*, [3,4]furano [2,3]furano, pyridino, thiopheno, piperidino, piperazino, pyrazidino, pyrrolidino, and the like) or combinations of such bridges. In one specific embodiment, the tether is -NH-.

As will be recognized by skilled artisans, the actual electron distribution or double bonding pattern of the “B” ring will depend upon the identities of substituents X, Y, Z, T and/or U.

Suitable heterocycles include, for example, isoxazoles, pyrazoles, oxadiazoles, oxazoles, thiazoles, imidazoles, triazoles, thiadiazoles and hydro isomers thereof. Suitable hydro isomers of the afore-mentioned heterocyclic compounds include, for example, dihydro isomers as well as tetrahydro isomers. Such hydro isomers include, for example, 2-isoxazoline, 3-isoxazoline, 4-isoxazolines, isoxazolidines, 1,2-pyrazolines, 1,2-pyrazolidines, (3H)-dihydro-1,2,4-oxadiazoles, (5H)-dihydro-1,2,4-oxadiazoles, oxazolines, oxazolidines, (3H)-dihydrothiazoles, (5H)-dihydrothiazoles, thiazolidines (tetrahydrothiazoles), (3H)-dihydrotriazoles, (5H)-dihydrotriazoles, triazolidines (tetrahydrotriazoles), dihydro-oxadiazoles, tetrahydro-oxadiazoles, (3H)-dihydro-1,2,4-thiadiazoles, (5H)-dihydro-1,2,4-thiadiazoles, 1,2,4-thiadiazolidines (tetrahydrothiadiazoles), (3H)-dihydroimidazoles, (5H)-dihydroimidazoles and tetrahydroimidazoles.

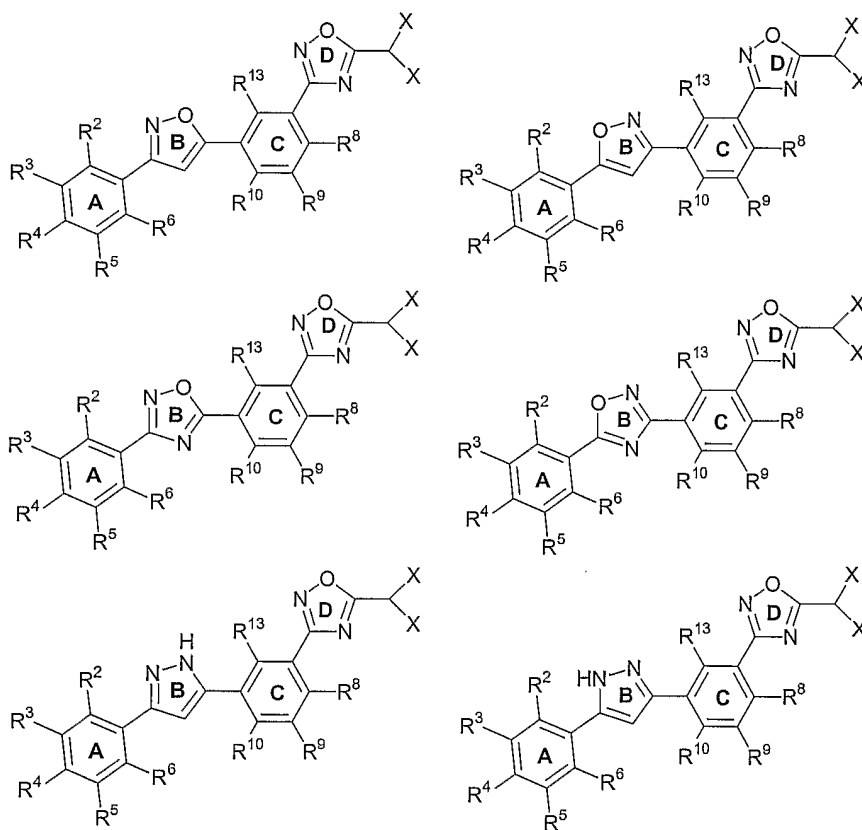
Furthermore, the oxadiazole compounds are intended to include those compounds having an “A”, “B” and “C” ring, hydro isomers, and positional ring isomers thereof as disclosed in US Patent No. 6,759,538 and US Serial Nos. 60/467,650, filed May 2, 2003, 60/467,811, filed May 2, 2003, 10/440,349, filed May 15, 2003 and 10/646,348, filed August 22, 2003 the contents of which are incorporated herein in their entirety.

Therefore, it should be understood that in certain embodiments when the “C” ring is a pyridyl ring, the carbon bearing R¹⁰ is replaced by a nitrogen atom, thus forming the pyridyl ring. The skilled artisan would be able to prepare such compounds in view of the above-identified applications (See for example, compound (Ia)).

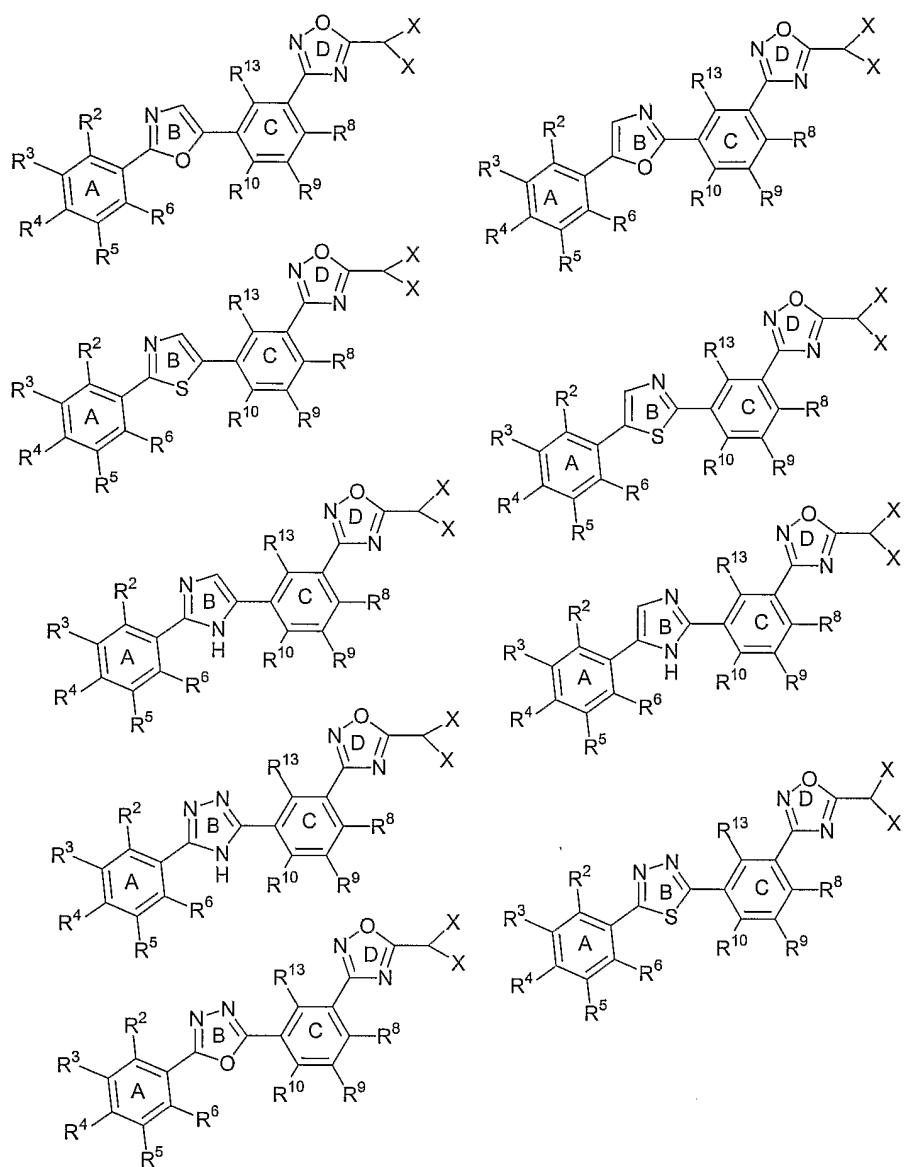


(Ia)

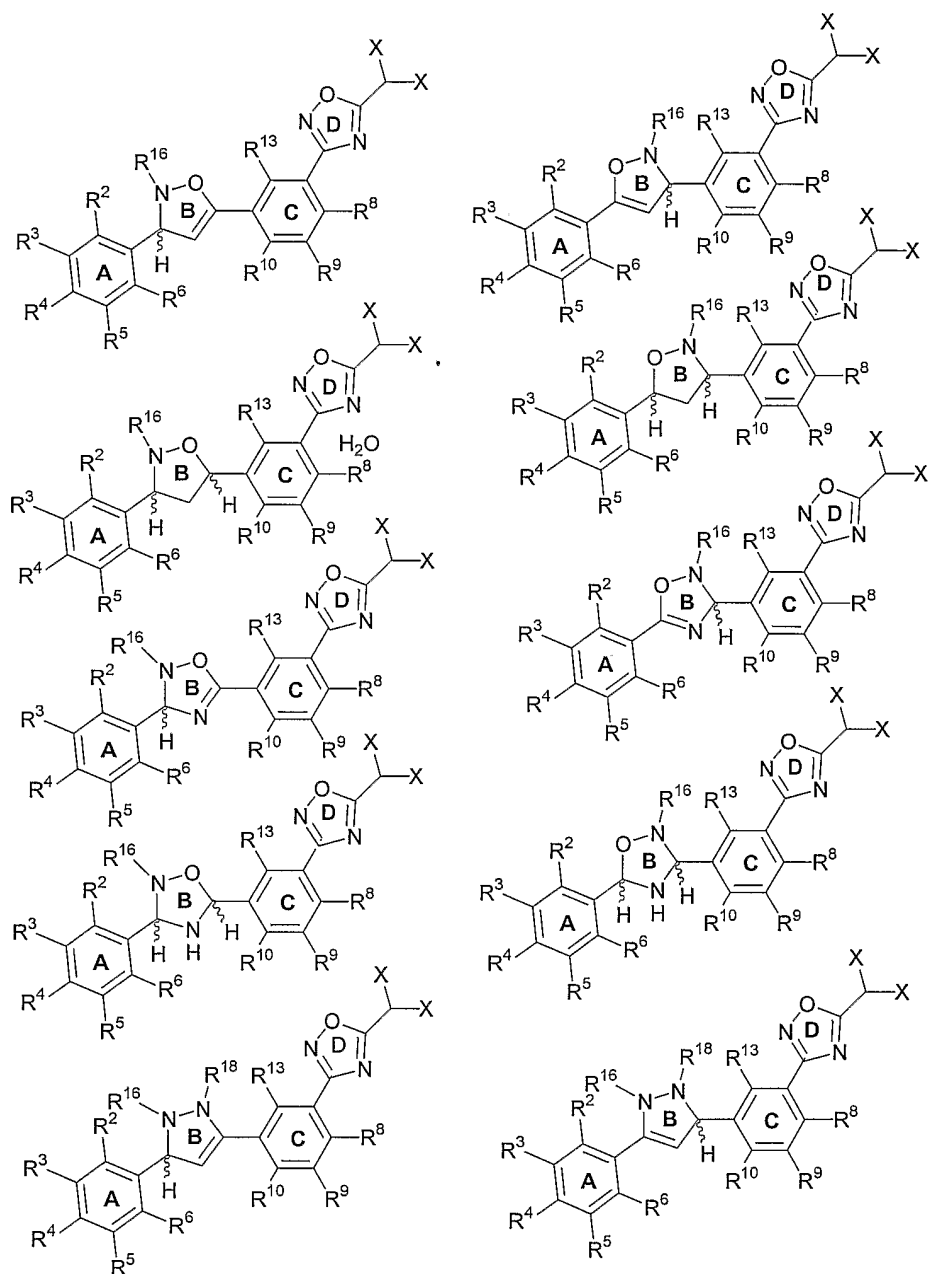
As illustrated, structural formula (I) is specifically intended to include at least the following six structures:

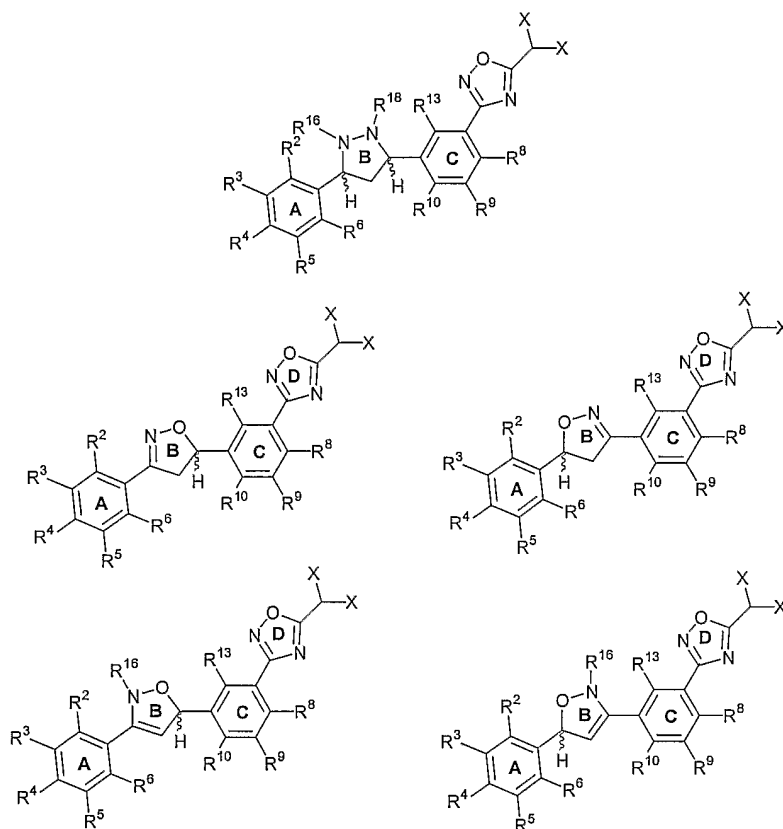


As illustrated, structural formula (I) is also specifically intended to include, for example, at least the following structures:

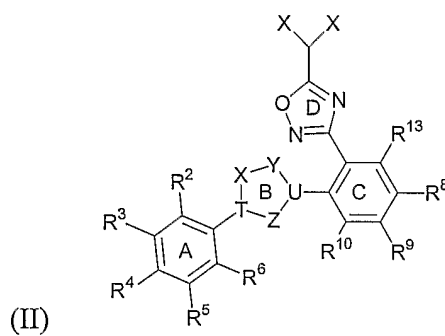


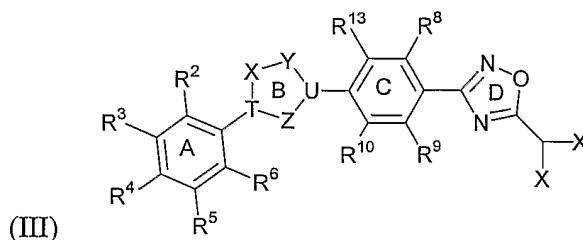
As illustrated, structural formula (I) is specifically intended to include, for example, at least the following B-ring hydro isomers:





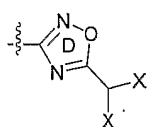
In another aspect, the present invention provides additional substituted diphenyl heterocycles having an oxadiazole moiety that are potent inhibitors of Hepatitis C virus ("HCV") replication and/or proliferation. In one embodiment, the compounds are substituted diphenyl heterocycles having an oxadiazole moiety ("D" ring) and B-ring hydro isomers thereof according to structural formula (II) or (III):



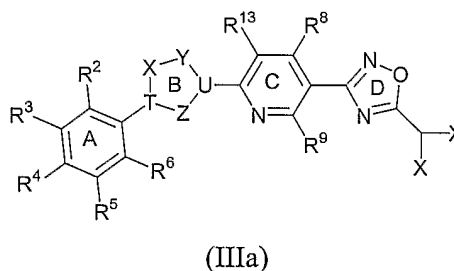


where the B ring is an aromatic or nonaromatic ring that includes from one to four heteroatoms, wherein X, Y, Z of the heterocyclic ring are each, independently of one another, selected from C, CH, N, NR¹⁶, NR¹⁸, S or O, provided X and Y are not both O. U and T are each, independently of one another, selected from C, CH or N, provided that two oxygen atoms are not adjacent to each other in the B ring. In certain embodiments, T and U, each independently, are C or CH.

The “A” phenyl ring for compounds (II) and (III) is as described above. The “C” ring is substituted at the *ortho* or *para* positions with a group of the formula



wherein each X of the $-CHX_2$ group, independently, is a leaving group, such as a halogen atom (I, Br, Cl, F). It should be understood, that the “C” ring can be a pyridyl group, where, for example, the carbon bearing R¹⁰ is replaced by a nitrogen atom. Similarly, the carbons bearing R⁹ or R⁸ can be replaced by a nitrogen atom, thereby providing *ortho*, *meta* or *para* pyridyl moieties (See for example, compound (IIIa)).

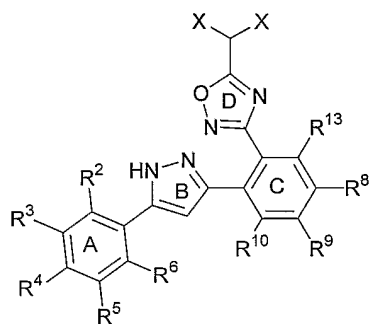
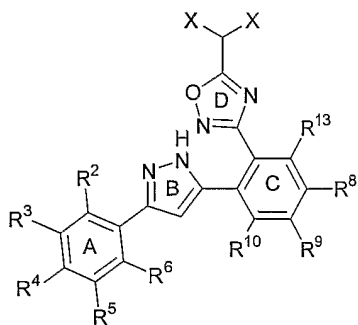
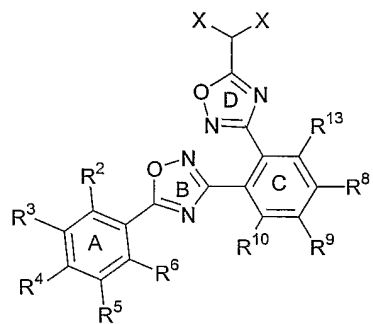
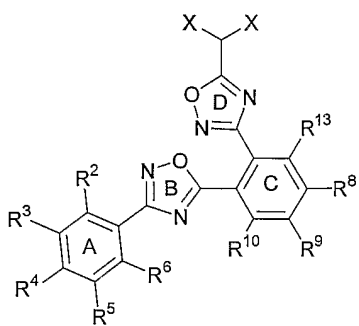
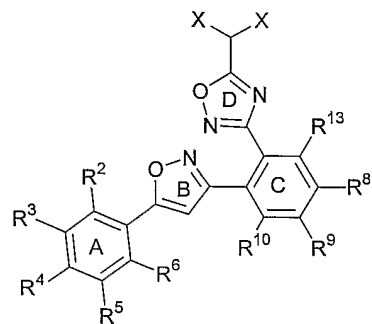
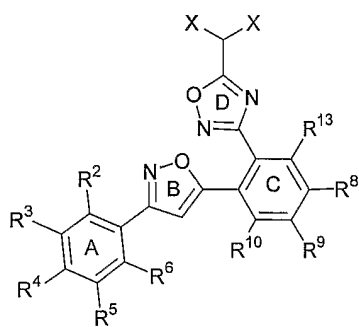


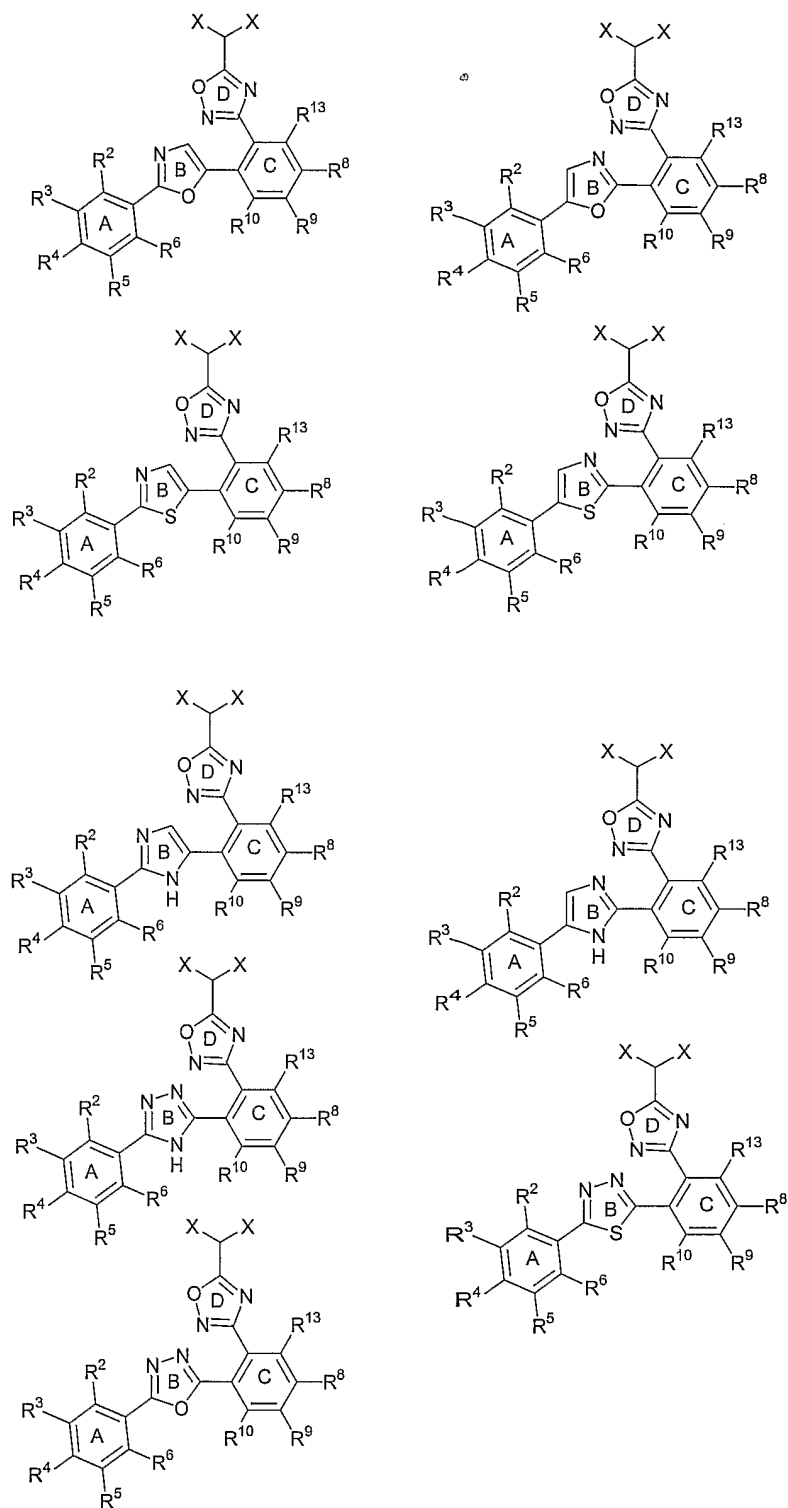
The “D” ring is an oxadiazole, wherein each X of the $-CHX_2$ group, independently, is a leaving group, such as a halogen atom (I, Br, Cl, F). As described

above, the “D” ring may be attached to the phenyl “B” ring via a tether (“Q”). In one aspect, the tether is via an –NH–.

