INHIBITORS OF SERINE PROTEASES, PARTICULARLY HEPATITIS C VIRUS NS3 PROTEASE

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a novel class of compounds that are useful as protease inhibitors, particularly as serine protease inhibitors, and more particularly as hepatitis C NS3 protease inhibitors. As such, they act by interfering with the life cycle of the hepatitis C virus and are also useful as antiviral agents.

This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting HCV NS3 protease activity and consequently, may be advantageously used as therapeutic agents against the hepatitis C virus and other viruses that are dependent upon a serine protease for proliferation. This invention also relates to methods for inhibiting the activity of proteases, including hepatitis C virus NS3 protease and other serine proteases, using the compounds of this invention and related compounds.

BACKGROUND OF THE INVENTION

Infection by hepatitis C virus ("HCV") is a compelling human medical problem. HCV is recognized as

the causative agent for most cases of non-A, non-B hepatitis, with an estimated human seroprevalence of 1% globally [Purcell, R.H., "Hepatitis C virus: Historical perspective and current concepts" FEMS Microbiology Reviews 14, pp. 181-192 (1994); Van der Poel, C.L., "Hepatitis C Virus. Epidemiology, Transmission and Prevention in Hepatitis C Virus. Current Studies in Hematology and Blood Transfusion, H.W. Reesink, Ed., (Basel: Karger), pp. 137-163 (1994)]. Four million individuals may be infected in the United States alone [Alter, M.J. and Mast, E.E., "The Epidemiology of Viral Hepatitis in the United States, Gastroenterol. Clin. North Am. 23, pp. 437-455 (1994)].

Upon first exposure to HCV only about 20% of infected individuals develop acute clinical hepatitis while others appear to resolve the infection spontaneously. In most instances, however, the virus establishes a chronic infection that persists for decades [Iwarson, S. "The Natural Course of Chronic Hepatitis" FEMS Microbiology Reviews 14, pp. 201-204 (1994)]. This usually results in recurrent and progressively worsening liver inflammation, which often leads to more severe disease states such as cirrhosis and hepatocellular carcinoma [Kew, M.C., "Hepatitis C and Hepatocellular Carcinoma", FEMS Microbiology Reviews, 14, pp. 211-220 (1994); Saito, I., et al. "Hepatitis C Virus Infection is Associated with the Development of Hepatocellular Carcinoma" Proc. Natl. Acad. Sci. USA 87, pp. 6547-6549 (1990)]. Unfortunately, there are no broadly effective treatments for the debilitating progression of chronic HCV.

The HCV genome encodes a polyprotein of 3010-3033 amino acids [Choo, Q.-L., et al. "Genetic Organization and Diversity of the Hepatitis C Virus", Proc. Natl. Acad. Sci. USA, 88, pp. 2451-2455 (1991); Kato, N. et al., Molecular Cloning of the Human Hepatitis C Virus Genome From Japanese Patients with Non-A, Non-B Hepatitis", Proc. Natl. Acad. Sci. USA, 87, pp. 9524-9528 (1990); Takamizawa, A. et al., "Structure and Organization of the Hepatitis C Virus Genome Isolated From Human Carriers", J. Virol., 65, pp. 1105-1113 (1991)]. The HCV nonstructural (NS) proteins are presumed to provide the essential catalytic machinery for viral replication. The NS proteins are derived by proteolytic cleavage of the polyprotein [Bartenschlager, R. et al., "Nonstructural Protein 3 of the Hepatitis C Virus Encodes a Serine-Type Proteinase Required for Cleavage at the NS3/4 and NS4/5 Junctions", J. Virol., 67, pp. 3835-3844 (1993); Grakoui, A. et al. "Characterization of the Hepatitis C Virus-Encoded Serine Proteinase: Determination of Proteinase-Dependent Polyprotein Cleavage Sites", J. Virol., 67, pp. 2832-2843 (1993); Grakoui, A. et al., Expression and Identification of Hepatitis C Virus Polyprotein Cleavage Products", J. Virol., 67, pp. 1385-1395 (1993); Tomei, L. et al., "NS3 is a serine protease required for processing of hepatitis C virus polyprotein", J. Virol., 67, pp. 4017-4026 (1993)].

The HCV NS protein 3 (NS3) contains a serine protease activity that helps process the majority of the viral enzymes, and is thus considered essential for viral replication and infectivity. It is known that mutations

in the yellow fever virus NS3 protease decreases viral infectivity [Chambers, T.J. et. al., "Evidence that the N-terminal Domain of Nonstructural Protein NS3 From Yellow Fever Virus is a Serine Protease Responsible for Site-Specific Cleavages in the Viral Polyprotein", Proc. Natl. Acad. Sci. USA, 87, pp. 8898-8902 (1990)]. The first 181 amino acids of NS3 (residues 1027-1207 of the viral polyprotein) have been shown to contain the serine protease domain of NS3 that processes all four downstream sites of the HCV polyprotein [C. Lin et al., "Hepatitis C Virus NS3 Serine Proteinase: *Trans*-Cleavage Requirements and Processing Kinetics", J. Virol., 68, pp. 8147-8157 (1994)].

The HCV NS3 serine protease and its associated cofactor, NS4A, helps process all of the viral enzymes, and is thus considered essential for viral replication. This processing appears to be analogous to that carried out by the human immunodeficiency virus aspartyl protease, which is also involved in viral enzyme processing HIV protease inhibitors, which inhibit viral protein processing are potent antiviral agents in man, indicating that interrupting this stage of the viral life cycle results in therapeutically active agents. Consequently it is an attractive target for drug discovery. Unfortunately, there are no serine protease inhibitors available currently as anti-HCV agents.

Furthermore, the current understanding of HCV has not led to any other satisfactory anti-HCV agents or treatments. The only established therapy for HCV disease is interferon treatment. However, interferons have significant side effects (Janssen et al., 1994; Renault

and Hoofnagle, 1989) [Janssen, H. L. A., et al. "Suicide Associated with Alfa-Interferon Therapy for Chronic Viral Hepatitis" J. Hepatol., 21, pp. 241-243 (1994)]; Renault, P.F. and Hoofnagle, J.H., "Side effects of alpha interferon. Seminars in Liver Disease *9*, 273-277. (1989)] and induce long term remission in only a fraction (~ 25%) of cases [Weiland, O. "Interferon Therapy in Chronic Hepatitis C Virus Infection", FEMS Microbiol. Rev., 14, PP. 279-288 (1994)]. Moreover, the prospects for effective anti-HCV vaccines remain uncertain.

Thus, there is a need for more effective anti-HCV therapies. Such inhibitors would have therapeutic potential as protease inhibitors, particularly as serine protease inhibitors, and more particularly as HCV NS3 protease inhibitors. Specifically, such compounds may be useful as antiviral agents, particularly as anti-HCV agents.

SUMMARY OF THE INVENTION

The present invention provides compounds, and pharmaceutically acceptable derivatives thereof, that are useful as protease inhibitors, particularly as serine protease inhibitors, and more particularly as HCV NS3 protease inhibitors. These compounds can be used alone or in combination with immunomodulatory agents, such as α-, β- or γ-interferons; other antiviral agents such as ribavirin and amantadine; other inhibitors of hepatitic C protease; inhibitors of other targets in the HCV life cycle including the helicase, polymerase,

metalloprotease, or internal ribosome entry; or combinations thereof.

The present invention also provides methods for inhibiting proteases, particularly serine proteases, and more particularly HCV NS3 protease.

The present invention also provides pharmaceutical compositions comprising the compounds of this invention, as well as multi-component compositions comprising additional immunomodulatory agents, such as $\alpha-, \beta-$ or γ-interferons; other antiviral agents such as ribavirin and amantadine; other inhibitors of hepatitic C protease; inhibitors of other targets in the HCV life cycle including the helicase polymerase metalloprotease or internal ribosome entry; or combinations thereof. The invention also provides methods of using the compounds of this invention, as well as other related compounds, for the inhibition of HCV.

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description is set forth. In the description, the following abbreviations are used:

Designation	Reagent or Fragment
Abu	aminobutyric acid
Ac	acetyl
AcOH	acetic acid
Bn	benzyl
Boc	tert-butyloxycarbonyl
Bz	benzoyl

Cbz	carbobenzyloxy
CDI	carbonyldiimidazole
DCE	1,2-dichloroethane
DCM	dichloromethane
DIEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DPPA	diphenylphosphorylazide
DMSO	dimethylsulfoxide
Et	ethyl
EtOAc	ethyl acetate
FMOC	9-fluorenylmethoxycarbonyl
HbtU	O-benzotriazolyl-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBt	N-hydroxybenzotriazole
HPLC	high performance liquid chromatography
Me	methyl
MS	mass spectrometry
NMP	N-methyl pyrrolidinone
ND	not determined
Pip	piperidine
Prz	piperazine
PyBrop	bromo-tris-pyrrolidinophosphonium hexafluorophosphate
Pyr	pyridine
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TFE	trifluoroethanol

Tol toluene

The following terms are used herein:

Unless expressly stated to the contrary, the terms "$-SO_2-$" and "$-S(O)_2-$" as used herein refer to a sulfone or sulfone derivative (i.e., both appended groups linked to the S), and not a sulfinate ester.

The term "substituted" refers to the replacement of one or more hydrogen radicals in a given structure with a radical selected from a specified group. When more than one hydrogen radical may be replaced with a substituent selected from the same specified group, the substituents may be either the same or different at every position.

As used herein, the term "amino" refers to a trivalent nitrogen which may be primary or which may be substituted with 1-2 alkyl groups.

The term "alkyl" or "alkane", alone or in combination with any other term, refers to a straight-chain or branched-chain saturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, preferably from 1-10 and more preferably from 1-5 carbon atoms. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl and the like.

The term "alkenyl" or "alkene", alone or in combination with any other term, refers to a straight-chain or branched-chain mono- or poly-unsaturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, preferably from 2-10 carbon atoms and more preferably, from 2-5 carbon atoms. Examples of alkenyl radicals include, but are not limited to, ethenyl, E- and Z-propenyl, E- and Z-isobutenyl, E- and Z-pentenyl, E- and

Z-hexenyl, E,E-, E,Z-, Z,E-, and Z-Z-hexadienyl and the like.

The term "alkynyl" or "alkyne", alone or in combination with any other term, refers to a straight-chain or branched-chain mono or poly-unsaturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, preferably from 2-10 carbon atoms and more preferably, from 2-5 carbon atoms, wherein at least one of the unsaturated aliphatic hydrocarbon radicals comprises a triple bond. Examples of alkynyl radicals include, but are not limited to, ethynyl, propynyl, isobutynyl, pentynyl, hexynyl, hexenynyl, and the like.

The term "aryl", alone or in combination with any other term, refers to a carbocyclic aromatic radical containing the specified number of carbon atoms, and which may be optionally fused, for example benzofused, with one to three cycloalkyl, aromatic, heterocyclic or heteroaromatic rings. Preferred aryl groups have from 6-14 carbon atoms, and more preferred groups from 6-10 carbon atoms. Examples of aryl radicals include, but are not limited to, phenyl, naphthyl, anthracenyl and the like.

The term "carbocycle", alone or in combination with any other term, refers to a stable non-aromatic 3- to 8-membered carbon ring radical which may be saturated, mono-unsaturated or poly-unsaturated, and which may be optionally fused, for example benzofused, with one to three cycloalkyl, aromatic, heterocyclic or heteroaromatic rings. The carbocycle may be attached at any endocyclic carbon atom which results in a stable structure.

The terms "cycloalkyl" or "cycloalkane", alone or in combination with any other term, refers to a stable

non-aromatic 3- to 8-membered carbon ring radical which is saturated and which may be optionally fused, for example benzofused, with one to three cycloalkyl, aromatic, heterocyclic or heteroaromatic rings. The cycloalkyl may be attached at any endocyclic carbon atom which results in a stable structure. Preferred carbocycles have 5 to 6 carbons. Examples of carbocycle radicals include, but are not limited to, cyclopropyl, cyclbutyl, cyclpentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, indane, tetrahydronaphthalene and the like.

The term "cycloalkenyl" or "cycloalkene" alone or in combination with any other term, refers to a stable cyclic hydrocarbon ring radical containing at least one endocyclic carbon-carbon double bond. The carbocycle may be attached at any cyclic carbon atom which results in a stable structure. Where no number of carbon atoms is specified, a cycloalkenyl radical preferably has from 5-7 carbon atoms. Examples of cycloalkenyl radicals include, but are not limited to, cyclopentenyl, cyclohexenyl, cyclopentadienyl, indenyl and the like.

The term "cycloalkylidenyl", alone or in combination with any other term, refers to a stable cyclic hydrocarbon ring radical containing at least one exocyclic carbon-carbon double bond, wherein the cyclic hydrocarbon ring may be optionally fused, for example benzofused, with one to three cycloalkyl, aromatic, heterocyclic or heteroaromatic rings. The carbocycle may be attached at any cyclic carbon atom, which results in a stable structure. Where no number of carbon atoms is specified, a cycloalkylidenyl radical preferably has from

5-7 carbon atoms. Examples of cycloalkylidenyl radicals include, but are not limited to, cyclopentylidenyl, cyclohexylidenyl, cyclopentenylidenyl and the like.

The skilled practitioner would realize that certain groups could be classified either as cycloalkanes or as aryl groups. Examples of such groups include indanyl and tetrahydro naphthyl groups.

The term "monocycle" or "monocyclic" alone or in combination with any other term, unless otherwise defined herein, refers to a 5-7 membered ring system.

The term "bicycle" or "bicyclic" alone or in combination with any other term, unless otherwise defined herein, refers to a 6-11 membered ring system.

The term "tricycle" or "tricyclic" alone or in combination with any other term, unless otherwise defined herein, refers to a 11-15 membered ring system.