The “C” ring may optionally include from 1 to 4 additional substituents (R^8 , R^9 , R^{10} and/or R^{13}), which may be the same or different. As for the “A” phenyl ring, the nature of the optional R^2 , R^3 , R^4 , R^5 and R^6 substituents can vary broadly. Groups useful for substituting the “C” phenyl ring are the same as those described for the “A” phenyl ring, *supra*. In one embodiment, the “C” ring does not include optional substituents, such that R^8 , R^9 , R^{10} and R^{13} are each hydrogen.

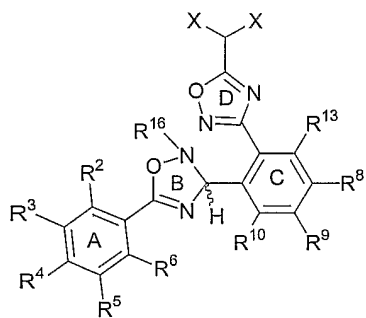
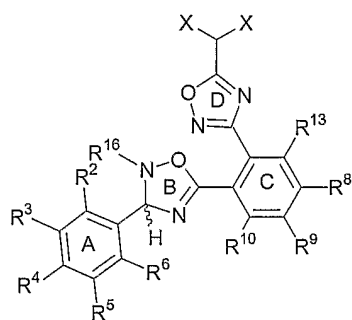
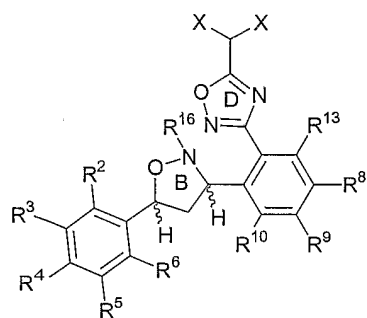
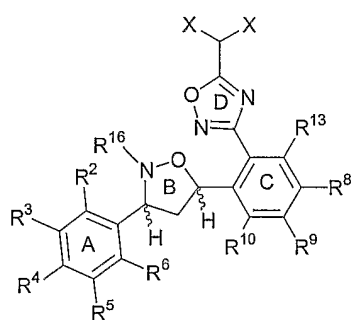
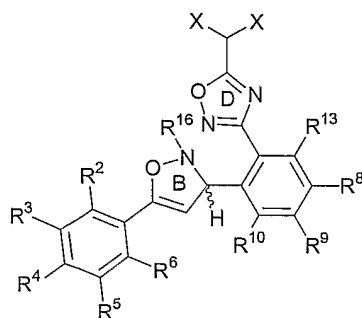
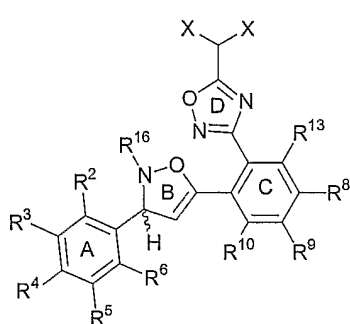
As will be recognized by skilled artisans, the actual electron distribution or double bonding pattern of the “B” ring in formulae (II) and (III) will depend upon the identities of substituents X, Y, Z, T and/or U. As illustrated, structural formulae (II) are specifically intended to include at least the following structures:

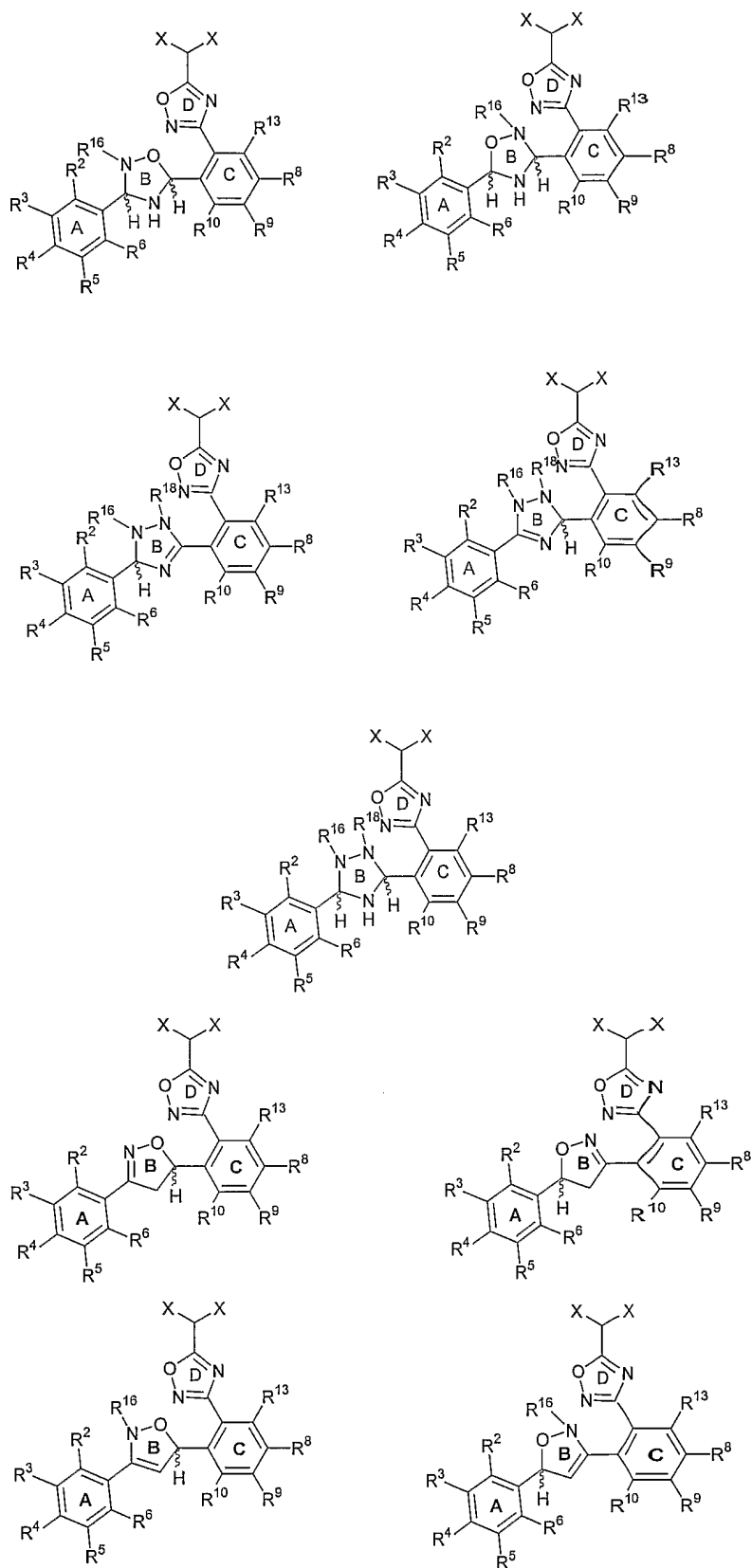




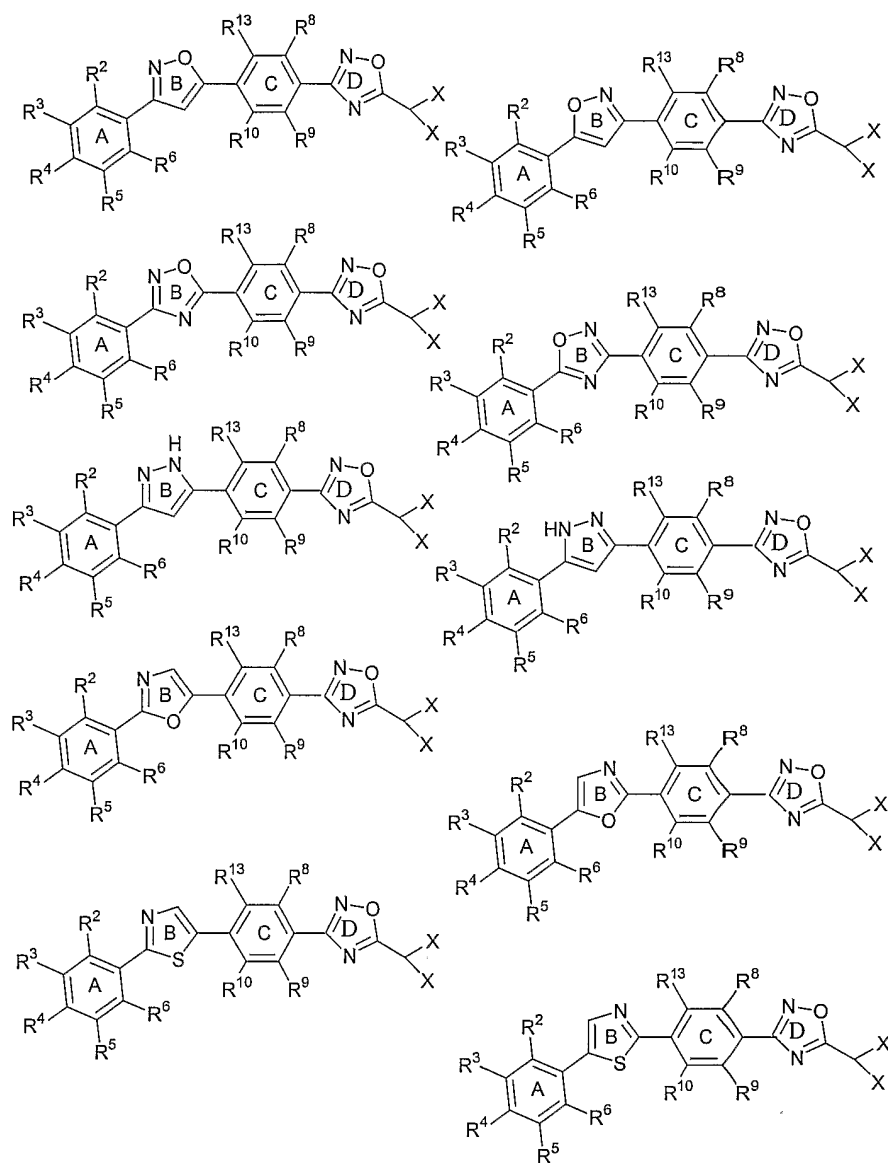
and B-ring hydro isomers thereof.

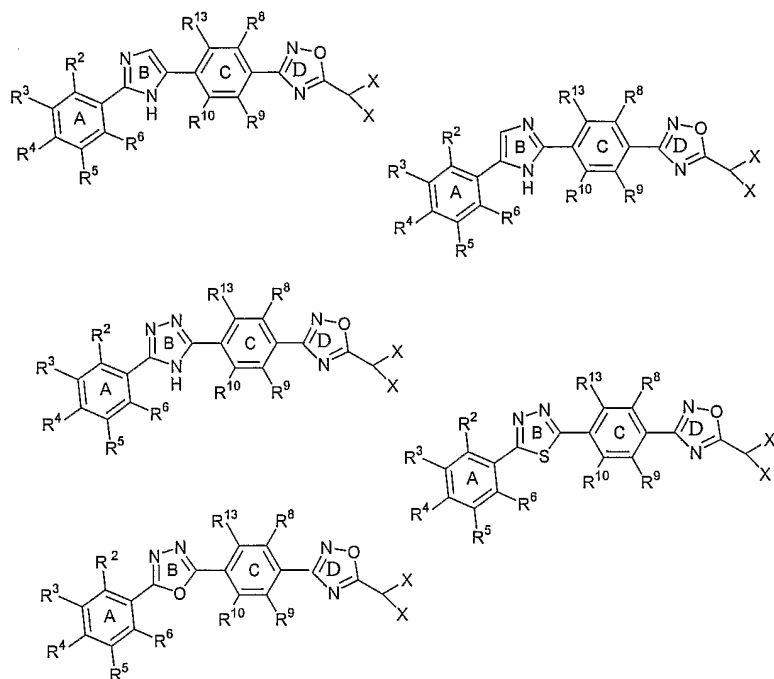
As further illustrated, B-ring hydro isomers of structural formula (II) include, for example, at least the following structures:





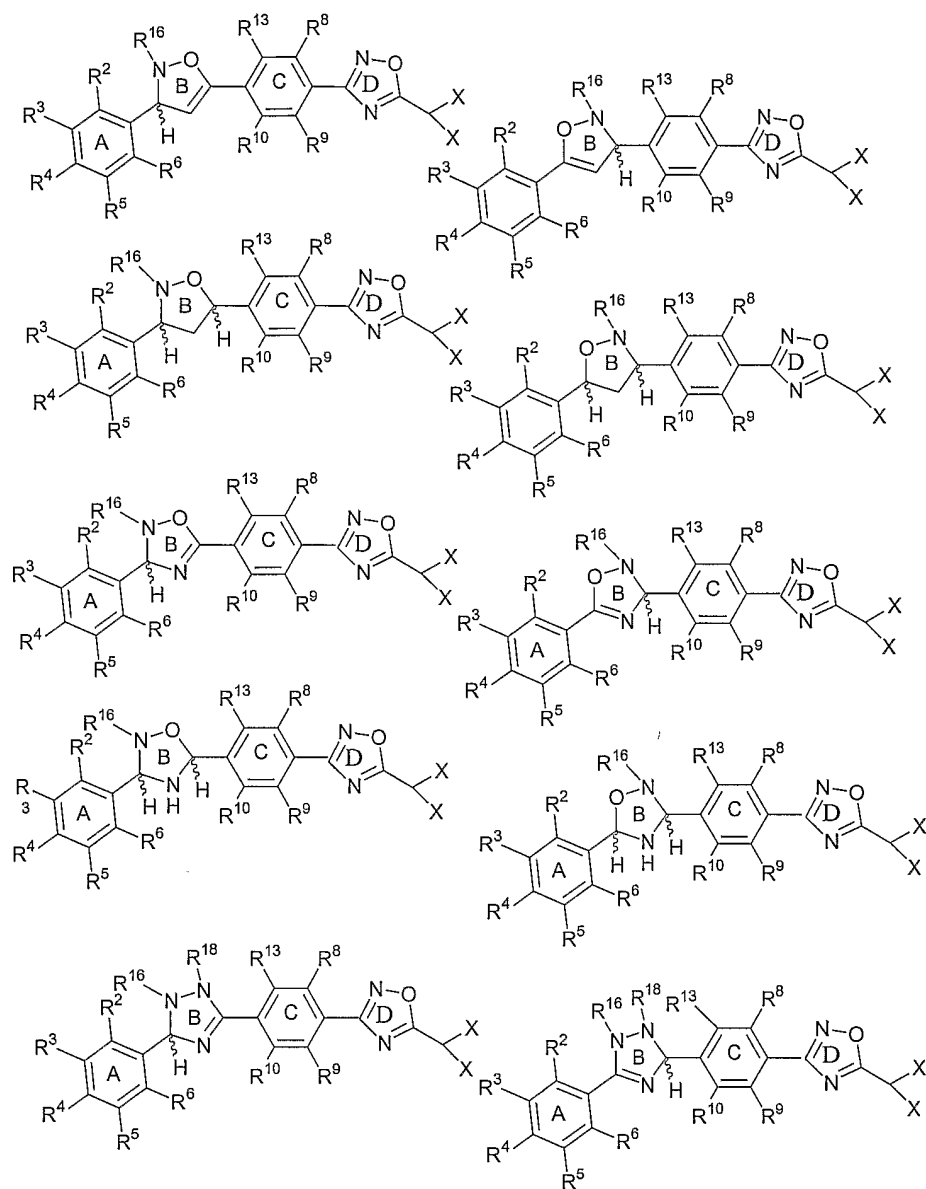
As further illustrated, structural formulae (III) are specifically intended to include at least the following structures:

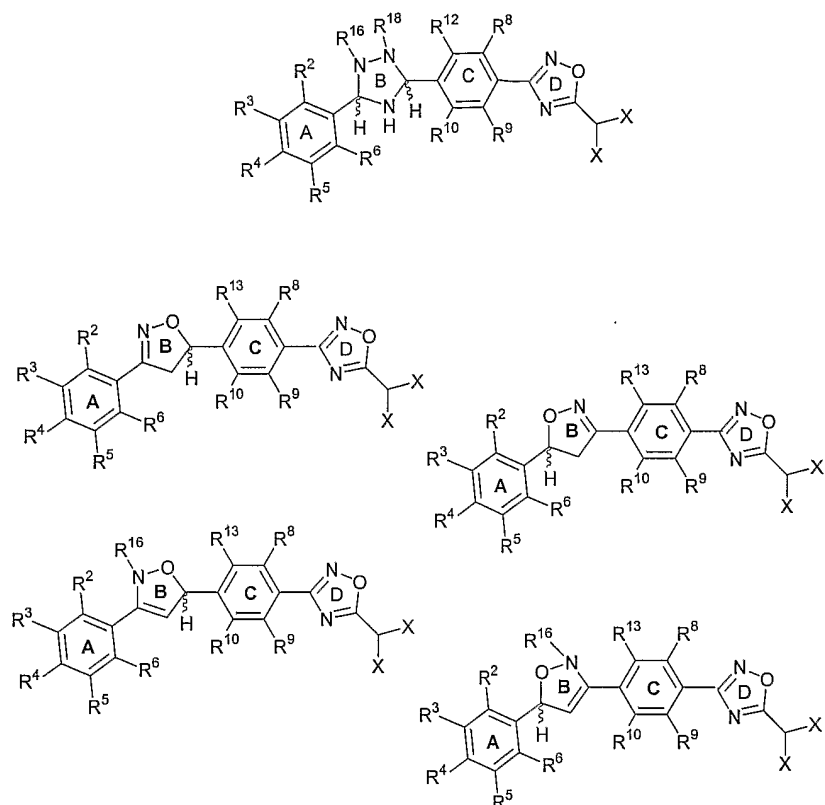




and B-ring hydro isomers thereof.

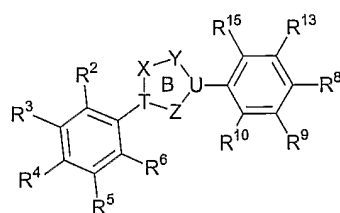
As further illustrated, B-ring hydro isomers of structural formula (III) include, for example, at least the following structures:



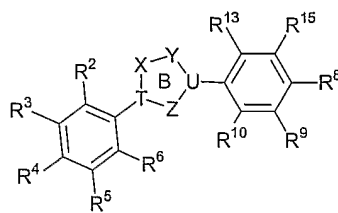


In another aspect, the invention provides starting and intermediate compounds useful for synthesizing the compounds of the invention. For example, representative starting and intermediate compounds useful for synthesizing isoxazoles and hydro isomers of the invention include compounds depicted in FIGS. 1 through 6.

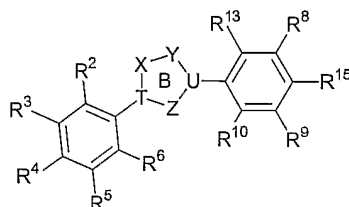
In one embodiment, the intermediates are compounds according to structural formulae (IV), (V), (VI):



(IV)



(V)



(VI)

wherein R^{15} is one of $-\text{CN}$, $-\text{C}(\text{NH}_2)=\text{N}-\text{OH}$ or $-\text{CHX}_2$, wherein each X of the $-\text{CHX}_2$ group, independently is a leaving group, such as a halogen atom, and X, Y, Z of the heterocyclic ring, T, U, R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , R^9 , R^{10} and R^{13} are as previously defined for structural formulae (I), (II) and (III) and subject to the same provisos. Like the compounds of structural formulae (I) through (III), the double bonding pattern will depend upon the identities of substituents X, Y, Z, T and U.

In another aspect, the invention provides methods of making, for example, the substituted diphenyl heterocycle compounds having an oxadiazole moiety of structural formula (I), (II) or (III). Specific exemplary embodiments of the methods are illustrated in FIGS. 1 through 3.

In another aspect, the present invention provides compositions comprising the compounds of the invention. The compositions generally comprise a substituted diphenyl heterocycles having an oxadiazole moiety of the invention, or a salt, hydrate, solvate, N-oxide or prodrug thereof and a suitable excipient, carrier or diluent. The composition may be formulated for veterinary uses or for use in humans.