The terms "heterocyclyl" and "heterocycle", alone or in combination with any other term, unless otherwise defined herein, refers to a stable 5- to 15-membered mono-, bi-, or tricyclic, heterocyclic ring which is either saturated or partially unsaturated, but not aromatic, and which may be optionally fused, for example benzofused, with one to three cycloalkyl, aromatic, heterocyclic or heteroaromatic rings. Each heterocycle consists of one or more carbon atoms and from one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. As used herein, the terms "nitrogen and sulfur heteroatoms" include any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. A heterocycle

may be attached at any endocyclic carbon or heteroatom which results in the creation of a stable structure.

Preferred heterocycles defined above include, for example, imidazolidinyl, indazolinolyl, perhydropyridazyl, pyrrolinyl, pyrrolidinyl, piperidinyl, pyrazolinyl, piperazinyl, morpholinyl, thiamorpholinyl, β-carbolinyl, thiazolidinyl, thiamorpholinyl sulfone, oxopiperidinyl, oxopyrroldinyl, oxoazepinyl, azepinyl, furazanyl, tetrahydropyranyl, tetrahydrofuranyl, oxathiolyl, dithiolyl, tetrahydrothiophenyl, dioxanyl, dioxolanyl, tetrahydrofurotetrahydrofuranyl, tetrahydropyranotetrahydrofuranyl, tetrahydrofurodihydrofuranyl, tetrahydropyranodihydrofuranyl, dihydropyranyl, dihydrofuranyl, dihydrofurotetrahydrofuranyl, dihydropyranotetrahydrofuranyl, sulfolanyl and the like.

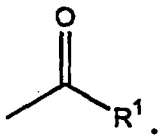
The terms "heteroaryl" and "heteroaromatic" alone or in combination with any other term, unless otherwise defined herein, refers to a stable 3- to 7-membered monocyclic heterocyclic ring which is aromatic, and which may be optionally fused, for example, benzofused, with one to three cycloalkyl, aromatic, heterocyclic or heteroaromatic rings. Each heteroaromatic ring consists of one or more carbon atoms and from one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. As used herein, the terms "nitrogen and sulfur heteroatoms" include any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. A heteroaromatic ring may be attached at any endocyclic carbon or

heteroatom which results in the creation of a stable, aromatic structure.

Preferred heteroaromatics defined above include, for example, benzimidazolyl, imidazolyl, quinolyl, isoquinolyl, indolyl, indazolyl, pyridazyl, pyridyl, pyrrolyl, pyrazolyl, pyrazinyl, quinoxolyl, pyranyl, pyrimidinyl, pyridazinyl, furyl, thienyl, triazolyl, thiazolyl, tetrazolyl, benzofuranyl, oxazolyl, benzoxazolyl, isoxazolyl, isothiazolyl, thiadiazolyl, thiophenyl, and the like.

The term "halo" refers to a radical of fluorine, chlorine, bromine or iodine. Preferred halogen radicals include fluorine and chlorine.

In chemical formulas, parentheses are used herein to indicate 1) the presence of more than one atom or group bonded to the same atom or group; or 2) a branching point in a chain (i.e., the group or atom immediately before the open parenthesis is bonded directly to the group or atom immediately after the closed parenthesis). An example of the first use is "$N(R^1)_2$" denoting two R^1 groups bound to the nitrogen atom. An example of the second use is "$-C(O)R^1$" denoting an oxygen atom and a R^1 bound to the carbon atom, as in the following structure:

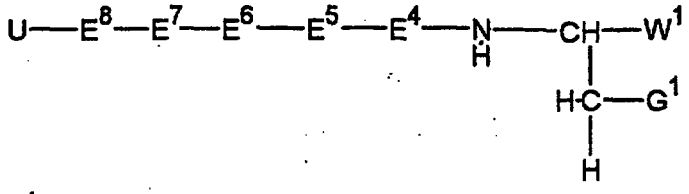


As used herein, "B" indicates a boron atom.

The present invention provides compounds that are useful as protease inhibitors, particularly as serine

protease inhibitors, and more particularly as HCV NS3 protease inhibitors. As such, they act by interfering with the life cycle of the HCV virus and other viruses that are dependent upon a serine protease for proliferation. Therefore, these compounds are useful as antiviral agents.

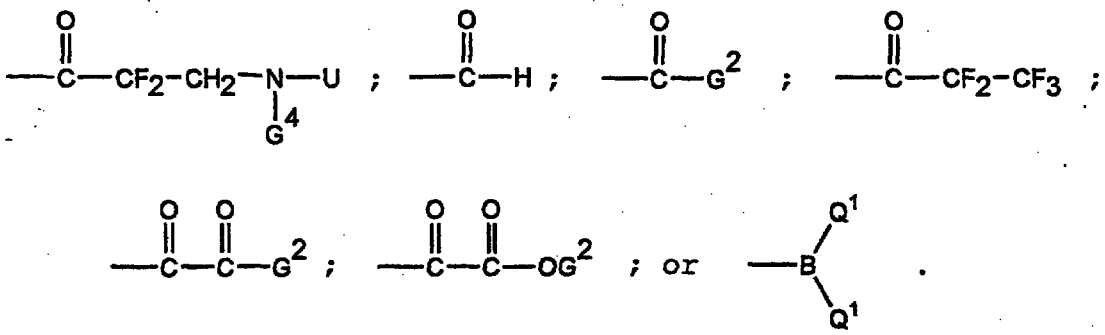
Accordingly, in one embodiment, the present invention provides a compound of the formula (I):

(I) 

wherein:

G^1 is thiol, hydroxyl, thiomethyl, alkenyl, alkynyl, trifluoromethyl, C_{1-2} alkoxy, C_{1-2} alkylthio, or C_{1-3} alkyl, wherein the C_{1-3} alkyl group is optionally substituted with thiol, hydroxyl, thiomethyl, alkenyl, alkynyl, trifluoromethyl, C_{1-2} alkoxy, or C_{1-2} alkylthio.

W^1 is:



G^2 is alkyl, aryl, aralkyl, or a mono-, bi- or tricyclic heterocycle, optionally substituted with 1-3 groups selected from alkyl, alkenyl, alkynyl, aralkyl, alkoxy, alkenoxy, aryloxy, heterocyclyl,

heterocyclylalkyl, aralkoxy, heterocyclylalkoxy, oxo, hydroxy, amino, alkanoylamino, alkoxycarbonylamino, ureido, carboxy, heterocyclyloxyalkyl, aryloxyalkyl, heterocyclylcaronyl, aroyl, arylsulfonyl, heterocyclylsulfonyl, heterocyclylsulfonylamino, arylsulfonamido, aralkylsulfonamido, heterocyclylalkanoyl, carboxyalkyl, carboxyamidoalkyl, alkanesulfonyl, sulfonamido, halo, cyano, or haloalkyl.

G^4 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, aryl, aralkyl, aralkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, hydroxyalkyl, alkoxyalkyl, alkylthioalkyl, arylthioalkyl, or heterocyclylthioalkyl.

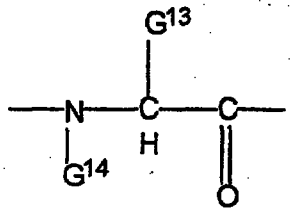
Each Q^1 is hydroxy, alkoxy, or aryloxy, or each Q^1 is an oxygen atom and together with the boron to which they are bound, form a 5-7 membered ring, wherein the ring atoms are carbon, nitrogen or oxygen.