The compounds of the invention are potent inhibitors of HCV replication and/or proliferation. Accordingly, in still another aspect, the present invention provides methods of inhibiting HCV replication and/or proliferation, comprising contacting a Hepatitis C virion with an amount of a compound or composition of the invention effective to inhibit its replication or proliferation. The methods may be

practiced either *in vitro* or *in vivo*, and may be used as a therapeutic approach towards the treatment and/or prevention of HCV infections.

In a final aspect, the present invention provides methods of treating and/or preventing HCV infections. The methods generally involve administering to a subject that has an HCV infection or that is at risk of developing an HCV infection an amount of a compound or composition of the invention effective to treat or prevent the HCV infection. The method may be practiced in animals in veterinary contexts or in humans.

5. BRIEF DESCRIPTION OF THE FIGURES

FIGS. 1 through 6 provide exemplary synthetic schemes for synthesizing representative compounds of the invention.

6. DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

6.1 Definitions

As used herein, the following terms are intended to have the following meanings:

“Alkyl,” by itself or as part of another substituent, refers to a saturated or unsaturated, branched, straight-chain or cyclic monovalent hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane, alkene or alkyne. Typical alkyl groups include, but are not limited to, methyl; ethyls such as ethanyl, ethenyl, ethynyl; propyls such as propan-1-yl, propan-2-yl, cyclopropan-1-yl, prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), cycloprop-1-en-1-yl; cycloprop-2-en-1-yl, prop-1-yn-1-yl, prop-2-yn-1-yl, *etc.*; butyls such as butan-1-yl, butan-2-yl, 2-methyl-propan-1-yl, 2-methyl-propan-2-yl, cyclobutan-1-yl, but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, *etc.*; and the like.

The term “alkyl” is specifically intended to include groups having any degree or level of saturation, *i.e.*, groups having exclusively single carbon-carbon bonds, groups having one or more double carbon-carbon bonds, groups having one or more

triple carbon-carbon bonds and groups having mixtures of single, double and triple carbon-carbon bonds. Where a specific level of saturation is intended, the expressions “alkanyl,” “alkenyl,” and “alkynyl” are used. Preferably, an alkyl group comprises from 1 to 15 carbon atoms (C₁-C₁₅ alkyl), more preferably from 1 to 10 carbon atoms (C₁-C₁₀ alkyl) and even more preferably from 1 to 6 carbon atoms (C₁-C₆ alkyl or lower alkyl).

“Alkanyl,” by itself or as part of another substituent, refers to a saturated branched, straight-chain or cyclic alkyl radical derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Typical alkanyl groups include, but are not limited to, methanyl; ethanyl; propanyls such as propan-1-yl, propan-2-yl (isopropyl), cyclopropan-1-yl, etc.; butanyls such as butan-1-yl, butan-2-yl (*sec*-butyl), 2-methyl-propan-1-yl (isobutyl), 2-methyl-propan-2-yl (*t*-butyl), cyclobutan-1-yl, etc.; and the like.

“Alkenyl,” by itself or as part of another substituent, refers to an unsaturated branched, straight-chain or cyclic alkyl radical having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. The group may be in either the *cis* or *trans* conformation about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, etc.; and the like.

“Alkynyl,” by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl radical having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Typical alkynyl groups include, but are not limited to, ethynyl; propynyls such as prop-1-yn-1-yl, prop-2-yn-1-yl, etc.; butynyls such as but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, etc.; and the like.

“Alkylidiyl” by itself or as part of another substituent refers to a saturated or unsaturated, branched, straight-chain or cyclic divalent hydrocarbon group derived by the removal of one hydrogen atom from each of two different carbon atoms of a parent alkane, alkene or alkyne, or by the removal of two hydrogen atoms from a single carbon atom of a parent alkane, alkene or alkyne. The two monovalent radical centers or each valency of the divalent radical center can form bonds with the same or different atoms. Typical alkylidiyl groups include, but are not limited to, methandiyl; ethylidiyls such as ethan-1,1-diyl, ethan-1,2-diyl, ethen-1,1-diyl, ethen-1,2-diyl; propylidiyls such as propan-1,1-diyl, propan-1,2-diyl, propan-2,2-diyl, propan-1,3-diyl, cyclopropan-1,1-diyl, cyclopropan-1,2-diyl, prop-1-en-1,1-diyl, prop-1-en-1,2-diyl, prop-2-en-1,2-diyl, prop-1-en-1,3-diyl, cycloprop-1-en-1,2-diyl, cycloprop-2-en-1,2-diyl, cycloprop-2-en-1,1-diyl, prop-1-yn-1,3-diyl, etc.; butylidiyls such as, butan-1,1-diyl, butan-1,2-diyl, butan-1,3-diyl, butan-1,4-diyl, butan-2,2-diyl, 2-methyl-propan-1,1-diyl, 2-methyl-propan-1,2-diyl, cyclobutan-1,1-diyl; cyclobutan-1,2-diyl, cyclobutan-1,3-diyl, but-1-en-1,1-diyl, but-1-en-1,2-diyl, but-1-en-1,3-diyl, but-1-en-1,4-diyl, 2-methyl-prop-1-en-1,1-diyl, 2-methanylidene-propan-1,1-diyl, buta-1,3-dien-1,1-diyl, buta-1,3-dien-1,2-diyl, buta-1,3-dien-1,3-diyl, buta-1,3-dien-1,4-diyl, cyclobut-1-en-1,2-diyl, cyclobut-1-en-1,3-diyl, cyclobut-2-en-1,2-diyl, cyclobuta-1,3-dien-1,2-diyl, cyclobuta-1,3-dien-1,3-diyl, but-1-yn-1,3-diyl, but-1-yn-1,4-diyl, buta-1,3-diyn-1,4-diyl, etc.; and the like. Where specific levels of saturation are intended, the nomenclature alkanyldiyl, alkenyldiyl and/or alkynyldiyl is used. Where it is specifically intended that the two valencies are on the same carbon atom, the nomenclature “alkylidene” is used. In preferred embodiments, the alkylidiyl group comprises from 1 to 6 carbon atoms (C1-C6 alkylidiyl). Also preferred are saturated acyclic alkanyldiyl groups in which the radical centers are at the terminal carbons, *e.g.*, methandiyl (methano); ethan-1,2-diyl (ethano); propan-1,3-diyl (propano); butan-1,4-diyl (butano); and the like (also referred to as alkyleneos, defined *infra*).

“Alkyleneo,” by itself or as part of another substituent, refers to a straight-chain saturated or unsaturated alkylidiyl group having two terminal monovalent radical centers derived by the removal of one hydrogen atom from each of the two terminal carbon atoms of straight-chain parent alkane, alkene or alkyne. The locant of a double

bond or triple bond, if present, in a particular alkyleno is indicated in square brackets. Typical alkyleno groups include, but are not limited to, methano; ethylenos such as ethano, etheno, ethyno; propylenos such as propano, prop[1]eno, propa[1,2]dieno, prop[1]yno, etc.; butylenos such as butano, but[1]eno, but[2]eno, buta[1,3]dieno, but[1]yno, but[2]yno, buta[1,3]diyno, etc.; and the like. Where specific levels of saturation are intended, the nomenclature alkano, alkeno and/or alkyno is used. In preferred embodiments, the alkyleno group is (C1-C6) or (C1-C3) alkyleno. Also preferred are straight-chain saturated alkano groups, *e.g.*, methano, ethano, propano, butano, and the like.

“Alkoxy,” by itself or as part of another substituent, refers to a radical of the formula -OR, where R is an alkyl or cycloalkyl group as defined herein. Representative examples alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, cyclopropyloxy, cyclopentyloxy, cyclohexyloxy and the like.

“Alkoxy carbonyl,” by itself or as part of another substituent, refers to a radical of the formula -C(O)-alkoxy, where alkoxy is as defined herein.

“Alkylthio,” by itself or as part of another substituent, refers to a radical of the formula -SR, where R is an alkyl or cycloalkyl group as defined herein. Representative examples of Alkylthio groups include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, butylthio tert-butylthio, cyclopropylthio, cyclopentylthio, cyclohexylthio, and the like.

“Aryl,” by itself or as part of another substituent, refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system, as defined herein. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene,

pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like. Preferably, an aryl group comprises from 6 to 20 carbon atoms (C₆-C₂₀ aryl), more preferably from 6 to 15 carbon atoms (C₆-C₁₅ aryl) and even more preferably from 6 to 10 carbon atoms (C₆-C₁₀ aryl).

"Arylalkyl," by itself or as part of another substituent, refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or *sp*³ carbon atom, is replaced with an aryl group as, as defined herein. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. Where specific alkyl moieties are intended, the nomenclature arylalkanyl, arylalkenyl and/or arylalkynyl is used. Preferably, an arylalkyl group is (C₆-C₃₀) arylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C₁-C₁₀) alkyl and the aryl moiety is (C₆-C₂₀) aryl, more preferably, an arylalkyl group is (C₆-C₂₀) arylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C₁-C₈) alkyl and the aryl moiety is (C₆-C₁₂) aryl, and even more preferably, an arylalkyl group is (C₆-C₁₅) arylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C₁-C₅) alkyl and the aryl moiety is (C₆-C₁₀) aryl.

"Aryloxy," by itself or as part of another substituent, refers to a radical of the formula -O-aryl, where aryl is as defined herein.

"Arylalkyloxy," by itself or as part of another substituent, refers to a radical of the formula -O-arylalkyl, where arylalkyl is as defined herein.

"Aryloxycarbonyl," by itself or as part of another substituent, refers to a radical of the formula -C(O)-O-aryl, where aryl is as defined herein.

"Carbamoyl," by itself or as part of another substituent, refers to a radical of the formula -C(O)NR'R'', where R' and R'' are each, independently of one another, selected from the group consisting of hydrogen, alkyl and cycloalkyl as defined herein, or alternatively, R' and R'', taken together with the nitrogen atom to which they are

bonded, form a 5-, 6- or 7-membered cycloheteroalkyl ring as defined herein, which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, S and N.

“Compounds of the invention” refers to compounds encompassed by the various descriptions and structural formulae disclosed herein. The compounds of the invention may be identified by either their chemical structure and/or chemical name. When the chemical structure and chemical name conflict, the chemical structure is determinative of the identity of the compound. The compounds of the invention may contain one or more chiral centers and/or double bonds and therefore may exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric isomers), rotamers, atropisomers, enantiomers or diastereomers. Accordingly, when stereochemistry at chiral centers is not specified, the chemical structures depicted herein encompass all possible configurations at those chiral centers including the stereoisomerically pure form (*e.g.*, geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the skilled artisan. The compounds of the invention may also exist in several tautomeric forms including the enol form, the keto form and mixtures thereof. Accordingly, the chemical structures depicted herein encompass all possible tautomeric forms of the illustrated compounds. The compounds of the invention may also include isotopically labeled compounds where one or more atoms have an atomic mass different from the atomic mass conventionally found in nature. Examples of isotopes that may be incorporated into the compounds of the invention include, but are not limited to, ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl . Compounds of the invention may exist in unsolvated forms as well as solvated forms, including hydrated forms and as N-oxides. In general, the hydrated, solvated and N-oxide forms are within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

“Cycloalkyl,” by itself or as part of another substituent, refers to a saturated or unsaturated cyclic alkyl radical, as defined herein. Where a specific level of saturation is intended, the nomenclature “cycloalkanyl” or “cycloalkenyl” is used. Typical cycloalkyl groups include, but are not limited to, groups derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane, and the like. Preferably, the cycloalkyl group comprises from 3 to 10 ring atoms (C₃-C₁₀ cycloalkyl) and more preferably from 3 to 7 ring atoms (C₃-C₇ cycloalkyl).

“Cycloheteroalkyl,” by itself or as part of another substituent, refers to a saturated or unsaturated cyclic alkyl radical in which one or more carbon atoms (and optionally any associated hydrogen atoms) are independently replaced with the same or different heteroatom. Typical heteroatoms to replace the carbon atom(s) include, but are not limited to, N, P, O, S, Si, *etc.* Where a specific level of saturation is intended, the nomenclature “cycloheteroalkanyl” or “cycloheteroalkenyl” is used. Typical cycloheteroalkyl groups include, but are not limited to, groups derived from epoxides, azirines, thiiranes, imidazolidine, morpholine, piperazine, piperidine, pyrazolidine, pyrrolidone, quinuclidine, and the like. Preferably, the cycloheteroalkyl group comprises from 3 to 10 ring atoms (3-10 membered cycloheteroalkyl) and more preferably from 5 to 7 ring atoms (5-7 membered cycloheteroalkyl).

A cycloheteroalkyl group may be substituted at a heteroatom, for example, a nitrogen atom, with a lower alkyl group. As specific examples, N-methyl-imidazolidinyl, N-methyl-morpholinyl, N-methyl-piperazinyl, N-methyl-piperidinyl, N-methyl-pyrazolidinyl and N-methyl-pyrrolidinyl are included within the definition of “cycloheteroalkyl.” A cycloheteralkyl group may be attached to the remainder of the molecule *via* a ring carbon atom or a ring heteroatom.

“Dialkylamino” or “Monoalkylamino,” by themselves or as part of other substituents, refer to radicals of the formula –NRR and –NHR, respectively, where each R is independently selected from the group consisting of alkyl and cycloalkyl, as defined herein. Representative examples of dialkylamino groups include, but are not limited to, dimethylamino, methylethylamino, di-(1-methylethyl)amino, (cyclohexyl)(methyl)amino, (cyclohexyl)(ethyl)amino, (cyclohexyl)(propyl)amino and the like. Representative examples of monalkylamino groups include, but are not

limited to, methylamino, ethylamino, propylamino, isopropylamino, cyclohexylamino, and the like.

“Halogen” or “Halo,” by themselves or as part of another substituent, refer to a fluoro, chloro, bromo and/or iodo radical.

“Haloalkyl,” by itself or as part of another substituent, refers to an alkyl group as defined herein in which one or more of the hydrogen atoms is replaced with a halo group. The term “haloalkyl” is specifically meant to include monohaloalkyls, dihaloalkyls, trihaloalkyls, *etc.* up to perhaloalkyls. The halo groups substituting a haloalkyl can be the same, or they can be different. For example, the expression “(C₁-C₂) haloalkyl” includes 1-fluoromethyl, 1-fluoro-2-chloroethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1, 1-difluoroethyl, 1, 2-difluoroethyl, 1,1,1-trifluoroethyl, perfluoroethyl, *etc.*

“Haloalkyloxy,” by itself or as part of another substituent, refers to a group of the formula -O-haloalkyl, where haloalkyl is as defined herein.

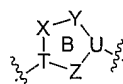
“Heteroalkyl,” “Heteroalkanyl,” “Heteroalkenyl,” “Heteroalkynyl,” “Heteroalkyldiyl” and “Heteroalkyleno,” by themselves or as part of other substituents, refer to alkyl, alkanyl, alkenyl, alkynyl, alkyldiyl and alkyleno groups, respectively, in which one or more of the carbon atoms (and optionally any associated hydrogen atoms), are each, independently of one another, replaced with the same or different heteroatoms or heteroatomic groups. Typical heteroatoms or heteroatomic groups which can replace the carbon atoms include, but are not limited to, O, S, N, Si, -NH-, -S(O)-, -S(O)₂-, -S(O)NH-, -S(O)₂NH- and the like and combinations thereof. The heteroatoms or heteroatomic groups may be placed at any interior position of the alkyl, alkenyl or alkynyl groups. Examples of such heteroalkyl, heteroalkanyl, heteroalkenyl and/or heteroalkynyl groups include -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -CH₂-CH=N-O-CH₃, and -CH₂-CH₂-O-C=CH. For heteroalkyldiyl and heteroalkyleno groups, the

heteratom or heteratomic group can also occupy either or both chain termini. For such groups, no orientation of the group is implied.

“Heteroaryl,” by itself or as part of another substituent, refers to a monovalent heteroaromatic radical derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring systems, as defined herein. Typical heteroaryl groups include, but are not limited to, groups derived from acridine, β -carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like. Preferably, the heteroaryl group comprises from 5 to 20 ring atoms (5-20 membered heteroaryl), more preferably from 5 to 10 ring atoms (5-10 membered heteroaryl). Preferred heteroaryl groups are those derived from furan, thiophene, pyrrole, benzothiophene, benzofuran, benzimidazole, indole, pyridine, pyrazole, quinoline, imidazole, oxazole, isoxazole and pyrazine.

“Heteroarylalkyl” by itself or as part of another substituent refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heteroaryl group. Where specific alkyl moieties are intended, the nomenclature heteroarylalkanyl, heteroarylalkenyl and/or heteroarylalkynyl is used. In preferred embodiments, the heteroarylalkyl group is a 6-21 membered heteroarylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the heteroarylalkyl is (C1-C6) alkyl and the heteroaryl moiety is a 5-15-membered heteroaryl. In particularly preferred embodiments, the heteroarylalkyl is a 6-13 membered heteroarylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety is (C1-C3) alkyl and the heteroaryl moiety is a 5-10 membered heteroaryl.

“Heterocycle” refers to those compounds encompassed by the invention defined by the “B-ring” as depicted herein. Such compounds can be aromatic or nonaromatic (hydro isomers). The B-ring has the general formula:



that includes from one to four heteroatoms, wherein X, Y, Z of the heterocyclic ring are each, independently of one another, C, CH, N, NR¹⁶, NR¹⁸, S or O; and U and T are each, independently of one another, C, CH or N. R¹⁶ and R¹⁸ are each, independently of one another, selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, lower heteroalkyl, substituted lower heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower alkylthio, substituted lower alkylthio, lower alkoxy, substituted lower alkoxy, methoxy, substituted methoxy, lower heteroalkoxy, substituted lower heteroalkoxy, cycloalkoxy, substituted cycloalkoxy, cycloheteroalkoxy, substituted cycloheteroalkoxy, lower haloalkoxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, lower di- or monoalkylamino, substituted lower di- or monoalkylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, phenoxy, substituted phenoxy, arylalkyl, substituted arylalkyl, arylalkyloxy, substituted arylalkyloxy, benzyl, benzyloxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylalkyl, substituted heteroarylalkyl, heteroarylalkyloxy, substituted heteroarylalkyloxy, carboxyl, lower alkoxy carbonyl, substituted lower alkoxy carbonyl, aryloxy carbonyl, substituted aryloxy carbonyl, arylalkyloxy carbonyl, substituted arylalkyloxy carbonyl, carbamate, substituted carbamate, carbamoyl, substituted carbamoyl, sulfamoyl, substituted sulfamoyl and a group of the formula -L-R¹⁴, where "L" is a linker and R¹⁴ is cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl.

Suitable heterocycles include, for example, isoxazoles, pyrazoles, oxadiazoles, oxazoles, thiazoles, imidazoles, triazoles, thiadiazoles and hydro isomers thereof. Suitable hydro isomers of the afore-mentioned heterocyclic compounds include, for example, dihydro isomers as well as tetrahydro isomers. Such hydro isomers include, for example, 2-isoxazoline, 3-isoxazoline, 4-isoxazolines, isoxazolidines, 1,2-pyrazolines, 1,2-pyrazolidines, (3H)-dihydro-1,2,4-oxadiazoles, (5H)-dihydro-1,2,4-

oxadiazoles, oxazolines, oxazolidines, (3H)-dihydrothiazoles, (5H)-dihydrothiazoles, thiazolidines (tetrahydrothiazoles), (3H)-dihydrotriazoles, (5H)-dihydrotriazoles, triazolidines (tetrahydrotriazoles), dihydro-oxadiazoles, tetrahydro-oxadiazoles, (3H)-dihydro-1,2,4-thiadiazoles, (5H)-dihydro-1,2,4-thiadiazoles, 1,2,4-thiadiazolidines (tetrahydrothiadiazoles), (3H)-dihydroimidazoles, (5H)-dihydroimidazoles and tetrahydroimidazoles.

“Parent Aromatic Ring System” refers to an unsaturated cyclic or polycyclic ring system having a conjugated π electron system. Specifically included within the definition of “parent aromatic ring system” are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, fluorene, indane, indene, phenalene, *etc.* Typical parent aromatic ring systems include, but are not limited to, aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like.

“Parent Heteroaromatic Ring System” refers to a parent aromatic ring system in which one or more carbon atoms (and optionally any associated hydrogen atoms) are each independently replaced with the same or different heteroatom. Typical heteroatoms to replace the carbon atoms include, but are not limited to, N, P, O, S, Si, *etc.* Specifically included within the definition of “parent heteroaromatic ring system” are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, benzodioxan, benzofuran, chromane, chromene, indole, indoline, xanthene, *etc.* Typical parent heteroaromatic ring systems include, but are not limited to, arindole, carbazole, β -carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole,

pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene and the like.

“Pharmaceutically acceptable salt” refers to a salt of a compound of the invention which is made with counterions understood in the art to be generally acceptable for pharmaceutical uses and which possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like; or (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, morpholine, piperidine, dimethylamine, diethylamine and the like. Also included are salts of amino acids such as arginates and the like, and salts of organic acids like glucurmic or galactunoric acids and the like (*see, e.g., Berge et al., 1977, J. Pharm. Sci. 66:1-19*).

“Pharmaceutically acceptable vehicle” refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered.

“Protecting group” refers to a group of atoms that, when attached to a reactive functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the

course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, *Protective Groups in Organic Chemistry*, 3rd Ed., 1999, John Wiley & Sons, NY and Harrison *et al.*, *Compendium of Synthetic Organic Methods*, Vols. 1-8, 1971-1996, John Wiley & Sons, NY. Representative amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), *tert*-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("SES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("Fmoc"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxyl protecting groups include, but are not limited to, those where the hydroxyl group is either acylated (*e.g.*, methyl and ethyl esters, acetate or propionate groups or glycol esters) or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (*e.g.*, TMS or TIPPS groups) and allyl ethers.

"Prodrug" refers to a derivative of an active compound (drug) that undergoes a transformation under the conditions of use, such as within the body, to release an active drug. Prodrugs are frequently, but not necessarily, pharmacologically inactive until converted into the active drug. Prodrugs are typically obtained by masking a functional group in the drug believed to be in part required for activity with a progroup (defined below) to form a promoiety which undergoes a transformation, such as cleavage, under the specified conditions of use to release the functional group, and hence the active drug. The cleavage of the promoiety may proceed spontaneously, such as by way of a hydrolysis reaction, or it may be catalyzed or induced by another agent, such as by an enzyme, by light, by acid, or by a change of or exposure to a physical or environmental parameter, such as a change of temperature. The agent may be endogenous to the conditions of use, such as an enzyme present in the cells to which the prodrug is administered or the acidic conditions of the stomach, or it may be supplied exogenously. In a specific embodiment, the term prodrug includes hydro isomers of the compounds of the invention. Such hydro isomers encompassed by the invention can be oxidized under physiological conditions to the corresponding aromatic ring system.

A wide variety of progroups, as well as the resultant promoieties, suitable for masking functional groups in active compounds to yield prodrugs are well-known in

the art. For example, a hydroxyl functional group may be masked as a sulfonate, ester or carbonate promoiety, which may be hydrolyzed *in vitro* to provide the hydroxyl group. An amino functional group may be masked as an amide, imine, phosphinyl, phosphonyl, phosphoryl or sulfenyl promoiety, which may be hydrolyzed *in vivo* to provide the amino group. A carboxyl group may be masked as an ester (including silyl esters and thioesters), amide or hydrazide promoiety, which may be hydrolyzed *in vivo* to provide the carboxyl group. Other specific examples of suitable progroups and their respective promoieties will be apparent to those of skill in the art.

“Progroup” refers to a type of protecting group that, when used to mask a functional group within an active drug to form a promoiety, converts the drug into a prodrug. Progroups are typically attached to the functional group of the drug *via* bonds that are cleavable under specified conditions of use. Thus, a progroup is that portion of a promoiety that cleaves to release the functional group under the specified conditions of use. As a specific example, an amide promoiety of the formula -NH-C(O)CH_3 comprises the progroup -C(O)CH_3 .

“Substituted,” when used to modify a specified group or radical, means that one or more hydrogen atoms of the specified group or radical are each, independently of one another, replaced with the same or different substituent(s). Substituent groups useful for substituting saturated carbon atoms in the specified group or radical include, but are not limited to -R^a , halo, -O^- , $=\text{O}$, -OR^b , -SR^b , -S^- , $=\text{S}$, $\text{-NR}^c\text{R}^c$, $=\text{NR}^b$, $=\text{N-OR}^b$, trihalomethyl, -CF_3 , -CN , -OCN , -SCN , -NO , -NO_2 , $=\text{N}_2$, -N_3 , $\text{-S(O)}_2\text{R}^b$, $\text{-S(O)}_2\text{O}^-$, $\text{-S(O)}_2\text{OR}^b$, $\text{-OS(O)}_2\text{R}^b$, $\text{-OS(O)}_2\text{O}^-$, $\text{-OS(O)}_2\text{OR}^b$, $\text{-P(O)(O}^-)_2$, $\text{-P(O)(OR}^b)_2$, $\text{-P(O)(OR}^b)_2$, -C(O)R^b , -C(S)R^b , $\text{-C(NR}^b)_2$, -C(O)O^- , -C(O)OR^b , -C(S)OR^b , $\text{-C(O)NR}^c\text{R}^c$, $\text{-C(NR}^b)_2\text{NR}^c\text{R}^c$, -OC(O)R^b , -OC(S)R^b , -OC(O)O^- , -OC(O)OR^b , -OC(S)OR^b , $\text{-NR}^b\text{C(O)R}^b$, $\text{-NR}^b\text{C(S)R}^b$, $\text{-NR}^b\text{C(O)O}^-$, $\text{-NR}^b\text{C(O)OR}^b$, $\text{-NR}^b\text{C(S)OR}^b$, $\text{-NR}^b\text{C(O)NR}^c\text{R}^c$, $\text{-NR}^b\text{C(NR}^b)_2$ and $\text{-NR}^b\text{C(NR}^b)_2\text{NR}^c\text{R}^c$, where R^a is selected from the group consisting of alkyl, cycloalkyl, heteroalkyl, cycloheteroalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl; each R^b is independently hydrogen or R^a ; and each R^c is independently R^b or alternatively, the two R^c s are taken together with the nitrogen atom to which they are bonded form a 5-, 6- or 7-membered cycloheteroalkyl which may optionally include from 1 to 4 of the same or different additional heteroatoms

selected from the group consisting of O, N and S. As specific examples, $-NR^cR^c$ is meant to include $-NH_2$, $-NH$ -alkyl, N-pyrrolidinyl and N-morpholinyl.

Similarly, substituent groups useful for substituting unsaturated carbon atoms in the specified group or radical include, but are not limited to, $-R^a$, halo, $-O^-$, $-OR^b$, $-SR^b$, $-S^-$, $-NR^cR^c$, trihalomethyl, $-CF_3$, $-CN$, $-OCN$, $-SCN$, $-NO$, $-NO_2$, $-N_3$, $-S(O)_2R^b$, $-S(O)_2O^-$, $-S(O)_2OR^b$, $-OS(O)_2R^b$, $-OS(O)_2O^-$, $-OS(O)_2OR^b$, $-P(O)(O^-)_2$, $-P(O)(OR^b)(O^-)$, $-P(O)(OR^b)(OR^b)$, $-C(O)R^b$, $-C(S)R^b$, $-C(NR^b)R^b$, $-C(O)O^-$, $-C(O)OR^b$, $-C(S)OR^b$, $-C(O)NR^cR^c$, $-C(NR^b)NR^cR^c$, $-OC(O)R^b$, $-OC(S)R^b$, $-OC(O)O^-$, $-OC(O)OR^b$, $-OC(S)OR^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NR^bC(O)O^-$, $-NR^bC(O)OR^b$, $-NR^bC(S)OR^b$, $-NR^bC(O)NR^cR^c$, $-NR^bC(NR^b)R^b$ and $-NR^bC(NR^b)NR^cR^c$, where R^a , R^b and R^c are as previously defined.

Substituent groups useful for substituting nitrogen atoms in heteroalkyl and cycloheteroalkyl groups include, but are not limited to, $-R^a$, $-O^-$, $-OR^b$, $-SR^b$, $-S^-$, $-NR^cR^c$, trihalomethyl, $-CF_3$, $-CN$, $-NO$, $-NO_2$, $-S(O)_2R^b$, $-S(O)_2O^-$, $-S(O)_2OR^b$, $-OS(O)_2R^b$, $-OS(O)_2O^-$, $-OS(O)_2OR^b$, $-P(O)(O^-)_2$, $-P(O)(OR^b)(O^-)$, $-P(O)(OR^b)(OR^b)$, $-C(O)R^b$, $-C(S)R^b$, $-C(NR^b)R^b$, $-C(O)OR^b$, $-C(S)OR^b$, $-C(O)NR^cR^c$, $-C(NR^b)NR^cR^c$, $-OC(O)R^b$, $-OC(S)R^b$, $-OC(O)OR^b$, $-OC(S)OR^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NR^bC(O)OR^b$, $-NR^bC(S)OR^b$, $-NR^bC(O)NR^cR^c$, $-NR^bC(NR^b)R^b$ and $-NR^bC(NR^b)NR^cR^c$, where R^a , R^b and R^c are as previously defined.

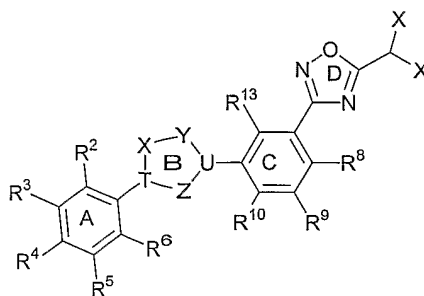
Substituent groups from the above lists useful for substituting other specified groups or atoms will be apparent to those of skill in the art.

The substituents used to substitute a specified group can be further substituted, typically with one or more of the same or different groups selected from the various groups specified above.

“Sulfamoyl,” by itself or as part of another substituent, refers to a radical of the formula $-S(O)_2NR'R''$, where R' and R'' are each, independently of one another, selected from the group consisting of hydrogen, alkyl and cycloalkyl as defined herein, or alternatively, R' and R'' , taken together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered cycloheteroalkyl ring as defined herein, which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, S and N.

6.2 The Compounds

The invention provides substituted diphenyl heterocycle compounds having an oxadiazole moiety that are potent inhibitors of HCV replication and/or proliferation. In one embodiment, the compounds of the invention are substituted diphenyl heterocycles having an oxadiazole moiety and hydro isomers thereof, according to structural formula (I):



(I)

including the pharmaceutically acceptable salts, hydrates, solvates and N-oxides thereof, wherein:

the B ring is an aromatic or nonaromatic ring that includes from one to four heteroatoms, wherein X, Y, Z of the heterocyclic ring are each, independently of one another, C, CH, N, NR¹⁶, NR¹⁸, S or O, provided that X and Y are not both O;

U and T are each, independently of one another, C, CH or N;

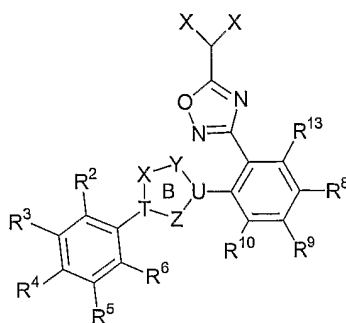
each X of the -CHX₂ group, independently, is a leaving group;

R², R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰ and R¹³ are each, independently of one another, selected from the group consisting of hydrogen, -OH, -SH, -CN, -NO₂, -N₃, halo, fluoro, chloro, bromo, iodo, lower alkyl, substituted lower alkyl, lower heteroalkyl, substituted lower heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower alkylthio, substituted lower alkylthio, lower alkoxy, substituted lower alkoxy, methoxy, substituted methoxy, lower heteroalkoxy, substituted lower heteroalkoxy, cycloalkoxy, substituted cycloalkoxy, cycloheteroalkoxy, substituted cycloheteroalkoxy, lower haloalkoxy,

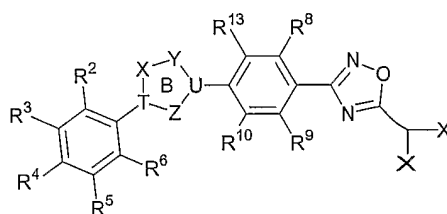
monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, amino, lower di- or monoalkylamino, substituted lower di- or monoalkylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, phenoxy, substituted phenoxy, arylalkyl, substituted arylalkyl, arylalkyloxy, substituted arylalkyloxy, benzyl, benzyloxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylalkyl, substituted heteroarylalkyl, heteroarylalkyloxy, substituted heteroarylalkyloxy, carboxyl, lower alkoxycarbonyl, substituted lower alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, arylalkyloxycarbonyl, substituted arylalkyloxycarbonyl, carbamate, substituted carbamate, carbamoyl, substituted carbamoyl, sulfamoyl, substituted sulfamoyl and a group of the formula $-L-R^{14}$, where "L" is a linker and R^{14} is cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl; and

R^{16} and R^{18} are each, independently of one another, selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, lower heteroalkyl, substituted lower heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower alkylthio, substituted lower alkylthio, lower alkoxy, substituted lower alkoxy, methoxy, substituted methoxy, lower heteroalkoxy, substituted lower heteroalkoxy, cycloalkoxy, substituted cycloalkoxy, cycloheteroalkoxy, substituted cycloheteroalkoxy, lower haloalkoxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, lower di- or monoalkylamino, substituted lower di- or monoalkylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, phenoxy, substituted phenoxy, arylalkyl, substituted arylalkyl, arylalkyloxy, substituted arylalkyloxy, benzyl, benzyloxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylalkyl, substituted heteroarylalkyl, heteroarylalkyloxy, substituted heteroarylalkyloxy, carboxyl, lower alkoxycarbonyl, substituted lower alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, arylalkyloxycarbonyl, substituted arylalkyloxycarbonyl, carbamate, substituted carbamate, carbamoyl, substituted carbamoyl, sulfamoyl, substituted sulfamoyl and a group of the formula $-L-R^{14}$, where "L" is a linker and R^{14} is cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl.

In another embodiment, the compounds of the invention are substituted diphenyl heterocycles having an oxadiazole moiety and hydro isomers thereof, according to structural formula (II) or (III):



(II)



(III)

including the pharmaceutically acceptable salts, hydrates, solvates, N-oxides and prodrugs thereof, wherein:

the B ring is an aromatic or nonaromatic ring that includes from one to four heteroatoms, wherein X, Y, Z of the heterocyclic ring are each, independently of one another, C, CH, N, NR¹⁶, NR¹⁸, S or O, provided that X and Y are not both O;

each X of the -CHX₂ group, independently, is a leaving group;

U and T are each, independently of one another, C, CH or N;

R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , R^9 , R^{10} and R^{13} are each, independently of one another, selected from the group consisting of hydrogen, -OH, -SH, -CN, -NO₂, -N₃, halo, fluoro, chloro, bromo, iodo, lower alkyl, substituted lower alkyl, lower heteroalkyl, substituted lower heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower alkylthio, substituted lower alkylthio, lower alkoxy, substituted lower alkoxy, methoxy, substituted methoxy, lower heteroalkoxy, substituted lower heteroalkoxy, cycloalkoxy, substituted cycloalkoxy, cycloheteroalkoxy, substituted cycloheteroalkoxy, lower haloalkoxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, amino, lower di- or monoalkylamino, substituted lower di- or monoalkylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, phenoxy, substituted phenoxy, arylalkyl, substituted arylalkyl, arylalkyloxy, substituted arylalkyloxy, benzyl, benzyloxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylalkyl, substituted heteroarylalkyl, heteroarylalkyloxy, substituted heteroarylalkyloxy, carboxyl, lower alkoxycarbonyl, substituted lower alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, arylalkyloxycarbonyl, substituted arylalkyloxycarbonyl, carbamate, substituted carbamate, carbamoyl, substituted carbamoyl, sulfamoyl, substituted sulfamoyl and a group of the formula -L- R^{14} , where "L" is a linker and R^{14} is cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl; and

R^{16} and R^{18} are each, independently of one another, selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, lower heteroalkyl, substituted lower heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower alkylthio, substituted lower alkylthio, lower alkoxy, substituted lower alkoxy, methoxy, substituted methoxy, lower heteroalkoxy, substituted lower heteroalkoxy, cycloalkoxy, substituted cycloalkoxy, cycloheteroalkoxy, substituted cycloheteroalkoxy, lower haloalkoxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, lower di- or monoalkylamino, substituted lower di- or monoalkylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, phenoxy, substituted phenoxy, arylalkyl, substituted

arylalkyl, arylalkyloxy, substituted arylalkyloxy, benzyl, benzyloxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylalkyl, substituted heteroarylalkyl, heteroarylalkyloxy, substituted heteroarylalkyloxy, carboxyl, lower alkoxycarbonyl, substituted lower alkoxycarbonyl, aryloxy carbonyl, substituted aryloxy carbonyl, arylalkyloxy carbonyl, substituted arylalkyloxy carbonyl, carbamate, substituted carbamate, carbamoyl, substituted carbamoyl, sulfamoyl, substituted sulfamoyl and a group of the formula -L-R¹⁴, where “L” is a linker and R¹⁴ is cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl.

In the compounds of formulae (I) through (III), one alternative group for substituents R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , R^9 , R^{10} and R^{13} is a group of the formula $-L-R^{14}$, where "L" is a linker. The linker may be any group of atoms suitable for attaching the R^{14} moiety to the illustrated phenyl group. Suitable linkers include, but are not limited to, moieties selected from the group consisting of $-(CH_2)_{1-6}-$, O, S, $-C(O)-$, $-SO_2-$, $-NH-$, $-NHC(O)-$, $-C(O)-$, $-SO_2NH-$ and combinations thereof. In one embodiment, "L" is selected from the group consisting of $-(CH_2)_{1-3}-$, $-O-(CH_2)_{1-3}-$, $-S-(CH_2)_{1-3}-$ and $-SO_2-$.

In such L-R¹⁴ moieties, R¹⁴ is as defined above. In one embodiment, R¹⁴ is selected from the group consisting of morpholinyl, N-morpholinyl, piperazinyl, N-piperazinyl, N-methyl-N-piperazinyl, imidazoliny, N-imidazolidinyl, N-methyl-N-imidazolidinyl, piperidinyl, N-piperidinyl, pyrrolidinyl, N-pyrrolidinyl, pyrazolidinyl, N-pyrazolidinyl and N-methyl-N-pyrazolidinyl.

In the compounds of formula (I) through (III), specific examples of substituent groups when R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , R^9 , R^{10} and/or R^{13} are a substituted alkyl group include methyl, ethyl or propyl groups substituted with a single substituent selected from the group consisting of halo, fluoro, chloro, bromo, hydroxy, lower alkoxy, -CN, -NO₂, -C(O)OR^e, -OC(O)OR^e, -C(O)NR^fR^g and -OC(O)NR^fR^g, where each R^e is independently hydrogen, lower alkyl or cycloalkyl; and R^f and R^g are each, independently of one another, selected from the group consisting of hydrogen, lower alkyl and cycloalkyl or, alternatively, R^f and R^g, taken together with the nitrogen atom to which they are bonded form a 5-, 6- or 7-membered cycloheteroalkyl ring which may optionally include from 1 to 4 of the same or different additional heteroatoms

selected from the group consisting of O, S and N. Further specific examples of substituent groups when R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , R^9 , R^{10} and/or R^{13} are a substituted alkyl group include $-\text{CH}_2\text{-R}^{17}$, where R^{17} is halo, Br, -OH, lower alkoxy, -CN, NO_2 , $-\text{C}(\text{O})\text{R}^e$, $-\text{OC}(\text{O})\text{R}^e$, $-\text{C}(\text{O})\text{NR}^f\text{R}^g$ and $-\text{OC}(\text{O})\text{NR}^f\text{R}^g$, where R^e , R^f and R^g are as defined above.

Specific examples of substituent groups when R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , R^9 , R^{10} and/or R^{13} are a substituted lower alkoxy group include lower alkoxy groups substituted at the terminal methyl group with a substituent selected from the group consisting of halo, -OH, -CN, $-\text{NO}_2$, $-\text{C}(\text{O})\text{R}^e$, $-\text{OC}(\text{O})\text{R}^e$, $-\text{C}(\text{O})\text{NR}^f\text{R}^g$ and $-\text{OC}(\text{O})\text{NR}^f\text{R}^g$, where R^e , R^f and R^g are as previously defined.

Specific examples of substituent groups when R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , R^9 , R^{10} and/or R^{13} are aryl or heteroaryl groups include phenyl, 5- or 6-membered heteroaryl, furanyl, imidazolyl, isothiazolyl, isoxazolyl, pyranal, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl and thiophenyl. The various heteroaryl groups may be connected to the remainder of the molecule via any available carbon atom or heteroatom. In one embodiment, heteroaryl groups containing ring nitrogen atoms are attached to the remainder of the molecule via a ring nitrogen atom. The heteroaryl groups may also be substituted at one or more ring nitrogen atoms with a lower alkyl, lower alkanyl or methyl group.

Specific examples of substituent groups when R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , R^9 , R^{10} and/or R^{13} are carbamoyl or substituted carbamoyl groups include groups of the formula $-\text{C}(\text{O})\text{NR}^h\text{R}^i$, where R^h and R^i are taken together with the nitrogen atom to which they are bonded to form a 5- or 6-membered cycloheteroalkyl ring which may optionally include from 1 to 4 of the same or different additional heteratoms selected from O, S and N and which is optionally substituted at one or more ring carbon or heteratoms with a substituent selected from the group consisting of lower alkyl, lower alkanyl, methyl, -OH, =O, $-\text{C}(\text{O})\text{OR}^e$, $-\text{C}(\text{O})\text{NR}^f\text{R}^g$, $-\text{OC}(\text{O})\text{R}^e$, $-\text{OC}(\text{O})\text{NR}^f\text{R}^g$ and aryl, where R^e , R^f and R^g are as previously defined. Further specific examples include sulfamoyl or substituted sulfamoyl groups of the formula $-\text{C}(\text{O})\text{NR}^h\text{R}^i$, where NR^hR^i is selected from the group consisting of N-methyl-piperazine, 4-oxo-piperidine, 4-amino-piperidine, 4-(mono- or dialkylamino) piperidine and 4-hydroxy-piperidine.

Specific examples of substituent groups when R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , R^9 , R^{10} and/or R^{13} are a substituted mono- or dialkylamino group include those mono or

dialkylamino groups in which at least one of the alkyl moieties is substituted, preferably at a terminal methyl group, with a substituent selected from the group consisting of $-\text{OH}$ and $-\text{NR}^e\text{R}^e$, where each R^e is as previously defined. Specific examples of such substituted mono- and dialkylamino groups include $-\text{N}(\text{R}^k)-(\text{CH}_2)_{1-3}-\text{NR}^k\text{R}^k$ and $-\text{N}(\text{R}^k)-(\text{CH}_2)_{1-3}-\text{OR}^k$, where each R^k is independently hydrogen, lower alkyl or methyl.