U is hydrogen, G^9-C(O)-, G^9-SO_2-, G^9-C(O)-C(O)-, $(G^9)_2$-N-C(O)-C(O)-, $(G^9)_2$-N-SO_2-, $(G^9)_2$N-C(O)-, or G^9-O-C(O)-.

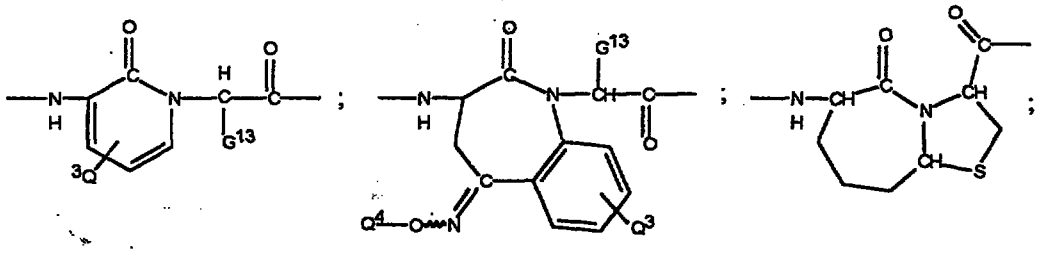
G^9 is hydrogen, alkyl, carboxyalkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, or heterocyclyalkenyl optionally substituted with 1-3 groups selected from alkyl, alkenyl, aralkyl, alkoxy, alkenoxy, aryloxy, heterocyclyl, carboxyalkyl, carboxyamidoalkyl, alkylsulfonyl, or sulfonamido; or two G^9 groups, together with the nitrogen atom to which they are bound, form a 4-10 membered nitrogen containing monocyclic or bicyclic

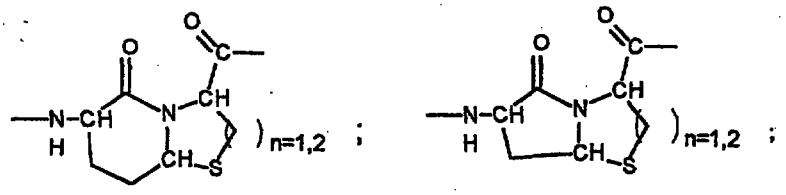
saturated or partially unsaturated ring system, wherein 1-2 of the atoms forming the ring are N, S, or O and the other atoms forming the ring are C; wherein the ring system is optionally substituted by one or two groups selected from alkyl, alkenyl, aralkyl, alkoxy, alkenoxy, aryloxy, aralkoxy, heterocyclyl, keto, hydroxy, amino, alkanoyl amino, carboxy, carboxyalkyl, carboxamidoalkyl, sulfonyl, or sulfonamido.

E^4 is a bond;

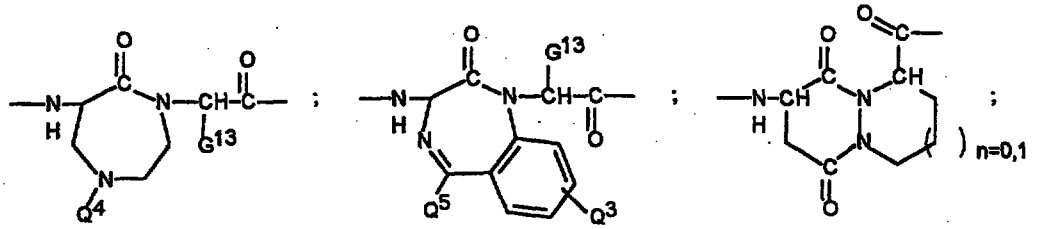


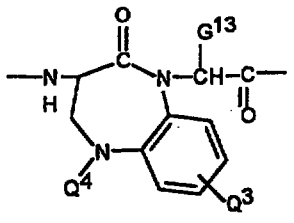
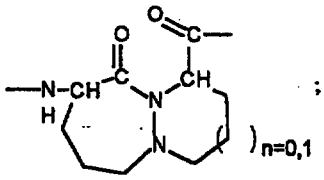
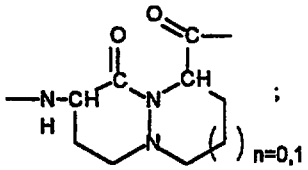
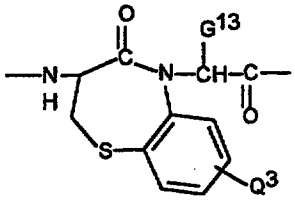
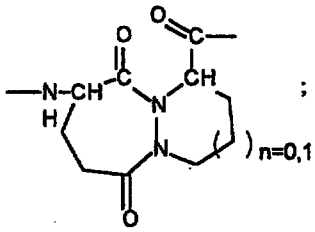
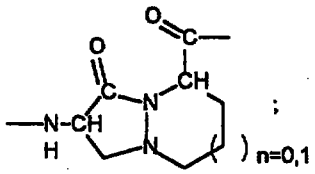
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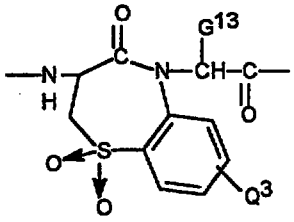
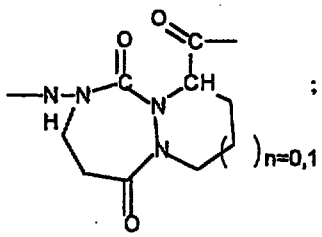
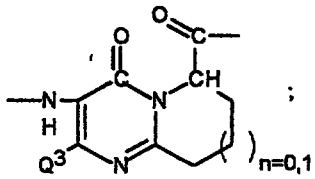
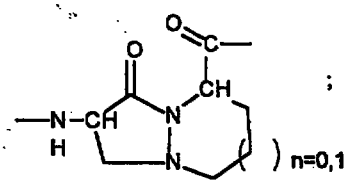
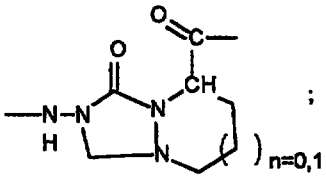
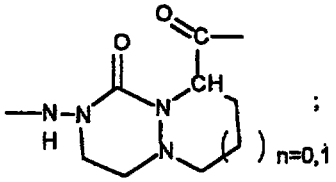
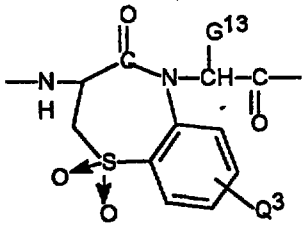
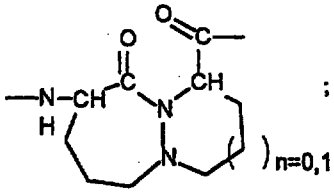
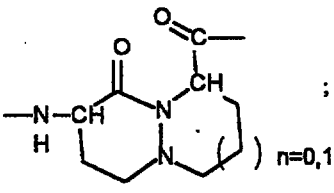


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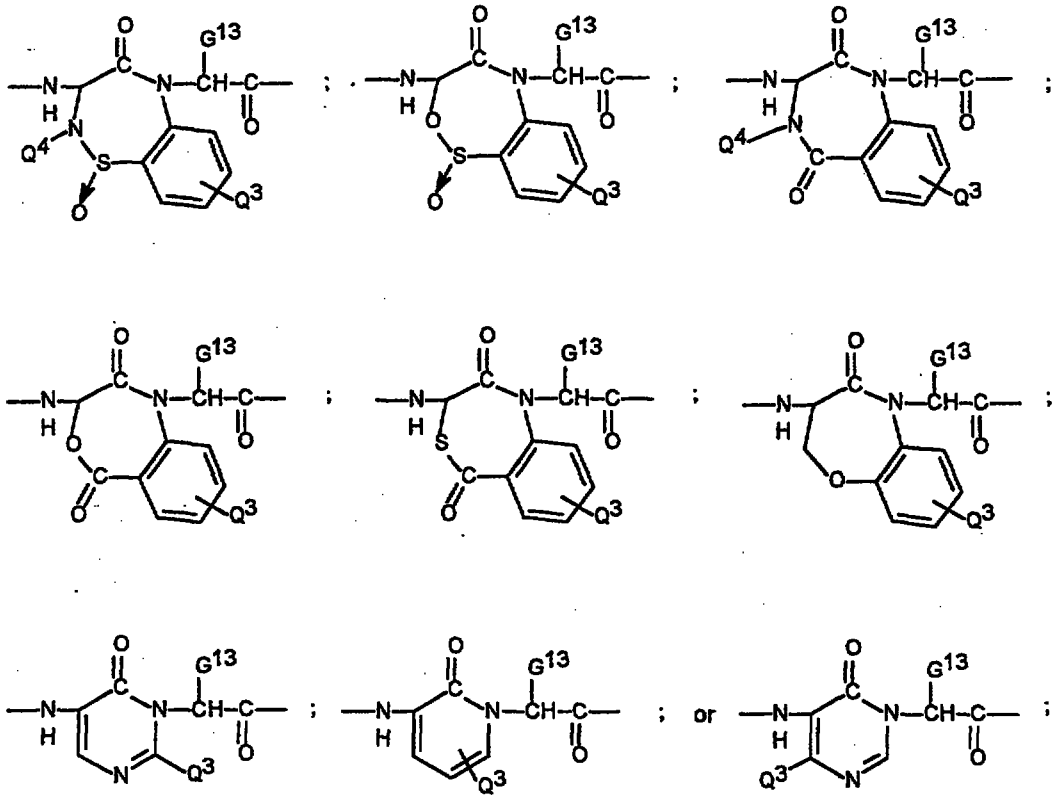


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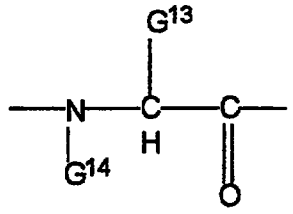
wherein:

G^{13} is cycloalkylalkyl, aralkyl, heterocycylalkyl, aralkoxyalkyl, heterocycylalkoxyalkyl, aralkylthioalkyl, or heterocycylalkylthioalkyl, optionally substituted by 1-2 alkyl, alkenyl, aralkyl, alkoxy, alkenoxy, aryloxy, aralkoxy, heterocyclyl, oxo, hydroxy, amino, alkanoylamino, carboxy, carboxyalkyl, carboxamidoalkyl, sulfonyl, or sulfonamido groups.

G^{14} is hydrogen, alkyl, alkenyl, hydroxy, alkoxy, or $-CH_2-G^8$, wherein G^8 is aryl, aralkyl, carbocyclyl or heterocyclyl, where the ring portion each aryl, aralkyl, or heterocycle is optionally substituted with 1-3 groups selected from alkyl, alkenyl, aralkyl, alkoxy, alkenoxy, aryloxy, heterocyclyl,

heterocyclylalkyl, aralkoxy, heterocyclylalkoxy, oxo, hydroxy, amino, alkanoylamino, alkoxycarbonylamino, ureido, carboxy, carboxyalkyl, carboxyamidoalkyl, alkanesulfonyl, sulfonamido, halo, cyano, or haloalkyl; or

when E^4 is:



;

G^{13} and G^{14}, together with the atoms to which they are bound (carbon and nitrogen, respectively), form a nitrogen-containing heterocyclic ring system having 4-7 members, which optionally contains one to two additional heteroatoms, wherein the resulting ring system is optionally fused with an additional carbocyclic or heterocyclic ring system to form a bicyclic ring system comprising 7-11 atoms; and wherein the monocyclic or bicyclic ring system is optionally substituted by one or two groups selected from oxo, hydroxy, alkyl, alkenyl, aryl,aralkyl, alkyl, alkenoxy, aryloxy, aralkyloxy, halo, or nitro.

Each Q^3 is halogen, nitro, cyano, alkyl, alkenyl, aralkyl, alkoxy, alkenoxy, aryloxy, aralkoxy, heterocyclyl, heterocyclylalkyl, hydroxy, amino, alkylamino, alkanoylamino, carboxy, carboxyalkyl, carboxamidoalkyl, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, alkylsulfonamido, arylsulfonamido, or aralkylsulfonamido, wherein any alkyl, alkenyl, aryl, or heterocyclyl groups is optionally substituted with 1-3

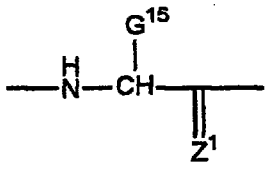
groups selected from keto, hydroxy, nitro, cyano, halo, amino, alkyl, alkoxy, or alkylthio; wherein Q^3, when not bonded to a specific atom, may be bonded to any substitutable atom.

Q^4 is independently alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, alkanoyl, arylcarbonyl, aralkylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, wherein any of said alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl groups is optionally substituted with one or more groups independently selected from keto, hydroxy, nitro, cyano, halo, amino, alkyl, alkoxy, or alkylthio.

Q^5 is aryl or an aromatic heterocycle, wherein:

the aryl or aromatic heterocycle is monocyclic, bicyclic, or tricyclic having 5-14 atoms, and is optionally substituted with 1-3 groups selected from hydroxy, nitro, cyano, halo, amino, alkyl, alkoxy, alkanoyl, alkylamino, or alkylthio.

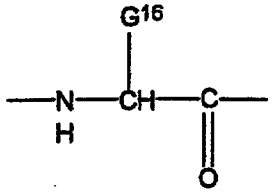
E^5 is a bond or



, wherein G^{15} is alkyl, alkenyl, cycloalkylalkyl, aralkyl, heterocyclylalkyl, carboxyalkyl, or carboxamidoalkyl, where the ring of any aralkyl or heterocyclylalkyl group is optionally substituted with 1-2 alkyl, alkenyl, aralkyl, alkoxy, alkenoxy, aryloxy, aralkoxy, heterocyclyl, oxo, hydroxy,

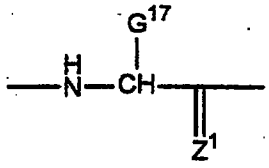
amino, alkanoylamino, carboxy, carboxyalkyl, carboxamidoalkyl, sulfonyl, or sulfonamido groups.