Specific examples of substituent groups when $\text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^8, \text{R}^9, \text{R}^{10}$ and/or R^{13} is a cycloheteroalkyl or substituted cycloheteroalkyl group include 5- or 6-membered cycloheteroalkyl, imidazolidinyl, morpholinyl, piperazinyl, piperadinyl, pyrazolidinyl and pyrrolidinyl, wherein the ring may be optionally substituted at a ring carbon atom with a substituent selected from the group consisting of $-\text{OR}^e$, $-\text{NR}^f\text{R}^g$ and $-\text{C}(\text{O})\text{OR}^e$, where R^e, R^f and R^g are as previously defined. The cycloheteroalkyl or substituted cycloheteroalkyl may be attached to the remainder of the molecule *via* any available ring carbon or heteroatom. In one embodiment, the cycloheteroalkyl or substituted cycloheteroalkyl is attached to the remainder of the molecule *via* a ring nitrogen atom. Further specific examples of substituted cycloheteroalkyls suitable as $\text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^8, \text{R}^9, \text{R}^{10}$ and/or R^{13} substituents include N-piperidinyl substituted at the 4-position, or N-pyrrolidinyl substituted at the 3-position, with a lower alkoxy carbonyl, amino, mono- or dialkylamino or N-piperidinyl group.

Additional specific examples of $\text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^8, \text{R}^9, \text{R}^{10}$ and R^{13} , as well as specific combinations of substituents for the "A" and "C" phenyl rings are provided in TABLES 1 through 4, *infra*.

In one embodiment of the compounds of structural formula (I), Z is $-\text{CH}-$ and the "B" ring is a hydro isomer so that the compounds are hydro isomers of isoxazoles or pyrazoles. In another embodiment of the compounds of structural formula (I), Z is N such that the compounds are oxadiazoles. In another embodiment, the compounds of structural formula (I) are hydro isomers of isoxazoles.

In another embodiment of the compounds of structural formula (I), three of $\text{R}^8, \text{R}^9, \text{R}^{10}$ and R^{13} are hydrogen. In a specific embodiment, $\text{R}^9, \text{R}^{10}$ and R^{13} are each hydrogen.

In yet another embodiment of the compounds of structural formula (I), $\text{R}^8, \text{R}^9, \text{R}^{10}$ and R^{13} are each, independently of one another, selected from the group consisting of hydrogen, halo, fluoro, chloro, bromo, iodo, sulfamoyl, lower alkylthio, lower

haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl and $-L-R^{14}$, where L is $-(CH_2)_{1-3}-$ or $-O-(CH_2)_{1-3}-$ and R^{14} is a 5- or 6-membered cycloheteroalkyl or N-morpholinyl. In one specific embodiment, three of R^8 , R^9 , R^{10} and R^{13} are hydrogen. In another specific embodiment, R^9 , R^{10} and R^{13} are each hydrogen.

In yet another embodiment of the compounds of structural formula (I), R^2 and/or R^6 are each, independently of one another, selected from the group consisting of $-OH$, $-NO_2$, halo, fluoro, chloro, bromo, iodo, lower alkyl, methyl, lower heteroalkyl, (C3-C6) cycloalkyl, 5- or 6-membered cycloheteroalkyl, N-morpholinyl, N-methyl-N-piperazinyl, N-piperadiny, substituted N-piperadiny, 4-(N-piperadiny)-N-piperadiny, 4-amino-N-piperadiny, lower alkoxy, methoxy, ethoxy, lower alkylthio, methylthio, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower haloalkyloxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, aryl, phenyl, arylalkyl, benzyl, aryloxy, phenoxy, arylalkyloxy, benzyloxy, 5- or 6-membered heteroaryl, lower alkyloxycarbonyl, sulfamoyl and $-L-R^{14}$, where L is $-(CH_2)_{1-3}-$ or $-O-(CH_2)_{1-3}-$ and R^{14} is a 5- or 6-membered cycloheteroalkyl or N-morpholinyl.

In another embodiment of the compounds of structural formula (I), R^3 and R^5 are each, independently of one another, selected from the group consisting of hydrogen, halo, fluoro, chloro, lower alkoxy, lower alkanyloxy, carboxyl, lower alkanyloxycarbonyl, monohalomethyl, dihalomethyl, trihalomethyl and trifluoromethyl.

In still another embodiment of the compounds of structural formula (I), R^4 is selected from the group consisting of hydrogen, lower dialkylamino, lower dialkylamino, dimethylamino, halo, fluoro, chloro and $-L-R^{14}$, where L is $-O-(CH_2)_{1-3}-$ and R^{14} is 6-membered cycloheteroalkyl, N-morpholinyl or N-piperazinyl.

In yet another embodiment of the compounds of structural formula (I), R^3 , R^4 , R^5 , R^8 , R^9 , R^{10} and R^{13} are each hydrogen. Preferably, in this embodiment, R^2 and R^6 are each, independently of one another, selected from the group consisting of hydroxyl, chloro, fluoro, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy and N-morpholinyl. In a specific embodiment, R^2 and R^6 are the same or different halo or are each chloro. In another specific embodiment, R^2 is fluoro and R^6 is

trifluoromethyl. Preferably, in the above embodiments, Z is $-\text{CH}-$ and/or X is N and Y is O.

In another embodiment of the compounds of structural formula (I), X or Y is N and Z is O, N or S.

In still another embodiment of the compounds of structural formula (I), X, Y and Z are N.

In yet another embodiment of the compounds of structural formula (I), X and Y are N and Z is O or S.

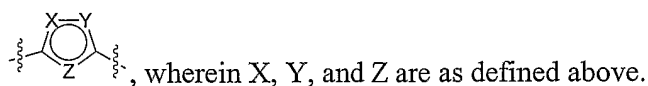
In one embodiment of the compounds of structural formulae (II) or (III), Z is $\text{CH}-$ such that the compounds are isoxazoles or pyrazoles. In another embodiment, compounds of the structural formulae (II) or (III), Z is N such that the compounds are isoxazoles.

In another embodiment of the compounds of structural formulae (II) or (III), X or Y is N and Z is O, N or S.

In still another embodiment of the compounds of structural formulae (II) or (III), X, Y and Z are N.

In yet another embodiment of the compounds of structural formulae (II) or (III), X and Y are N and Z is O or S.

In another aspect, in compounds of the structural formula (I), (II) or (III) at least one of R^2 or R^6 is other than hydrogen when the B ring is



In another aspect, in compounds of the structural formula (I), (II) or (III) at least one of R^2 or R^6 is other than hydrogen.

Exemplary compounds of the invention are provided in TABLES 1 through 4.

Those of skill in the art will appreciate that the compounds of the invention described herein may include functional groups that can be masked with progroups to create prodrugs. Such prodrugs are usually, but need not be, pharmacologically inactive until converted into their active drug form. In the prodrugs of the invention, any available functional moiety may be masked with a progroup to yield a prodrug. Myriad progroups suitable for masking such functional groups to yield promoieties

that are cleavable under the desired conditions of use are known in the art. Specific examples are described *supra*.

6.3 Methods of Synthesis

The compounds of the invention may be obtained *via* synthetic methods illustrated in FIGS. 1 through 6. It should be understood that in FIGS. 1 through 6, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰ and R¹³ are as previously defined for structural formulae (I) through (VI).

Starting materials useful for preparing compounds of the invention and intermediates thereof are commercially available or can be prepared by well-known synthetic methods (*see, e.g.*, Harrison *et al.*, "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996); "Beilstein Handbook of Organic Chemistry," Beilstein Institute of Organic Chemistry, Frankfurt, Germany; Feiser *et al.*, "Reagents for Organic Synthesis," Volumes 1-21, Wiley Interscience; Trost *et al.*, "Comprehensive Organic Synthesis," Pergamon Press, 1991; "Theilheimer's Synthetic Methods of Organic Chemistry," Volumes 1-45, Karger, 1991; March, "Advanced Organic Chemistry," Wiley Interscience, 1991; Larock "Comprehensive Organic Transformations," VCH Publishers, 1989; Paquette, "Encyclopedia of Reagents for Organic Synthesis," 3d Edition, John Wiley & Sons, 1995). Other methods for synthesis of the compounds described herein and/or starting materials are either described in the art or will be readily apparent to the skilled artisan. Alternatives to the reagents and/or protecting groups illustrated in FIGS. 1 through 6 may be found in the references provided above and in other compendiums well known to the skilled artisan. Guidance for selecting suitable protecting groups can be found, for example, in Greene & Wuts, "Protective Groups in Organic Synthesis," Wiley Interscience, 1999. Accordingly, the synthetic methods and strategy presented herein are illustrative rather than comprehensive.

One method for synthesizing substituted diphenyl isoxazoles and corresponding having an oxadiazole moiety according to structural formula (I) (when Z is -CH-) is provided in FIGS. 1 through 6.

It should be understood that in FIGS. 1 through 6 and throughout much of the specification, "C" ring *para* isomers are shown by example only. The methodology to

prepare either "C" ring *ortho*, *meta*, or *para* positional isomers can be selected by the skilled artisan. Therefore, when "C" ring *para* isomers are noted, similar synthetic methodology can be applied to prepare *meta* or *ortho* "C" ring isomers. The *para* isomer was chosen throughout FIGS. 1 and 4 for convenience and consistency to demonstrate the ability to prepare the compounds of interest. Examples of the *meta* "C" ring isomers are found in FIGS. 2 and 5. Examples of the *ortho* "C" ring isomers are found in FIGS. 3 and 6.

In FIGS. 1 through 6, substituents R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , R^9 , R^{10} and R^{13} may include reactive functional groups that require protection during synthesis. Selection of suitable protecting groups will depend on the identity of the functional group and the synthesis method employed, and will be apparent to those of skill in the art. Guidance for selecting suitable protecting groups can be found in Greene & Wuts, *supra*, and the various other references cited therein.

Further guidance for carrying out 1,3-dipolar cycloaddition reactions, also named 1,3-dipolar additions, [3+2] cyclizations or [3+2] cycloadditions, can be found in "Cycloaddition Reactions in Organic Synthesis", (Kobayashi, S. and Jorgensen, K. A., Editors), 2002, Wiley-VCH Publishers, pp. 1 - 332 pages (specifically, Chapters 6 and 7 on [3+2] cycloadditions and 1,3-dipolar additions, pp. 211 - 248 and 249 - 300); "1,3-Dipolar Cycloaddition", *Chemistry of Heterocyclic Compounds*, Vol. 59, (Padwa, A. and Pearson, W., Editors), 2002, John Wiley, New York, pp. 1-940; "Nitrile Oxides, Nitrones, Nitronates in Organic Synthesis: Novel Strategies in Synthesis", Torssell, K. B. G., 1988, VCH Publishers, New York, pp. 1-332; Barnes & Spriggs, 1945, *J. Am. Chem. Soc.* 67:134; Anjaneyulu *et al.*, 1995, *Indian J. Chem.*, Sect. 5 34(11):933-938; and T. L. Gilchrist, Pitman Publishing Ltd, 1985 ISBN0-273-02237-7; *Strategies for Organic Drug Synthesis and Design*, Lednicer, D., John Wiley and Sons, 1998.

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6.4 Assays For Modulation Of HCV

The compounds of the invention are potent inhibitors of HCV replication and/or proliferation. The activity of the compounds of the invention can be confirmed in *in vitro* assays suitable for measuring inhibition of viral or retroviral replication and/or proliferation. The assays may investigate any parameter that is directly or indirectly under the influence of HCV, including, but not limited to, protein-RNA binding, translation, transcription, genome replication, protein processing, viral particle formation, infectivity, viral transduction, etc. Such assays are well-known in the art. Regardless of the parameter being investigated, in one embodiment, to examine the extent of inhibition, samples, cells, tissues, etc.

comprising an HCV replicon or HCV RNA are treated with a potential inhibitory compound (test compound) and the value for the parameter compared to control cells (untreated or treated with a vehicle or other placebo). Control samples are assigned a relative activity value of 100%. Inhibition is achieved when the activity value of the test compound relative to the control is about 90%, preferably 50%, and more preferably 25-0%.

Alternatively, the extent of inhibition may be determined based upon the IC_{50} of the compound in the particular assay, as will be described in more detail, below.

In one embodiment, the inhibitory activity of the compounds can be confirmed in a replicon assay that assesses the ability of a test compound to block or inhibit HCV replication in replicon cells. One example of a suitable replicon assay is the liver cell-line Huh 7-based replicon assay described in Lohmann et al., 1999, Science 285:110-113. A specific example of this replicon assay which utilizes luciferase translation is provided in the Examples Section. In one embodiment of this assay, the amount of test compound that yields a 50% reduction in translation as compared to a control cell (IC_{50}) may be determined.

Alternatively, the inhibitory activity of the compounds can be confirmed using a quantitative Western immunoblot assay utilizing antibodies specific for HCV non-structural proteins, such as NS3, NS4A NS5A and NS5B. In one embodiment of this assay, replicon cells are treated with varying concentrations of test compound to determine the concentration of test compound that yields a 50% reduction in the amount of a non-structural protein produced as compared to a control sample (IC_{50}). A single non-structural protein may be quantified or multiple non-structural proteins may be quantified. Antibodies suitable for carrying out such immunoblot assays are available commercially (e.g., from BIODESIGN International, Saco, ME).

Alternatively, the inhibitory activity of the compounds may be confirmed in an HCV infection assay, such as the HCV infection assay described in Fournier *et al.*, 1998, J. Gen. Virol. 79(10):2367:2374, the disclosure of which is incorporated herein by reference. In one embodiment of this assay, the amount of test compound that yields a 50% reduction in HCV replication or proliferation as compared to a control cell (IC_{50}) may be determined. The extent of HCV replication may be determined by quantifying the amount of HCV RNA present in HCV infected cells. A specific method for carrying out such an assay is provided in the Examples section.

As yet another example, the inhibitory activity of the compounds can be confirmed using an assay that quantifies the amount of HCV RNA transcribed in treated replicon cells using, for example, a Taqman assay (Roche Molecular, Alameda, CA). In one embodiment of this assay, the amount of test compound that yields a 50% reduction in transcription of one or more HCV RNAs as compared to a control sample (IC_{50}) may be determined.

Regardless of the assay used, active compounds are generally those which exhibit IC_{50} s in the particular assay in the range of about 1 mM or less. Compounds which exhibit lower IC_{50} s, for example, in the range of about 100 μ M, 10 μ M, 1 μ M, 100 nM, 10 nM, 1 nM, or even lower, are particularly useful for as therapeutics or prophylactics to treat or prevent HCV infections.

6.5 Uses and Administration

Owing to their ability to inhibit HCV replication, the compounds of the invention and/or compositions thereof can be used in a variety of contexts. For example, the compounds of the invention can be used as controls in *in vitro* assays to identify additional more or less potent anti HCV compounds. As another example, the compounds of the invention and/or compositions thereof can be used as preservatives or disinfectants in clinical settings to prevent medical instruments and supplies from becoming infected with HCV virus. When used in this context, the compound of the invention and/or composition thereof may be applied to the instrument to be disinfected at a concentration that is a multiple, for example 1X, 2X, 3X, 4X, 5X or even higher, of the measured IC_{50} for the compound.

In a specific embodiment, the compounds and/or compositions can be used to “disinfect” organs for transplantation. For example, a liver or portion thereof being prepared for transplantation can be perfused with a solution comprising an inhibitory compound of the invention prior to implanting the organ into the recipient. This method has proven successful with lamivudine (3TC, Epivir[®], Epivir-HB[®]) for reducing the incidence of hepatitis B virus (HBV) infection following liver transplant surgery/therapy. Quite interestingly, it has been found that such perfusion therapy not only protects a liver recipient free of HBV infection (HBV-) from contracting HBV from a liver received from an HBV+ donor, but it also protects a liver from an HBV-

donor transplanted into an HBV+ recipient from attack by HBV. The compounds of the invention may be used in a similar manner prior to organ or liver transplantation.

The compounds of the invention and/or compositions thereof find particular use in the treatment and/or prevention of HCV infections in animals and humans. When used in this context, the compounds may be administered *per se*, but are typically formulated and administered in the form of a pharmaceutical composition. The exact composition will depend upon, among other things, the method of administration and will be apparent to those of skill in the art. A wide variety of suitable pharmaceutical compositions are described, for example, in *Remington's Pharmaceutical Sciences*, 20th ed., 2001).

Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the active compound suspended in diluents, such as water, saline or PEG 400; (b) capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as liquids, solids, granules or gelatin; (c) suspensions in an appropriate liquid; and (d) suitable emulsions. Tablet forms can include one or more of lactose, sucrose, mannitol, sorbitol, calcium phosphates, corn starch, potato starch, microcrystalline cellulose, gelatin, colloidal silicon dioxide, talc, magnesium stearate, stearic acid, and other excipients, colorants, fillers, binders, diluents, buffering agents, moistening agents, preservatives, flavoring agents, dyes, disintegrating agents, and pharmaceutically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, e.g., sucrose, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin or sucrose and acacia emulsions, gels, and the like containing, in addition to the active ingredient, carriers known in the art.

The compound of choice, alone or in combination with other suitable components, can be made into aerosol formulations (*i.e.*, they can be "nebulized") to be administered via inhalation. Aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like.

Suitable formulations for rectal administration include, for example, suppositories, which consist of the packaged nucleic acid with a suppository base. Suitable suppository bases include natural or synthetic triglycerides or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which

consist of a combination of the compound of choice with a base, including, for example, liquid triglycerides, polyethylene glycols, and paraffin hydrocarbons.

Formulations suitable for parenteral administration, such as, for example, by intraarticular (in the joints), intravenous, intramuscular, intradermal, intraperitoneal, and subcutaneous routes, include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. In the practice of this invention, compositions can be administered, for example, by intravenous infusion, orally, topically, intraperitoneally, intravesically or intrathecally. Parenteral administration, oral administration, subcutaneous administration and intravenous administration are the preferred methods of administration. A specific example of a suitable solution formulation may comprise from about 0.5-100 mg/ml compound and about 1000 mg/ml propylene glycol in water. Another specific example of a suitable solution formulation may comprise from about 0.5-100 mg/ml compound and from about 800-1000 mg/ml polyethylene glycol 400 (PEG 400) in water.

A specific example of a suitable suspension formulation may include from about 0.5-30 mg/ml compound and one or more excipients selected from the group consisting of: about 200 mg/ml ethanol, about 1000 mg/ml vegetable oil (e.g., corn oil), about 600-1000 mg/ml fruit juice (e.g., grapefruit juice), about 400-800 mg/ml milk, about 0.1 mg/ml carboxymethylcellulose (or microcrystalline cellulose), about 0.5 mg/ml benzyl alcohol (or a combination of benzyl alcohol and benzalkonium chloride) and about 40-50 mM buffer, pH 7 (e.g., phosphate buffer, acetate buffer or citrate buffer or, alternatively 5% dextrose may be used in place of the buffer) in water.

A specific example of a suitable liposome suspension formulation may comprise from about 0.5-30 mg/ml compound, about 100-200 mg/ml lecithin (or other phospholipid or mixture of phospholipids) and optionally about 5 mg/ml cholesterol in water. For subcutaneous administration of compounds of the invention, a liposome suspension formulation including 5 mg/ml compound in water with 100 mg/ml lecithin and 5 mg/ml compound in water with 100 mg/ml lecithin and 5 mg/ml cholesterol

provides good results. This formulation may be used for other compounds of the invention.

The formulations of compounds can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials. Injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form. The composition can, if desired, also contain other compatible therapeutic agents, discussed in more detail, below.

In therapeutic use for the treatment of HCV infection, the compounds utilized in the pharmaceutical method of the invention are administered to patients diagnosed with HCV infection at dosage levels suitable to achieve therapeutic benefit. By therapeutic benefit is meant that the administration of compound leads to a beneficial effect in the patient over time. For example, therapeutic benefit is achieved when the HCV titer or load in the patient is either reduced or stops increasing. Therapeutic benefit is also achieved if the administration of compound slows or halts altogether the onset of the organ damage or other adverse symptoms that typically accompany HCV infections, regardless of the HCV titer or load in the patient.

The compounds of the invention and/or compositions thereof may also be administered prophylactically in patients who are at risk of developing HCV infection, or who have been exposed to HCV, to prevent the development of HCV infection. For example, the compounds of the invention and/or compositions thereof may be administered to hospital workers accidentally stuck with needles while working with HCV patients to lower the risk of, or avoid altogether, developing an HCV infection.

Initial dosages suitable for administration to humans may be determined from *in vitro* assays or animal models. For example, an initial dosage may be formulated to achieve a serum concentration that includes the IC₅₀ of the particular compound being administered, as measured in an *in vitro* assay. Alternatively, an initial dosage for

humans may be based upon dosages found to be effective in animal models of HCV infection. Exemplary suitable model systems are described, for example, in Muchmore, 2001, Immunol. Rev. 183:86-93 and Lanford & Bigger, 2002, Virology, 293:1-9, and the referenced cited therein. As one example, the initial dosage may be in the range of about 0.01 mg/kg/day to about 200 mg/kg/day, or about 0.1 mg/kg/day to about 100 mg/kg/day, or about 1 mg/kg/day to about 50 mg/kg/day, or about 10 mg/kg/day to about 50 mg/kg/day, can also be used. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of a particular compound in a particular patient. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired or indicated.

6.6 Combination Therapy

In certain embodiments of the present invention, the compounds of the invention and/or compositions thereof can be used in combination therapy with at least one other therapeutic agent. A compound of the invention and/or composition thereof and the therapeutic agent can act additively or, more preferably, synergistically. The compound of the invention and/or a composition thereof may be administered concurrently with the administration of the other therapeutic agent(s), or it may be administered prior to or subsequent to administration of the other therapeutic agent(s).