E^6 is a bond or



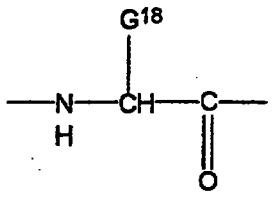
, wherein G^{16} is hydrogen, alkyl, alkenyl, aralkyl, or cycloalkylalkylyl;

E^7 is a bond or



, wherein G^{17} is alkyl optionally substituted with carboxy; wherein the alkyl is preferably C_{1-3} alkyl.

E^8 is a bond or



, wherein G^{18} is alkyl optionally substituted with carboxy; wherein the alkyl is preferably C_{1-3} alkyl.

Each Z^1 is independently O or H_2 provided that no more than two Z^1 groups is H_2 in a given compound.

Preferred compounds of formula (I) are those in which at least one substituent is defined as follows:

G^1 is vinyl, acetylenyl, $-CH_3$, $-CF_3$, $-CH_2CH_3$, $-CH_2CF_3$, $-SCH_3$, $-SH$, $-CH_2SH$, or $-CH_2OH$;

G^{13} is C_{3-6} branched alkyl or G^{13} and G^{14}, together with the atoms to which they are bound (carbon and nitrogen, respectively), form a nitrogen-containing heterocyclic ring system having 4-7 members, which optionally contains one to two additional heteroatoms, wherein the monocyclic or bicyclic ring system is optionally substituted by one or two groups selected from oxo, hydroxy, alkyl, alkenyl, aryl, aralkyl, alkyl, alkenoxy, aryloxy, aralkyloxy, halo, or nitro; and

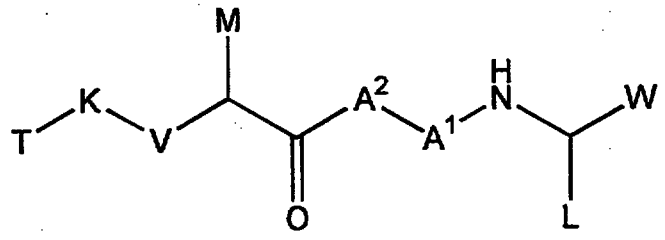
Z^1 is O.

More preferred compounds of formula (I) are those wherein G^1 is -SH, $-CH_2SH$, $-CF_3$, or $-CF_2CF_3$.

Most preferred compounds of formula (I) are those wherein G^1 is -SH or $-CF_3$.

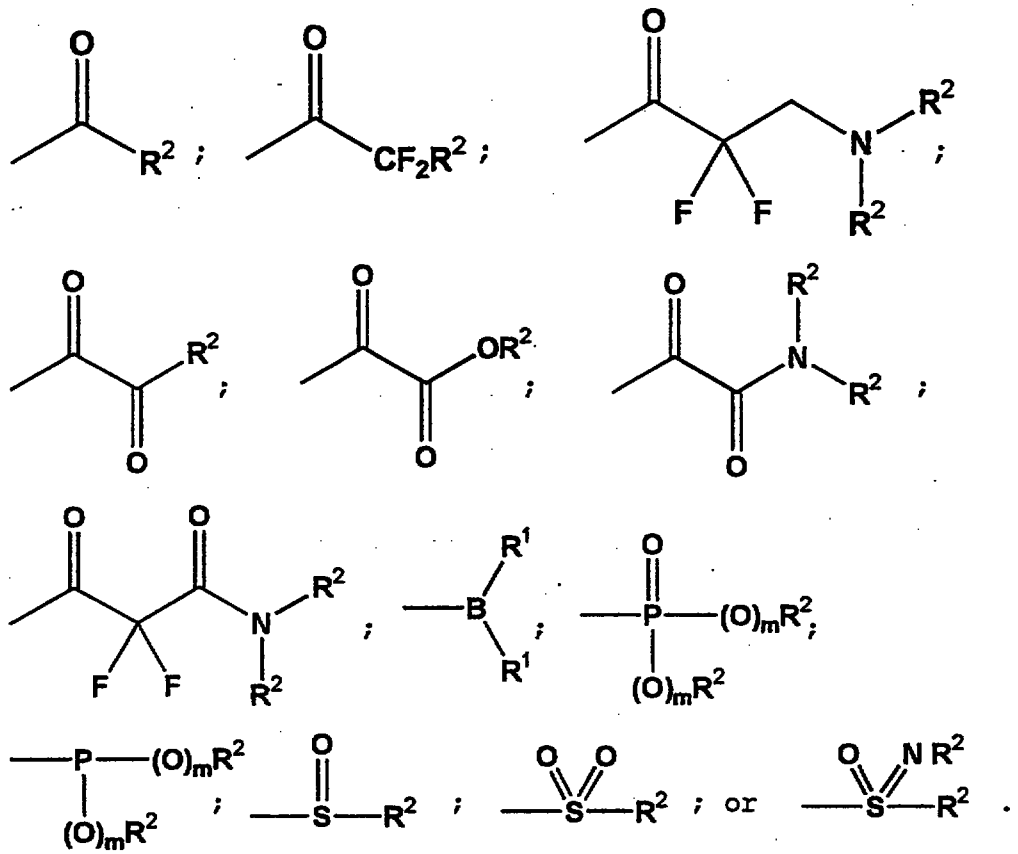
According to another embodiment, the present invention provides a compound of the formula (I), wherein W^1 is as defined below for W and the other substituents are as defined above.

According to another embodiment, the present invention provides a compound of the formula (II):

(II) 

In these compounds:

W is:



m is 0 or 1.

Each R^1 is hydroxy, alkoxy, or aryloxy, or each R^1 is an oxygen atom and together with the boron, to which they are each bound, form a 5-7 membered ring, wherein the ring atoms are carbon, nitrogen, or oxygen.

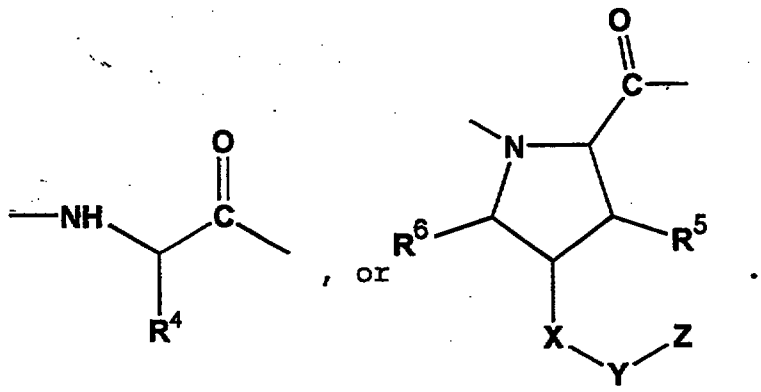
Each R^2 is independently hydrogen, alkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heteroaryl, or heteroaralkyl, or two R^2 groups, which are bound to the same nitrogen atom, form together with that nitrogen atom, a 5-7 membered monocyclic heterocyclic ring system; wherein any R^2 carbon atom is optionally substituted with J.

J is alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, cycloalkyl, cycloalkoxy, heterocyclyl, heterocyclyloxy, heterocyclylalkyl, keto, hydroxy, amino, alkylamino, alkanoylamino, aroylamino, aralkanoylamino, carboxy, carboxyalkyl, carboxamidoalkyl, halo, cyano, nitro, formyl, acyl, sulfonyl, or sulfonamido and is optionally substituted with 1-3 J^1 groups.

J^1 is alkyl, aryl, aralkyl, alkoxy, aryloxy, heterocyclyl, heterocyclyloxy, keto, hydroxy, amino, alkanoylamino, aroylamino, carboxy, carboxyalkyl, carboxamidoalkyl, halo, cyano, nitro, formyl, sulfonyl, or sulfonamido.

L is alkyl, alkenyl, or alkynyl, wherein any hydrogen bound to a carbon atoms is optionally substituted with halogen, and wherein any hydrogen or halogen atom bound to any terminal carbon atom is optionally substituted with sulfhydryl or hydroxy.

A^1 is a bond,



R^4 is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups.

R^5 and R^6 are independently hydrogen, alkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroaralkyl, and is optionally substituted with 1-3 J groups.

X is a bond, $-C(H)(R^7)-$, $-O-$, $-S-$, or $-N(R^8)-$.

R^7 is hydrogen, alkyl, alkenyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroaralkyl, and is optionally substitituted with 1-3 J groups.

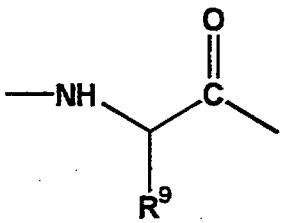
R^8 is hydrogen alkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, aralkanoyl, heterocyclanoyl, heteroaralkanoyl, $-C(O)R^{14}$, $-SO_2R^{14}$, or carboxamido, and is optionally substitituted with 1-3 J groups; or R^8 and Z, together with the atoms to which they are bound, form a nitrogen containing mono- or bicyclic ring system optionally substituted with 1-3 J groups.

R^{14} is alkyl, aryl, aralkyl, heterocyclyl, heterocyclyalkyl, heteroaryl, or heteroaralkyl.

Y is a bond, $-CH_2-$, $-C(O)-$, $-C(O)C(O)-$, $-S(O)-$, $-S(O)_2-$, or $-S(O)(NR^7)-$, wherein R^7 is as defined above.

Z is alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-OR^2$, or $-N(R^2)_2$, wherein any carbon atom is optionally substituted with J, wherein R^2 is as defined above.

A^2 is a bond or



R^9 is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups.

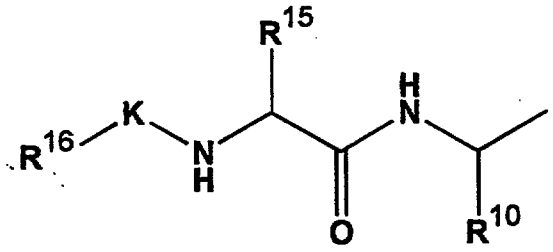
M is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroaralkyl, and is optionally substituted by 1-3 J groups, wherein any alkyl carbon atom may be replaced by a heteroatom.

V is a bond, $-CH_2-$, $-C(H)(R^{11})-$, $-O-$, $-S-$, or $-N(R^{11})-$.

R^{11} is hydrogen or C_{1-3} alkyl.

K is a bond, $-O-$, $-S-$, $-C(O)-$, $-S(O)-$, $-S(O)_2-$, or $-S(O)(NR^{11})-$, wherein R^{11} is as defined above.

T is $-R^{12}$, $-alkyl-R^{12}$, $-alkenyl-R^{12}$, $-alkynyl-R^{12}$, $-OR^{12}$, $-N(R^{12})_2$, $-C(O)R^{12}$, $-C(=NOalkyl)R^{12}$, or



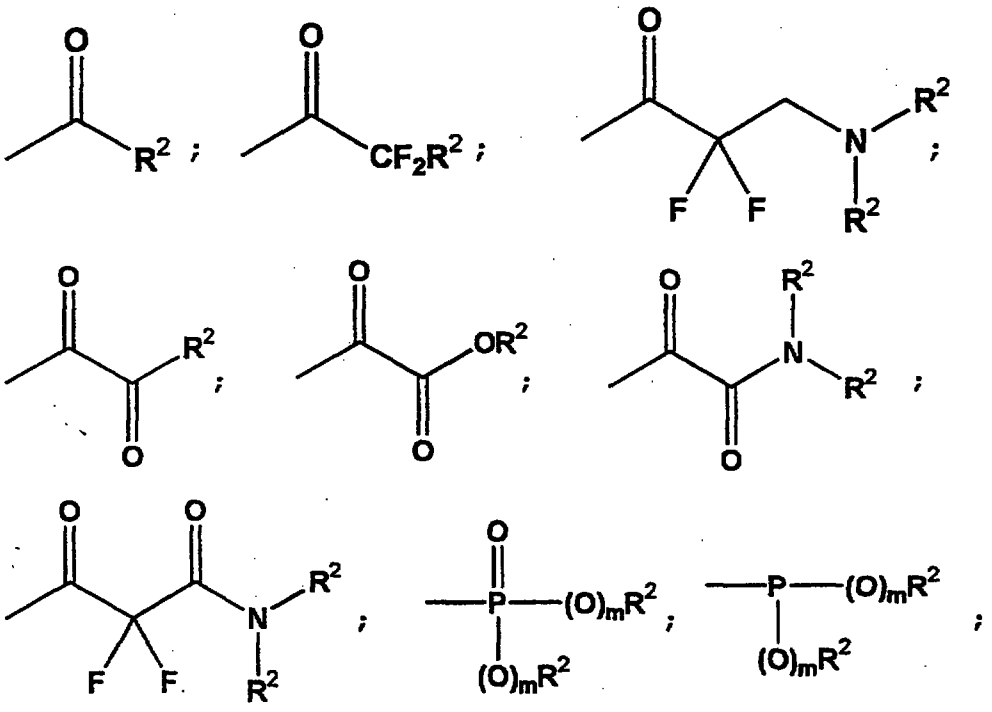
Each R^{12} is hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkylidenyl, or heterocycloalkylidenyl, and is optionally substituted with 1-3 J groups, or a first R^{12} and a second R^{12}, together with the nitrogen to which they are bound, form a mono- or bicyclic ring system optionally substituted by 1-3 J groups.

R^{10} is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 hydrogens J groups.

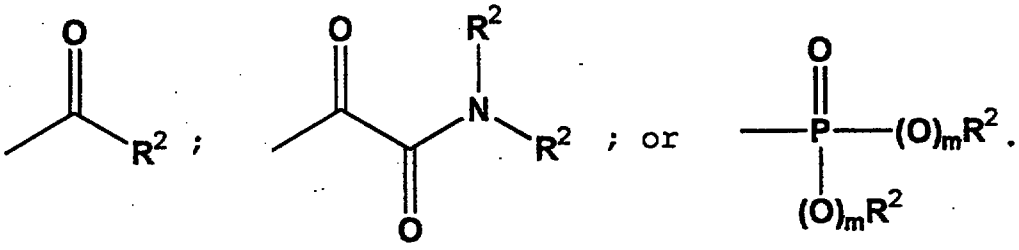
R^{15} is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups.