In one embodiment, the compounds of the invention and/or compositions thereof are used in combination therapy with other antiviral agents or other therapies known to be effective in the treatment or prevention of HCV. As a specific example, the compounds of the invention and/or compositions thereof may be used in combination with known antivirals, such as ribavirin (see, e.g., US Patent No. 4,530,901). As another specific example, the compounds of the invention and/or

compositions thereof may also be administered in combination with one or more of the compounds described in any of the following: U.S. Patent No. 6,143,715; U.S. Patent No. 6,323,180; U.S. Patent No. 6,329,379; U.S. Patent No. 6,329,417; U.S. Patent No. 6,410,531; U.S. Patent No. 6,420,380; and U.S. Patent No. 6,448,281.

In yet as another specific example, the compounds of the invention and/or compositions thereof may be used in combination with interferons such as α -interferon, β -interferon and/or γ -interferon. The interferons may be unmodified, or may be modified with moieties such as polyethylene glycol (pegylated interferons). Many suitable unpegylated and pegylated interferons are available commercially, and include, by way of example and not limitation, recombinant interferon alpha-2b such as Intron-A interferon available from Schering Corporation, Kenilworth, N.J., recombinant interferon alpha-2a such as Roferon interferon available from Hoffmann-La Roche, Nutley, N.J., recombinant interferon alpha-2C such as Berofer alpha 2 interferon available from Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, Conn., interferon alpha-n1, a purified blend of natural alpha interferons such as Sumiferon available from Sumitomo, Japan or as Wellferon interferon alpha-n1 (INS) available from the Glaxo-Wellcome Ltd., London, Great Britain, or a consensus alpha interferon such as those described in U.S. Pat. Nos. 4,897,471 and 4,695,623 (especially Examples 7, 8 or 9 thereof) and the specific product available from Amgen, Inc., Newbury Park, Calif., or interferon alpha-n3 a mixture of natural alpha interferons made by Interferon Sciences and available from the Purdue Frederick Co., Norwalk, Conn., under the Alferon Tradename, pegylated interferon-2b available from Schering Corporation, Kenilworth, N.J. under the tradename PEG-Intron A and pegylated interferon-2a available from Hoffman-LaRoche, Nutley, N.J. under the tradename Pegasys.

As yet another specific example, the compounds of the invention and/or compositions thereof may be administered in combination with both ribovirin and an interferon.

7. EXAMPLES

The following examples are provided by way of illustration only and not by way of limitation. Those of skill in the art will readily recognize a variety of

noncritical parameters that could be changed or modified to yield essentially similar results

7.1 Compound Syntheses

Compounds of TABLES 1 through 4 can be synthesized according to the methods described below or illustrated in FIGS. 1 through 3. Melting points were obtained on an Electrothermal IA9100 series digital melting point apparatus. All Melting points are uncorrected. NMR spectra were obtained on a 300 MHz Varian Mercury system. LC-MS was performed on a Waters Micromass ZQ instrument with electrospray ionization. The HPLC component was a Waters Model 2690 Separation module coupled to a Waters Model 996 photodiode array detector. The specific LC-MS method used to analyze particular compounds, indicated for each compound in parentheses, are provided below:

7.1.1 Synthesis of 5-Dichloromethyl-3-[4-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole (See Figure 1)

Synthesis of 2,6-Dichloro-N-hydroxybenzenecarboximidoyl Chloride

The general procedure of R.K. Howe, et al, *J. Org. Chem.*, 1980, 45, 3916-3918 was followed. 2,6-Dichlorobenzaldoxime (25.1 gm, 0.132 mol) was dissolved in dimethylformamide (150 mL). Then N-chlorosuccinimide (approximately 1.5 g) was added. After several minutes the reaction was heated until the internal temperature reached 50 °C. Then the remainder of the N-chlorosuccinimide was added in small portions to a total of 17.6 g (0.132 mol), keeping the reaction temperature at 40-50 °C. After the addition was complete, the reaction was allowed to stir for 0.5h, then was diluted with 600 mL of water. The mixture was extracted twice with ether. The combined ether extracts were washed three times with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was concentrated under reduced pressure to give the title α -chlorooxime as a white solid (m.p. 89-90 °C).

NMR (300 MHz, CDCl₃): 7.98 (s, 1H, exchanges with D₂O), 7.3-7.4 ppm (m, 3H).

Synthesis of 4-Ethynylbenzonitrile

4-Iodobenzonitrile (9.73 gm, 42.5 mmol) was dissolved in dioxane (80 mL) and then treated with diisopropylethylamine (30 mL). A stream of argon gas was then bubbled through the solution for several minutes, followed by the addition of dichlorobis(triphenylphosphine) palladium (II) (1.2 gm, 1.7 mmol), copper (I) iodide (0.67 gm, 3.5 mmol) and trimethylsilylacetylene (5.7 gm, 55.3 mmol). The reaction mixture was then heated at 60 °C for 5 h. This general procedure is known in the literature as the Sonogashira coupling (K. Sonogashira et.al., Tetrahedron Lett., 1975, 4467). The reaction mixture was then diluted with ethyl acetate and this solution was washed several times with brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with hexanes:ethyl acetate (1:1) to give the desired trimethylsilylethynyl benzonitrile. This product was dissolved in methanol (40 mL), tetrahydrofuran (20 mL) and water (5 mL). Then anhydrous potassium carbonate (5.5 gm, 39.8 mmol) was added and the mixture was stirred at room temperature for 6h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate and washed with brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by column chromatography, on silica gel, eluting with 8:2 hexanes:ethyl acetate provided 4-ethynylbenzonitrile as a beige solid (2.58 g).

NMR (300 MHz, CDCl₃): 7.59 (m, 4H), 3.29 ppm (s, 1H).

Synthesis of 3-(2,6-Dichlorophenyl)-5-(4-cyanophenyl) Isoxazole

2,6-Dichloro-N-hydroxybenzenecarboximidoyl chloride (2.67 g, 11.9 mmol) and 4-ethynylbenzonitrile (1.50 g, 11.9 mmol) were dissolved in anhydrous tetrahydrofuran (150 mL) and triethylamine (2.15 mL). The mixture was stirred at room temperature for 1h then heated at reflux for 6h to generate the 2,6-dichlorophenyl nitrile oxide intermediate, which reacted by a 1,3-dipolar cycloaddition reaction with 4-ethynylbenzonitrile. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed successively with water and brine. The ethyl acetate solution was dried over anhydrous sodium sulfate,

filtered and concentrated under reduced pressure. The resulting solid was purified by column chromatography on silica gel, eluting with 7:3 hexanes-ethyl acetate. The appropriate fractions were combined to give 3-(2,6-dichlorophenyl)-5-(4-cyanophenyl) isoxazole as a white solid, 0.58 g.

MW=315 confirmed by LC-MS, t_r =37.23 min (Method W) MH^+ =313-317.

Synthesis of 4-(5-(3-(2,6-Dichlorophenyl)isoxazolyl)benzamide Oxime

A mixture of 3-(2,6-dichlorophenyl)-5-(4-cyanophenyl) isoxazole (500 mg, 1.6 mmol), hydroxylamine hydrochloride (130 mg, 1.9 mmol) and triethylamine (0.3 mL, 1.9 mmol) in ethanol (25 mL) was heated at reflux for 5 h. The reaction mixture was cooled to room temperature and concentrated to dryness. The resulting white solid was carried forward without further purification or characterization.

Synthesis of 5-Dichloromethyl-3-[4-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole

A solution of 4-(5-(3-(2,6-dichlorophenyl)isoxazolyl)benzamide oxime (100 mg, 0.29 mmol) and dichloroacetic acid (95 μ L, 1.16 mmol) was heated at 85 °C until the solution became homogenous. Dichloroacetic anhydride (90 μ L, 0.58 mmol) was added dropwise. The resulting solution was heated at 85 °C for 90 min, then cooled to room temperature. The cooled reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate concentrated to provide a colorless oil. This oil was purified by column chromatography, on silica gel, eluting with 7:3 hexanes:ethyl acetate to provide 5-dichloromethyl-3-[4-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole as a white solid (32 mg). NMR (300 MHz, $CDCl_3$): 8.22 (m, 2H), 8.00 (m, 2H), 7.43 (m, 2H), 7.38 (m, 1H), 6.87 (s, 1H), 6.74 (s, 1H).

7.1.2 Oxadiazole Compounds

5-Dichloromethyl-3-[3-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole

MW=441 confirmed by LC-MS, t_r = 22.76 min (**Method X**) MH^+ = 439-443

5-Dichloromethyl-3-[4-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole

MW=441 confirmed by LC-MS, t_r = 18.62 min (**Method Y**) MH^+ = 439-443

5-Dichloromethyl-3-[2-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole

MW=441 confirmed by LC-MS, t_r = 34.63 min (**Method W**) MH^+ = 439-443

5-Dichloromethyl-3-amino-[3-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole

MW=456 confirmed by LC-MS, t_r = 17.18 min (**Method Y**) MH^+ = 454-458

5-Dichloromethyl-3-amino-[4-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole

MW=456 confirmed by LC-MS, t_r = 17.62 min (**Method Y**) MH^+ = 454-458

5-Dichloromethyl-2-[3-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]phenyl]-1,3,4-oxadiazole

MW=441 confirmed by LC-MS, t_r = 16.81 min (**Method Y**) MH^+ = 439-443

5-Dichloromethyl-2-[4-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]phenyl]-1,3,4-oxadiazole

MW=441 confirmed by LC-MS, t_r = 16.85 min (**Method Y**) MH^+ = 439-443

5-Dichloromethyl-3-[3-[3'-(2'-chloro-6'-(N-2-pyridyl-4-piperazinyl)phenyl)-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole

MW=567 confirmed by LC-MS, t_r = 15.73 min (**Method Y**) MH^+ = 565-569

5-Dichloromethyl-3-[3-[3'-(2'-chloro-6'-(N-ethyl-4-piperazinyl)phenyl)-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole

MW=518 confirmed by LC-MS, t_r = 12.37 min (**Method Y**) MH^+ = 516-520

5-Dichloromethyl-3-[3-[3'-(2'-chloro-6'-(N-acetyl-4-piperazinyl)phenyl)-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole

MW=532 confirmed by LC-MS, t_r = 18.20 min (**Method Y**) MH^+ = 530-534

5-Dichloromethyl-3-[3-[3'-(2'-methoxy-6'-trifluoromethylphenyl)-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole

MW=470 confirmed by LC-MS, t_r = 16.91 min (**Method Y**) MH^+ = 468-472

5-Dichloromethyl-3-[4-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]-4-pyridyl]-1,2,4-oxadiazole

MW=443 confirmed by LC-MS, t_r = 17.13 min (**Method Y**) MH^+ = 441-445

5-Dichloromethyl-3-[4-[3'-(2'-methoxy-6'-trifluoromethylphenyl)-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole

MW=470 confirmed by LC-MS, t_r = 17.29 min (**Method Y**) MH^+ =468-472

3-[4-[3'-(2',6'-Dichlorophenyl)-5'-isoxazolyl]phenyl]-5-trifluoromethyl-1,2,4-oxadiazole

MW=426 confirmed by LC-MS, t_r = 18.32 min (**Method Y**) MH^+ =424-428

5-Dichloromethyl-3-[4-[3'-[2'-chloro-(6'-N-morpholino)phenyl]-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole

MW=491 confirmed by LC-MS, t_r = 18.19 min (**Method Y**) MH^+ =489-493

5-Dichloromethyl-3-[4-[3'-(2'-fluoro-6'-trifluoromethylphenyl)-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole

MW=458 confirmed by LC-MS, t_r = 17.94 min (**Method Y**) MH^+ =456-460

5-Dichloromethyl-3-[4-[3'-(2'-chloro-6'-fluorophenyl)-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole

MW=424 confirmed by LC-MS, t_r = 17.73 min (**Method Y**) MH^+ =422-426

5-Dichloromethyl-3-[4-[3'-[2'-chloro-6'-(N-2-pyridyl-4-piperazinyl)phenyl]-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole

MW=567 confirmed by LC-MS, t_r = 16.52 min (**Method Y**) MH^+ =565–569

5-Dichloromethyl-3-[4-[3'-[2'-chloro-6'-(N-acetyl-4-piperazinyl)phenyl]-5'-isoxazolyl]phenyl]-1,2,4-oxadiazole

MW=532 confirmed by LC-MS, t_r = 17.21 min (**Method Y**) MH^+ =530–534

5-Dichloromethyl-3-[5-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]-2-furanyl]-1,2,4-oxadiazole

MW=431 confirmed by LC-MS, t_r = 16.75 min (**Method Y**) MH^+ =429–433

5-Dichloromethyl-3-[4-[3'-[2'-chloro-6'-(N-acetyl-4-piperazinyl)phenyl]-5'-isoxazolyl]-2-fluorophenyl]-1,2,4-oxadiazole

MW=549 confirmed by LC-MS, t_r = 15.98 min (**Method Y**) MH^+ =547–551

5-Dichloromethyl-3-[4-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]-6-fluorophenyl]-1,2,4-oxadiazole

MW=459 confirmed by LC-MS, t_r = 18.05 min (**Method Y**) MH^+ =457–461

5-Dichloromethyl-3-[4-[3'-[2'-chloro-6'-(N-acetyl-4-piperazinyl)phenyl]-5'-isoxazolyl]-2-chlorophenyl]-1,2,4-oxadiazole

MW=565 confirmed by LC-MS, t_r = 17.25 min (**Method Y**) MH^+ =563–567

5-Dichloromethyl-3-[4-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]-3-methylphenyl]-1,2,4-oxadiazole

MW=455 confirmed by LC-MS, t_r = 19.02 min (**Method Y**) MH^+ =453-457

5-Dichloromethyl-3-[4-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]-2-chlorophenyl]-1,2,4-oxadiazole

MW=474 confirmed by LC-MS, t_r = 18.43 min (**Method Y**) MH^+ =472-476

7.1.3 Physical Characterization Methods

Melting Point Methods

Melting points were obtained on an Electrothermal IA9100 series digital melting point apparatus. All Melting points are uncorrected.

Elemental Analysis

Elemental analysis was performed by Desert Analytics, Tuscon, AZ.

NMR Methods

NMR spectra were obtained on a 300 MHz Varian Mercury system.

LC-MS Methods

General

LC-MS was performed on a Waters Micromass ZQ instrument with electrospray ionization. The HPLC component was a Waters Model 2690 Separation

module coupled to a Waters Model 996 photodiode array detector at 254 nm wavelength.

Method W

This method utilized a 2.1x250 mm 5 μ M C-18 Altima reversed phase column (Alltech) with a flow rate of 0.25 mL/min and a gradient of 5-85% acetonitrile with water containing 0.1% trifluoroacetic acid over 36 min. The gradient was then ramped to 100% acetonitrile over 0.5 min and continued at 100% acetonitrile for 3.5 min.

Method X

This method utilized a 2.1x250 mm 5 μ M C-18 Altima reversed phase column (Alltech) with a flow rate of 0.25 mL/min and a gradient of 5-85% acetonitrile with water containing 0.1% trifluoroacetic acid over 15 min. The gradient then ramped to 100% acetonitrile over 0.5 min and continued at 100% acetonitrile for 25 min.

Method Y

This method utilized a 2.1x150 mm Agilent Zorbax 5 μ M C-18 reversed phase column with a flow rate of 0.3 mL/min and a gradient of 10-100% acetonitrile with water containing 0.1% trifluoroacetic acid over 16 min, then continuing for 2 min with 100% acetonitrile.

Method Z

This method utilized a 2.1x5 mm Agilent Zorbax 5 μ M C-18 reversed phase column with a flow rate of 0.5 mL/min and a gradient of 5-100% acetonitrile with water containing 0.1% trifluoroacetic acid over 8 min, then continuing for 2 min with 100% acetonitrile.

Method A

LC-MS was performed on a Waters Micromass ZMD instrument with electrospray ionization.

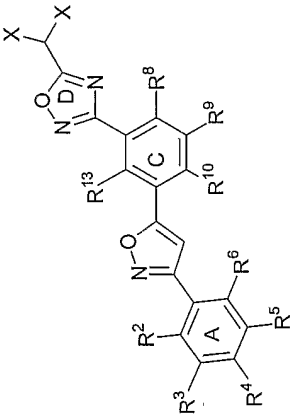
This method utilized a 2.1x5 mm Agilent Zorbax 5 μ M C-18 reversed phase column with a flow rate of 0.3 mL/min and a gradient of 10-100% acetonitrile with water containing 0.05% formic acid over 10 min, then continuing for 8 min with 100% acetonitrile.

7.2 Exemplary Compounds of the Invention Inhibit HCV Translation Or Replication

7.2.1 Replicon Assay

The inhibitory activity of certain exemplary compounds of the invention was confirmed using an HCV replicon assay. The HCV replicon can include such features as the HCV 5' untranslated region including the HCV IRES, the HCV 3' untranslated region, selected HCV genes encoding HCV polypeptides, selectable markers, and a reporter gene such as luciferase, GFP, *etc.* In the assay, actively dividing 5-2 Luc replicon-comprising cells (obtained from Ralf Bartenschlager; see Lohmann *et al.*, 1999, Science 285:110-113) were seeded at a density of between about 5,000 and 7,500 cells/well onto 96 well plates (about 90 μ l of cells per well) and incubated at 37 °C and 5% CO₂ for 24 hours. Then, the test compound (in a volume of about 10 μ l) was added to the wells at various concentrations and the cells were incubated for an additional 24 hours before luciferase assay. Briefly, the Bright-Glo reagent was diluted 1:1 with PBS and 100 μ l of diluted reagent was added to each well. After 5 min of incubation at room temperature, luciferin emission was quantified with a luminometer. In this assay, the amount of test compound that yielded a 50% reduction in luciferase activity (IC₅₀) was determined.

TABLE 1



(I)

wherein R², R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹³ of the A and C rings and the X's of the oxadiazole D ring are as provided below for compound (I).

Replicon/ Western	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁸	R ⁹	R ¹⁰	R ¹³	X's
+	Cl	H	H	H		H	H	H	H	Cl
-	Cl	H	H	H		H	H	H	H	Cl

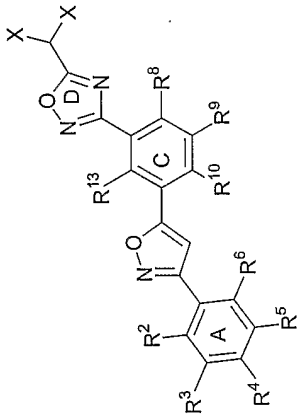
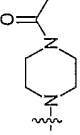
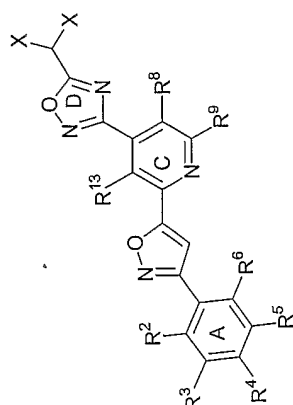
TABLE 1										
 (I) wherein R², R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹³ of the A and C rings and the X's of the oxadiazole D ring are as provided below for compound (I).										
Replicon/ Western	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁸	R ⁹	R ¹⁰	R ¹³	X's
-	Cl	H	H	H		H	H	H	H	Cl
-	CF ₃	H	H	H	OMe	H	H	H	H	Cl
+/+	Cl	H	H	H	Cl	H	H	H	H	Cl
+	Cl	H	H	H	Cl	F	H	H	H	Cl

TABLE 2

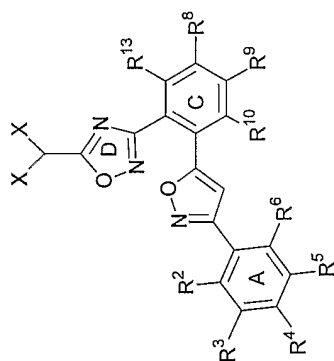


(Ia)

wherein R², R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹³ of the A and C rings and the X's of the oxadiazole D ring as provided below for compound (1a)

Replicon/ Western	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁸	R ⁹	No R ¹⁰	R ¹³	X's
-	Cl	H	H	H	Cl	H	H		H	Cl

TABLE 3

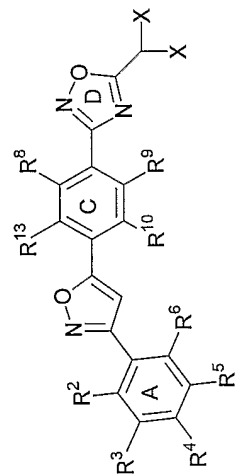


(II)

wherein R², R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹³ of the A and C rings and the X's of the oxadiazole D ring are as provided below for compound (II).

Replicon/ Western	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁸	R ⁹	R ¹⁰	R ¹³	X ⁷ s
+	Cl	H	H	H	Cl	H	H	H	H	Cl

TABLE 4



(III)

wherein R², R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹³ of the A and C rings and the X's of the oxadiazole D ring are as provided below for compound (III).

Replicon/ Western	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁸	R ⁹	R ¹⁰	R ¹³	X's
-	Cl	H	H	H		Cl	H	H	H	Cl
+	Cl	H	H	H	Cl	H	H	Me	H	Cl
+	Cl	H	H	H		F	H	H	H	Cl

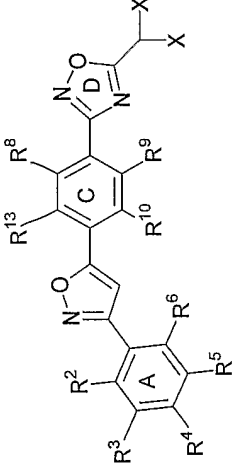
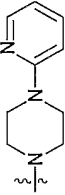
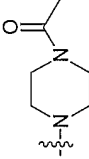
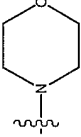
TABLE 4  (III) wherein R², R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹³ of the A and C rings and the X's of the oxadiazole D ring are as provided below for compound (III).										
Replicon/ Western	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁸	R ⁹	R ¹⁰	R ¹³	X's
+	Cl	H	H	H		H	H	H	H	Cl
+	Cl	H	H	H		H	H	H	H	Cl
+	Cl	H	H	H		H	H	H	H	Cl
+	CF ₃	H	H	H	F	H	H	H	H	Cl

TABLE 4 (III) wherein R², R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹³ of the A and C rings and the X's of the oxadiazole D ring are as provided below for compound (III).											
Replicon/ Western	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁸	R ⁹	R ¹⁰	R ¹³	X's	
+	Cl	H	H	H	F	H	H	H	H	Cl	
+	CF ₃	H	H	H	OMe	H	H	H	H	Cl	
+	Cl	H	H	H	Cl	H	H	H	H	Cl	
-	Cl	H	H	H	Cl	Cl	H	H	H	Cl	

7.2.2 Western Blot Assay

Certain exemplary compounds of the invention were also tested for their ability to inhibit HCV replication using a quantitative Western blot analysis with antibodies specific for the HCV nonstructural protein NS5A or NS3. Actively dividing 9-13 replicon cells were seeded into 6-well plates at a density of 1×10^5 cells/well in a volume of 2 ml/well and incubated at 37°C and 5% CO₂ for 24 hours. Various concentrations of test compounds (in a volume of 10 ul) were added to the wells and the cells incubated for another 48 hours. Protein samples were prepared from the cultured cells, resolved on a SDS-PAGE gel and transferred to a nitrocellulose membrane. The membrane was blocked with 5% non-fat milk in PBS for 1 hour at room temperature. Primary antibody (anti NS5A antibody; BIODSIGN International, Saco, ME or NS3 antibody, Rigel) incubation was performed for 1 hour at room temperature, after which the membrane was washed 3 times (for 15 min per time) with PBST (PBS plus 0.1% Tween 20). Horseradish peroxidase conjugated secondary antibody incubation was performed for 1 hour at room temperature and the membrane was washed 3 times (for 15 min per time) with PBST. The membrane was then soaked in substrate solution (Pierce) and exposed to a film or quantified using an imager. In this assay, the amount of test compound that yielded a 50% reduction in the amount of NS5A or NS3 protein translated as compared to a control sample (IC₅₀) was determined.

The results of the Replicon and Western blot assays are provided in TABLES 1 through 4. In TABLES 1 through 4 a value of “+” indicates an IC₅₀ of 10 µM or less in the specified assay; a value of “-” indicates an IC₅₀ of greater than 10 µM in the specified assay. Some of the compounds exhibited IC₅₀s in the Replicon assay in the nanomolar range.

7.2.3 Luciferase Counter Screen

A counter screen was used to identify non-specific inhibitors of the luciferase reporter gene. In the counter screen, a cell line carrying a construct such as a CMV-driven luciferase gene was used to identify compounds that inhibit the reporter gene, and not HCV. In these CMV-Luc cells, the DNA construct, which comprises a luciferase gene downstream of a CMV promoter, is permanently integrated into the chromosome of Huh7 cells. For the counter screen, actively dividing CMV-Luc cells were seeded at a density of 5000-7500 cells/well in a volume of 90 μ l/well into 96 well plate(s). The cells were then incubated at 37°C and 5% CO₂ for 24 hours. Various concentrations of test compounds (in a volume of 10 μ l) were added to the wells and the cells were incubated for another 24 hours. Bright-Glo (Pharmacia) luciferase assay reagents were added to each well according to the manufacturer's manual. Luciferin counts were taken using a luminometer. IC₅₀ values were greater than 10 μ M in the counter screen luciferase inhibition assay for the compounds of TABLES 1 through 4 that were tested.

7.2.4 PCR Assay

A TaqMan RT-PCR assay (Roche Molecular Systems, Pleasanton, CA) can be used to analyze HCV RNA copy numbers, which can confirm if the viral genome of HCV is being replicated. Actively dividing 9-13 replicon cells can be seeded at a density of 3×10^4 cells/well in a volume of 1 ml/well into 24-well plates. The cells can then be incubated at 37° C and 5% CO₂ for 24 hours. Various concentrations of test compounds (in a volume of 10 μ l) can be added to the wells and the cells can be incubated for an additional 24-48 hours. Media can be removed by aspiration and RNA samples can be prepared from each well. TaqMan one step RT-PCR (Roche Molecular Systems, Alameda, CA) can be performed using freshly prepared RNA samples according to the manufacturer's manual and analyzed on an ABI Prism 7700 Sequence Detector (Applied Biosystems). The ratio of HCV RNA to cellular GAPDH RNA can be used as an indication of specificity of HCV inhibition to confirm that the viral genome would not be replicated.

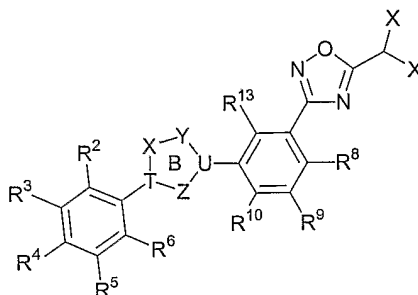
All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to one of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound according to structural formula (I):



(I)

including the pharmaceutically acceptable salts, hydrates, solvates, N-oxides and prodrugs thereof, wherein:

the B ring is an aromatic or nonaromatic ring that includes from one to four heteroatoms, wherein X, Y, Z of the heterocyclic ring are each, independently of one another, C, CH, N, NR¹⁶, NR¹⁸, S or O, provided X and Y are not both O;

U and T are each, independently of one another, C, CH or N;

each X of the -CHX₂ group, independently, is a leaving group;

R², R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰ and R¹³ are each, independently of one another, selected from the group consisting of hydrogen, -OH, -SH, -CN, -NO₂, -N₃, halo, fluoro, chloro, bromo, iodo, lower alkyl, substituted lower alkyl, lower heteroalkyl, substituted lower heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower alkylthio, substituted lower alkylthio, lower alkoxy, substituted lower alkoxy, methoxy, substituted methoxy, lower heteroalkoxy, substituted lower heteroalkoxy, cycloalkoxy, substituted cycloalkoxy, cycloheteroalkoxy, substituted cycloheteroalkoxy, lower haloalkoxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, amino, lower

di- or monoalkylamino, substituted lower di- or monoalkylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, phenoxy, substituted phenoxy, arylalkyl, substituted arylalkyl, arylalkyloxy, substituted arylalkyloxy, benzyl, benzyloxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylalkyl, substituted heteroarylalkyl, heteroarylalkyloxy, substituted heteroarylalkyloxy, carboxyl, lower alkoxycarbonyl, substituted lower alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, arylalkyloxycarbonyl, substituted arylalkyloxycarbonyl, carbamate, substituted carbamate, carbamoyl, substituted carbamoyl, sulfamoyl, substituted sulfamoyl and a group of the formula $-L-R^{14}$, where "L" is a linker and R^{14} is cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl; and

R^{16} and R^{18} are each, independently of one another, selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, lower heteroalkyl, substituted lower heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower alkylthio, substituted lower alkylthio, lower alkoxy, substituted lower alkoxy, methoxy, substituted methoxy, lower heteroalkoxy, substituted lower heteroalkoxy, cycloalkoxy, substituted cycloalkoxy, cycloheteroalkoxy, substituted cycloheteroalkoxy, lower haloalkoxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, lower di- or monoalkylamino, substituted lower di- or monoalkylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, phenoxy, substituted phenoxy, arylalkyl, substituted arylalkyl, arylalkyloxy, substituted arylalkyloxy, benzyl, benzyloxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylalkyl, substituted heteroarylalkyl, heteroarylalkyloxy, substituted heteroarylalkyloxy, carboxyl, lower alkoxycarbonyl, substituted lower alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, arylalkyloxycarbonyl, substituted arylalkyloxycarbonyl, carbamate, substituted carbamate, carbamoyl, substituted carbamoyl, sulfamoyl, substituted sulfamoyl and a group of the formula $-L-R^{14}$, where "L" is a linker and R^{14} is cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl.

2. The compound of Claim 1 in which the B ring is an oxazole or a hydro isomer thereof.
3. The compound of Claim 1 in which the B ring is a thiazole or a hydro isomer thereof.
4. The compound of Claim 1 in which the B ring is an imidazole or a hydro isomer thereof.
5. The compound of Claim 1 in which the B ring is a triazole or a hydro isomer thereof.
6. The compound of Claim 1 in which the B ring is an oxadiazole, isoxazole, pyrazole, or a hydro isomer thereof.
7. The compound of Claim 1 in which the B ring is a thiadiazole or a hydro isomer thereof.
8. The compound of any one of Claims 2-7 in which R^8 , R^9 , R^{10} and R^{13} are each hydrogen.
9. The compound of any one of Claims 2-7 in which R^3 and R^5 are each hydrogen.
10. The compound of Claim 9 in which R^4 is $-L-R^{14}$.
11. The compound of Claim 10 in which L is $-O-(CH_2)_{1-3}-$ and R^{14} is N-morpholinyl.
12. The compound of any one of Claims 2-7 in which R^3 , R^4 and R^5 are each hydrogen.
13. The compound of Claim 12 in which R^2 and R^6 are each, independently of one another, selected from the group consisting of $-OH$, $-NO_2$, halo, fluoro, chloro, bromo, iodo, lower alkyl, methyl, lower heteroalkyl, (C3-C6) cycloalkyl, 5- or 6-membered cycloheteroalkyl, N-morpholinyl, N-methyl-N-piperazinyl, N-piperadiny, substituted N-piperadiny, 4-(N-piperadiny)-N-piperadiny, 4-amino-N-piperadiny, lower alkoxy, methoxy, ethoxy, lower alkylthio, methylthio, lower haloalkyl,

monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower haloalkyloxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, aryl, phenyl, arylalkyl, benzyl, aryloxy, phenoxy, arylalkyloxy, benzyloxy, 5- or 6-membered heteroaryl, lower alkylloxycarbonyl, sulfamoyl and $-L-R^{14}$, where L is $-(CH_2)_{1-3}-$ or $-O-(CH_2)_{1-3}-$ and R^{14} is a 5- or 6-membered cycloheteroalkyl or N-morpholinyl.

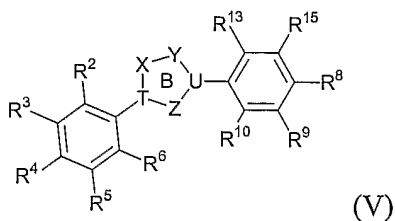
14. The compound of Claim 1 in which R², R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰ and R¹³ are selected from the substituents delineated in TABLE 1.

15. The compound of Claim 1 in which the “B” ring is selected from an oxazole, oxadiazole, isoxazole, thiazole, imidazole, pyrazole, triazole, thiadiazole and any regioisomer or hydro isomer thereof.

16. A method of inhibiting replication and/or proliferation of a hepatitis C (“HC”) virion, comprising the step of contacting an HC virion with an amount of a compound according to Claim 1 effective to inhibit replication and/or proliferation of the HC virion.

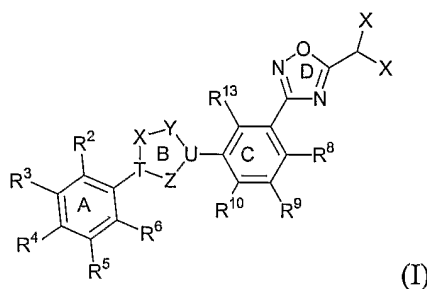
17. A method of treating or preventing an HCV infection, comprising the step of administering to a subject an amount of a compound according to Claim 1 effective to treat or prevent an HCV infection.

18. An intermediate compound useful for synthesizing substituted diphenyl heterocycle compounds, said intermediate compound having a structure defined by structural formula (V):



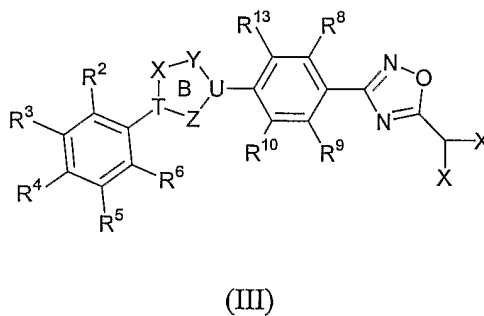
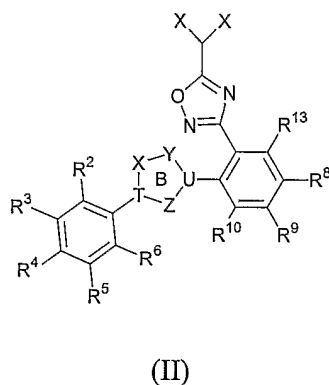
wherein R¹⁵ is -CN or -C(NH₂)=N-OH and the B ring, U, T, X, Y, Z, R², R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰ and R¹³ are as defined in Claim 1, or a protected analog of the compound of structural formula (II).

19. A method of synthesizing a substituted diphenyl heterocycle compound having an oxadiazole moiety according to structural formula (I):



wherein the B ring, U, T, X, Y, Z, R², R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹³ and -CHX₂ are as defined in Claim 1, comprising the steps of (1) combining an N-hydroxybenzenecarboximidoyl halide and a 4-ethynyl benzonitrile, (2) treating the resultant isoxazole from (1) with hydroxylamine and (3) treating the resultant isoxazolyl benzamide oxime from (2) with a dihaloacetic acid, thereby yielding a compound according to structural formula (I).

20. A compound according to either structural formula (II) or (III):



including the pharmaceutically acceptable salts, hydrates, solvates, N-oxides and prodrugs thereof, wherein:

the B ring is an aromatic or nonaromatic ring that includes from one to four heteroatoms, wherein X, Y, Z of the heterocyclic ring are each, independently of one another, C, CH, N, NR¹⁶, NR¹⁸, S or O;

U and T are each, independently of one another, C, CH or N, provided that two oxygen atoms are not adjacent to each other in the B ring;

each X of the -CHX₂ group, independently, is a leaving group;

R², R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰ and R¹³ are each, independently of one another, selected from the group consisting of hydrogen, -OH, -SH, -CN, -NO₂, -N₃, halo, fluoro, chloro, bromo, iodo, lower alkyl, substituted lower alkyl, lower heteroalkyl, substituted lower heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower alkylthio, substituted lower alkylthio, lower alkoxy, substituted lower alkoxy, methoxy, substituted methoxy, lower heteroalkoxy, substituted lower heteroalkoxy, cycloalkoxy, substituted cycloalkoxy, cycloheteroalkoxy, substituted cycloheteroalkoxy, lower haloalkoxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, amino, lower di- or monoalkylamino, substituted lower di- or monoalkylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, phenoxy, substituted phenoxy, arylalkyl, substituted arylalkyl, arylalkyloxy, substituted arylalkyloxy, benzyl, benzyloxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylalkyl, substituted heteroarylalkyl, heteroarylalkyloxy, substituted heteroarylalkyloxy, carboxyl, lower alkoxycarbonyl, substituted lower alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, arylalkyloxycarbonyl, substituted arylalkyloxycarbonyl, carbamate, substituted carbamate, carbamoyl, substituted carbamoyl, sulfamoyl, substituted sulfamoyl and a group of the formula -L-R¹⁴, where "L" is a linker and R¹⁴ is cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl, provided that at least one of R² or R⁶ is other than hydrogen; and

R^{16} and R^{18} are each, independently of one another, selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, lower heteroalkyl, substituted lower heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower alkylthio, substituted lower alkylthio, lower alkoxy, substituted lower alkoxy, methoxy, substituted methoxy, lower heteroalkoxy, substituted lower heteroalkoxy, cycloalkoxy, substituted cycloalkoxy, cycloheteroalkoxy, substituted cycloheteroalkoxy, lower haloalkoxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, lower di- or monoalkylamino, substituted lower di- or monoalkylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, phenoxy, substituted phenoxy, arylalkyl, substituted arylalkyl, arylalkyloxy, substituted arylalkyloxy, benzyl, benzyloxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylalkyl, substituted heteroarylalkyl, heteroarylalkyloxy, substituted heteroarylalkyloxy, carboxyl, lower alkoxy carbonyl, substituted lower alkoxy carbonyl, aryloxy carbonyl, substituted aryloxy carbonyl, arylalkyloxy carbonyl, substituted arylalkyloxy carbonyl, carbamate, substituted carbamate, carbamoyl, substituted carbamoyl, sulfamoyl, substituted sulfamoyl and a group of the formula $-L-R^{14}$, where "L" is a linker and R^{14} is cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl.

21. The compound of Claim 20 in which the B ring is an oxazole or a hydro isomer thereof.

22. The compound of Claim 20 in which the B ring is a thiazole or a hydro isomer thereof.

23. The compound of Claim 20 in which the B ring is an imidazole or a hydro isomer thereof.

24. The compound of Claim 20 in which the B ring is a triazole or a hydro isomer thereof.

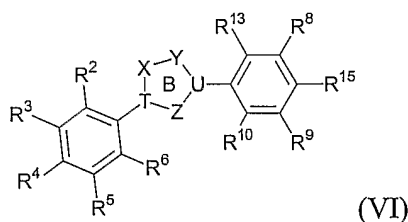
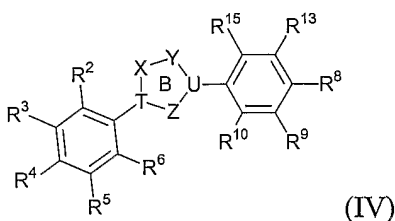
25. The compound of Claim 20 in which the B ring is an isoxazole, pyrazole, or oxadiazole or a hydro isomer thereof.

26. The compound of Claim 20 in which the B ring is a thiadiazole or a hydro isomer thereof.
27. The compound of any one of Claims 20-26 in which R^8 , R^9 , R^{10} and R^{13} are each hydrogen.
28. The compound of any one of Claims 20-26 in which R^3 and R^5 are each hydrogen.
29. The compound of Claim 28 in which R^4 is $-L-R^{14}$.
30. The compound of Claim 29 in which L is $-O-(CH_2)_{1-3}-$ and R^{14} is N-morpholinyl.
31. The compound of any one of Claims 20-26 in which R^3 , R^4 and R^5 are each hydrogen.
32. The compound of Claim 31 in which R^2 and R^6 are each, independently of one another, selected from the group consisting of $-OH$, $-NO_2$, halo, fluoro, chloro, bromo, iodo, lower alkyl, methyl, lower heteroalkyl, (C3-C6) cycloalkyl, 5- or 6-membered cycloheteroalkyl, N-morpholinyl, N-methyl-N-piperazinyl, N-piperadiny, substituted N-piperadiny, 4-(N-piperadiny)-N-piperadiny, 4-amino-N-piperadiny, lower alkoxy, methoxy, ethoxy, lower alkylthio, methylthio, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower haloalkyloxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, aryl, phenyl, arylalkyl, benzyl, aryloxy, phenoxy, arylalkyloxy, benzyloxy, 5- or 6-membered heteroaryl, lower alkyloxycarbonyl, sulfamoyl and $-L-R^{14}$, where L is $-(CH_2)_{1-3}-$ or $-O-(CH_2)_{1-3}-$ and R^{14} is a 5- or 6-membered cycloheteroalkyl or N-morpholinyl.
33. The compound of Claim 20 in which R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , R^9 , R^{10} and R^{13} are selected from the substituents delineated in TABLES 3 and 4
34. The compound of Claim 20 in which the "B" ring is selected from an oxazole, oxadiazole, isoxazole, thiazole, imidazole, pyrazole, triazole, thiadiazole and any regioisomer or hydro isomer thereof.

35. A method of inhibiting replication and/or proliferation of a hepatitis C (“HC”) virion, comprising the step of contacting an HC virion with an amount of a compound according to Claim 20 effective to inhibit replication and/or proliferation of the HC virion.

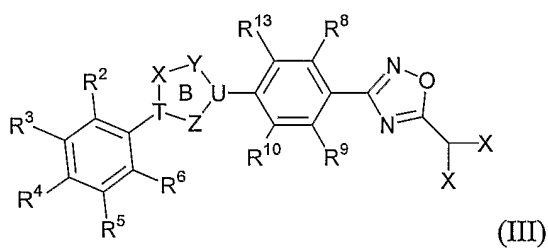
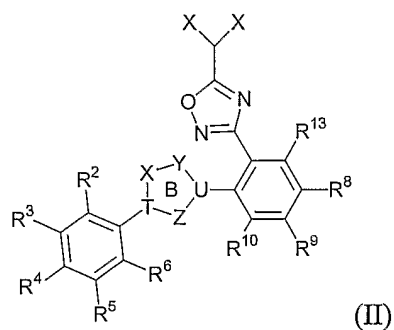
36. A method of treating or preventing an HCV infection, comprising the step of administering to a subject an amount of a compound according to Claim 20 effective to treat or prevent an HCV infection.

37. An intermediate compound useful for synthesizing substituted diphenyl heterocycle compounds, said intermediate compound having a structure defined by structural formulae (IV) or (VI):



where is R^{15} is $-\text{CN}$ or $-\text{C}(\text{NH}_2)=\text{N}-\text{OH}$ and the B ring, U, T, X, Y, Z, R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , R^9 , R^{10} and R^{13} are as defined in Claim 20, or a protected analog of the compound of structural formula (IV) or (VI).

38. A method of synthesizing a substituted diphenyl heterocycle compound having an oxadiazole moiety according to structural formulae (II) or (III):



wherein the B ring, U, T, X, Y, Z, R², R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹³ and -CHX₂ are as defined in Claim 1, comprising the steps of (1) combining an N-hydroxybenzenecarboximidoyl halide and a 4-ethynyl benzonitrile, (2) treating the resultant isoxazole from (1) with hydroxylamine and (3) treating the resultant isoxazolyl benzamide oxime from (2) with a dihaloacetic acid, thereby yielding a compound according to structural formulae (II) or (III).

FIG. 1

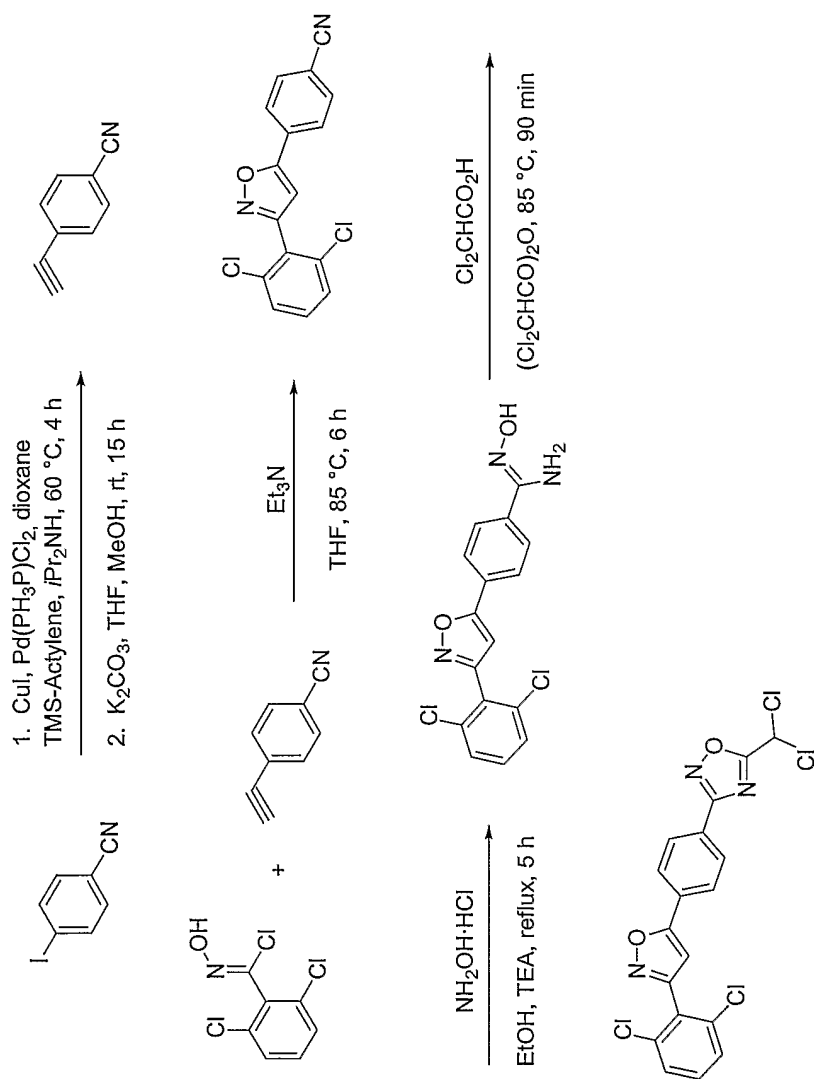


FIG. 2

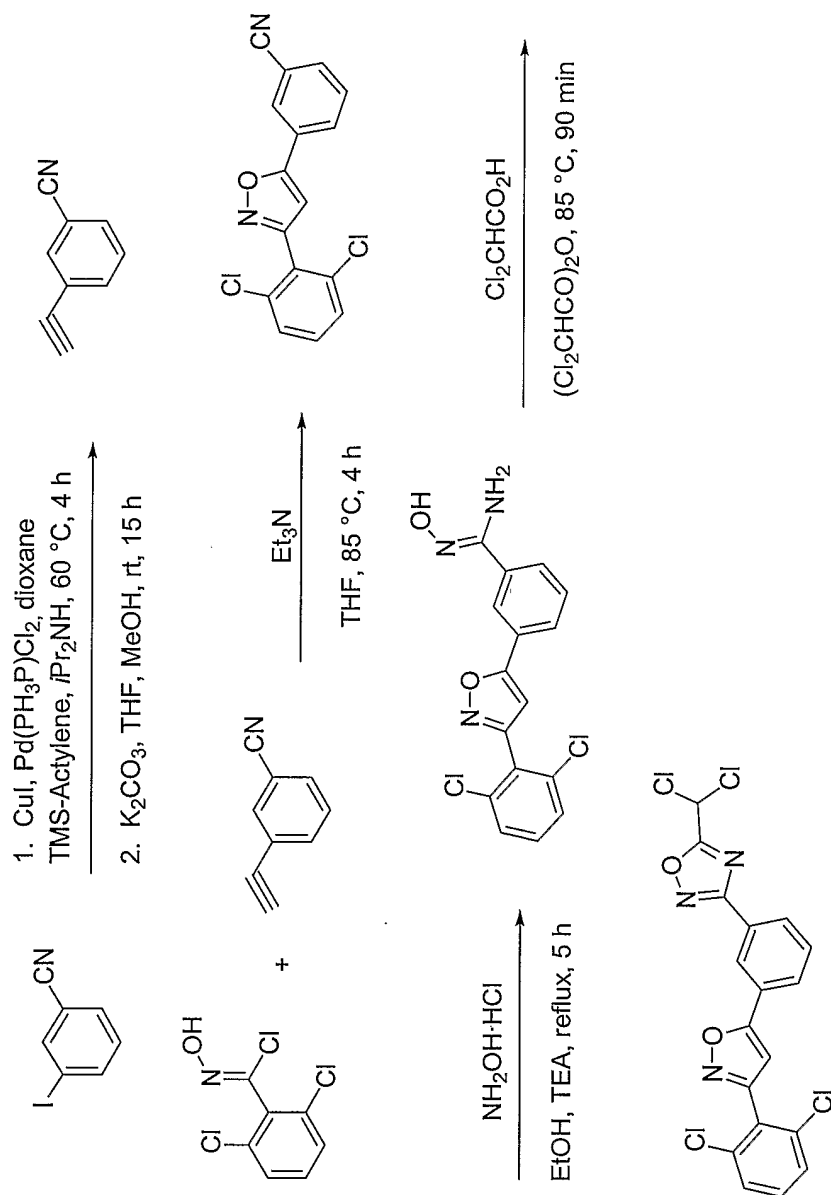


FIG. 3

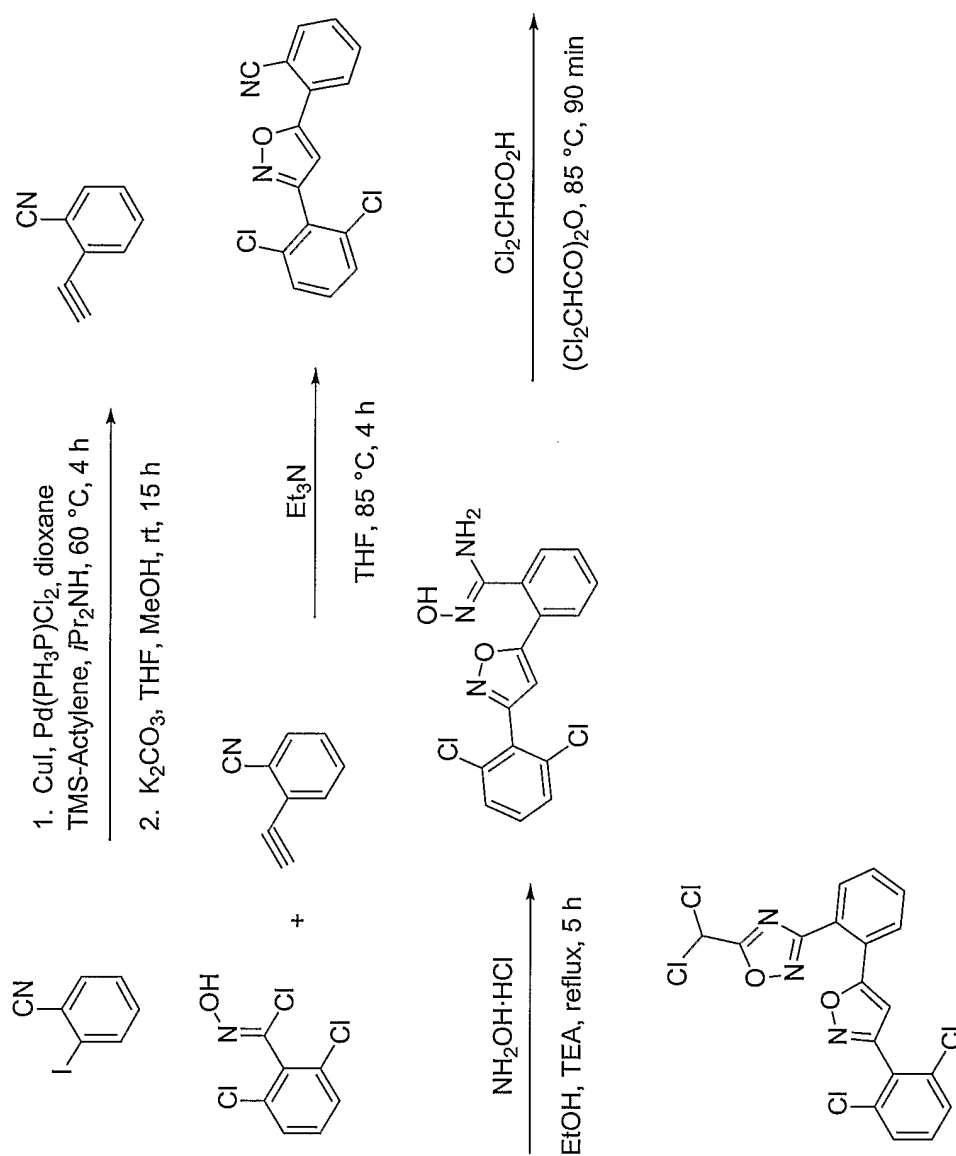


FIG. 4

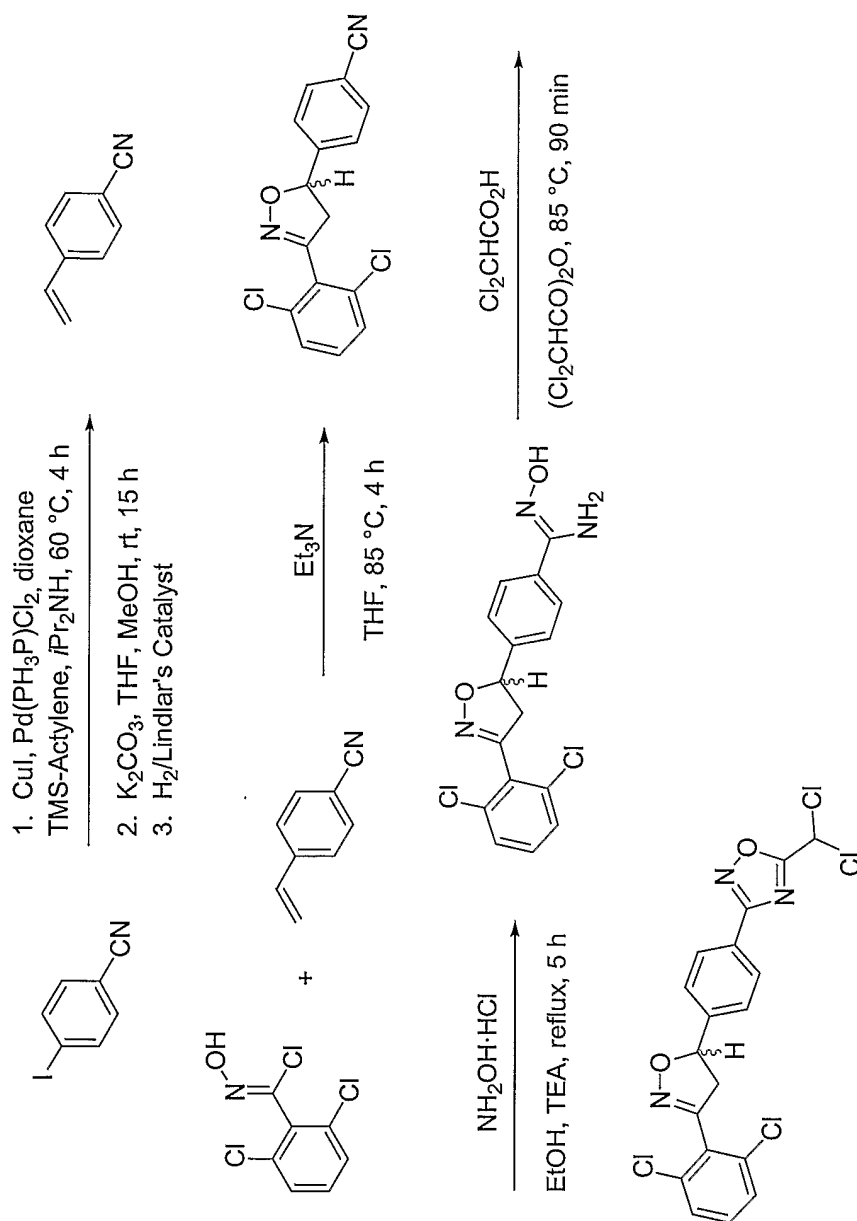


FIG. 5

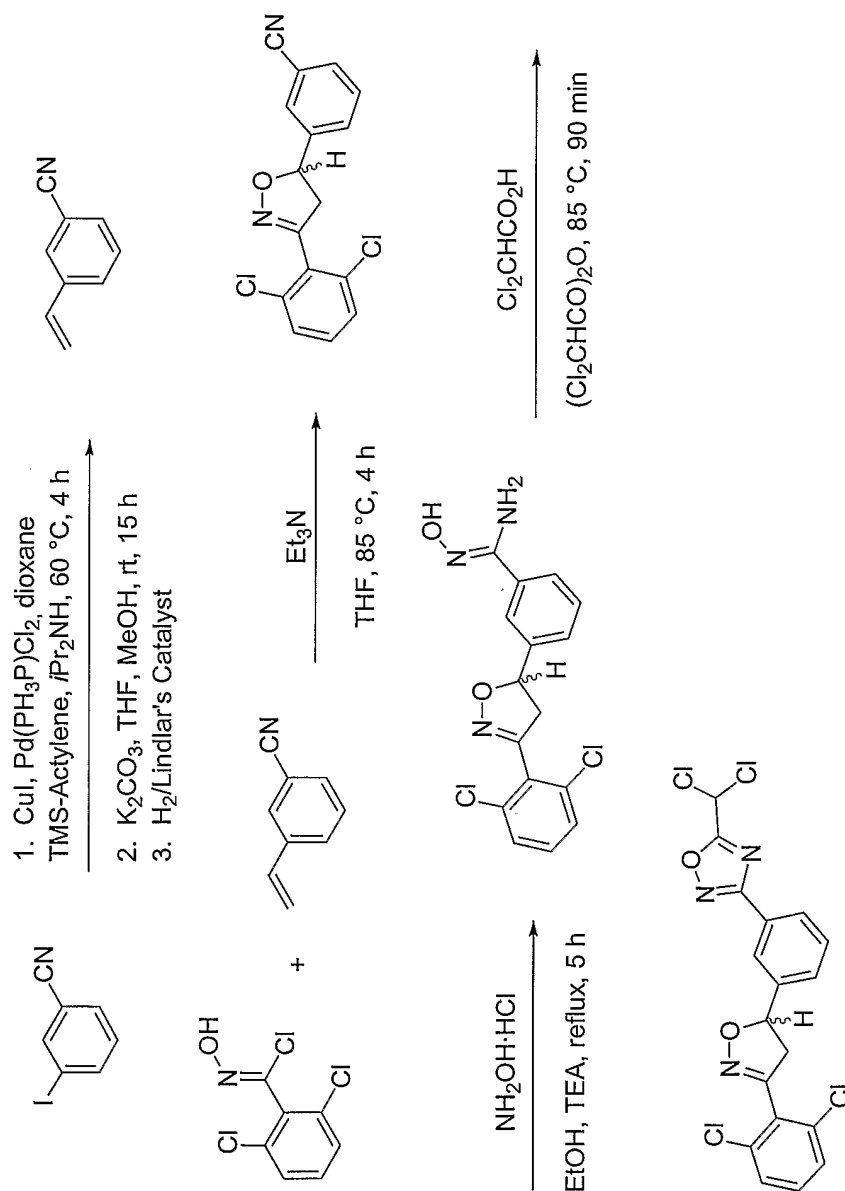
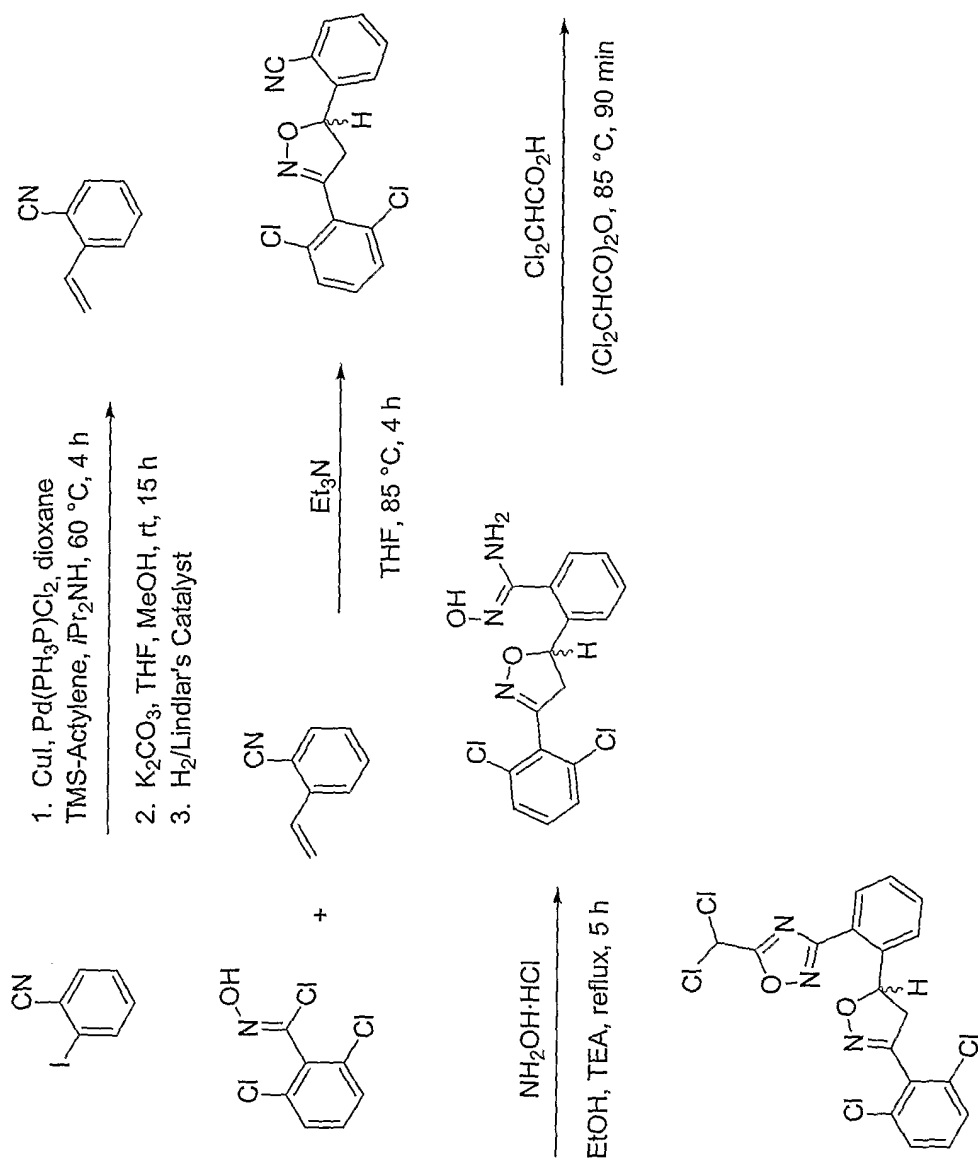


FIG. 6



INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/005528

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/10 A61K31/4245 A61P31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/005264 A (AXXIMA PHARMACEUTICALS AG; SALASSIDIS, KONSTADINOS; KURTENBACH, ALEXAN) 15 January 2004 (2004-01-15) the whole document	1-38
A	WO 03/040112 A (RIGEL PHARMACEUTICALS, INC; SINGH, RAJINDER; GOFF, DANE; LU, HENRY; IS) 15 May 2003 (2003-05-15) the whole document	1-38
X	RAM, B.; ET AL.: TETRAHEDRON, vol. 55, 1999, pages 10163-10172, XP004174814 compound 13	18
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

11 August 2005

Date of mailing of the international search report

22/08/2005

Name and mailing address of the ISA

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Authorized officer

Zellner, A

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/005528

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 600 092 A (OTSUKA PHARMACEUTICAL CO., LTD) 8 June 1994 (1994-06-08) example 28	37
X	WO 03/105771 A (MERCK & CO., INC; CHEN, WEIRONG; HALE, JEFFREY, J; LI, ZHEN; LYNCH, CH) 24 December 2003 (2003-12-24) page 45, line 1 - line 10	37
X	KAUFFMANN, J.M.; ET AL.: J. ORG. CHEM., vol. 68, 2003, pages 839-853, XP002339667 page 843; compound 14	37
X	VAINIATOLO, P.; ET AL.: TETRAHEDRON, vol. 46, no. 10, 1990, pages 3683-3692, XP002339668 compounds 1B, 2B	37

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/005528

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16, 17, 35 and 36 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/005528

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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