R^{16} is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl.

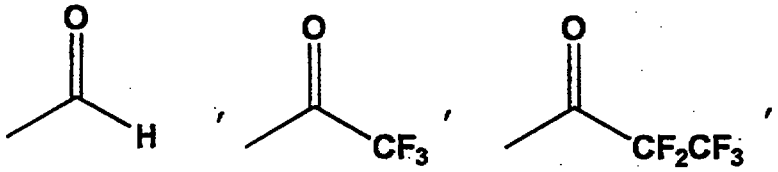
Preferably, W is

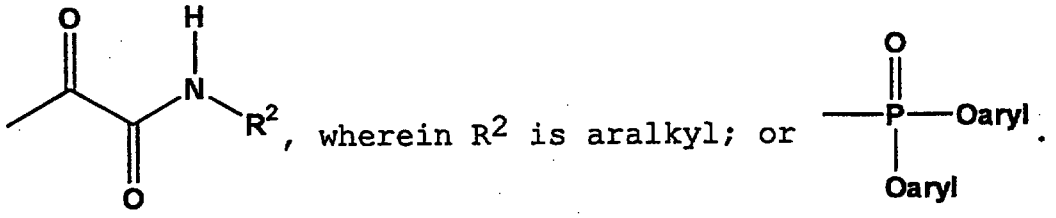


More preferably, W is



Most preferably, W is





Preferably, J is alkyl, alkoxy, aryloxy, aryl, aralkyl, aralkoxy, halo, heteroaryl, cyano, amino, nitro, heterocyclyl, acyl, carboxy, carboxyalkyl, alkylamino, hydroxy, heterocyclylalkyl, aralkanoylamino, aroylamino, alkanoylamino, formyl or keto.

More preferably, J is t-butyl, methyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, carboxy, phenyl, benzyl, phenoxy, benzyloxy, fluoro, chloro, bromo, isoxazolyl, pyridinyl, piperidinyl, carboxymethyl, carboxyethyl; dialkylamino, morpholinylmethyl, phenylacetylamino, or acylamino.

Preferably, J^1 is alkoxy, alkyl, halo or aryl.

More preferably, J^1 is C_{1-3} alkoxy, chloro, C_{1-3}alkyl, or phenyl.

Preferably, L is alkyl, alkenyl, allyl, or propargyl.

More preferably, L is trihalomethyl, sulfhydryl or alkyl substituted with trihalomethyl, sulfhydryl, or hydroxy.

Preferably, R^4 is alkyl, aralkyl, or cycloalkylalkyl, or cycloalkyl. More preferably, R^4 is phenylalkyl or cycloalkyl. Most preferably, R^4 is isobutyl, cyclohexylalkyl, or phenethyl.

Preferably, R^5 and R^6 are each hydrogen.

Preferably, X is -O- or $-N(R^8)-$.

Preferably, R^8 is hydrogen.

Preferably, Y is $-CH_2-$, -C(O)-, -C(O)C(O)-, or $-S(O)_2-$.

Preferably, R^2 is H, fluorine, trifluoromethyl, alkyl, aryl, aralkyl, heteroaralkyl, heterocyclyl, or heterocyclylalkyl.

Preferably, Z is alkyl, aryl, aralkyl, heterocyclyl, cycloalkyl, heteroaryl, OR^2, or $N(R^2)_2$, wherein R^2 is preferably aralkyl or alkenyl.

More preferably, Z is phenyl, 1,4-benzodioxanyl, 1,3-benzodioxolyl, benzothiazolyl, naphthyl, benzyl, oxadiazolyl, isoxazolyl, quinolyl, benzothiophenyl, thiazolyl, cyclohexyl, butyl, naphthyl, dioxolanyl, benzyl, pyridinyl, morpholinyl, N-anilinyl, N-aminobenzothiazole, N-aminobenzodioxole, N-aminonapthylene, N-benzylamine, N-aminopyridine, benzyloxy, allyloxy, or phenethyl, and is optionally substituted with J.

Most preferably, Z is naphtyl, 3,4-dichlorophenyl, 2-carbomethoxyphenyl.

Preferably, R^9 is alkyl. More preferably, R^9 is propyl. Most preferably, R^9 is isopropyl.

Preferably, M is alkyl, heteroaralkyl, aryl, cycloalkylalkyl, aralkyl, or aralkyl, wherein one of the alkyl carbon atoms is replaced by O or S.

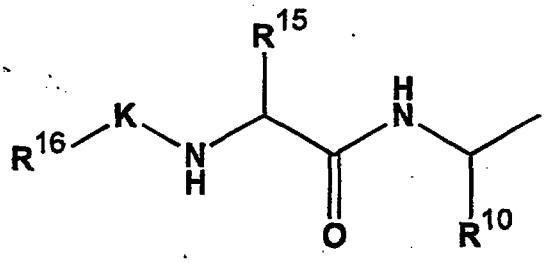
More preferably M is propyl, methyl, pyridylmethyl, benzyl, naphthylmethyl, phenyl, imidazolylmethyl, thiophenylmethyl, cyclohexylmethyl, phenethyl, benzylthiomethyl, or benzyloxyethyl.

Preferably, V is $-N(R^{11})-$.

Preferably, R^{11} is hydrogen.

Preferably, K is $-C(O)-$ or $-S(O)_2-$.

Preferably, T is $-R^{12}$, $-alkyl-R^{12}$, $-alkenyl-R^{12}$, $-OR^{12}$, $-N(R^{12})_2$, $-C(=NOalkyl)R^{12}$, or



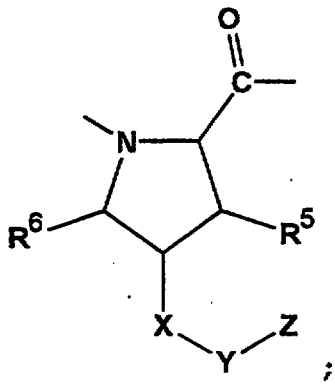
More preferably, T is $-R^{12}$ or $-alkyl-R^{12}$.

Preferably, R^{12} is aryl or heteroaryl and is optionally substituted by 1-3 J groups. More preferably, R^{12} is 1-naphthyl, isoquinolyl, indolyl, or 2-alkoxy-1-naphthyl.

Preferably, R^{10} is alkyl substituted with carboxy. More preferably, R^{10} is C_{1-3} alkyl substituted with carboxy.

Preferably, R^{15} is alkyl substituted with carboxy. More preferably, R^{15} is C_{1-3} alkyl substituted with carboxy.

In a preferred embodiment of formula (II), A^1 is :



; and

A^2 is a bond.

Preferably, in this preferred embodiment, X is O.

More preferably, Y is $-CH_2-$.

Alternatively, Y is $-C(O)-$.

Alternatively, Y is $-C(O)-$ and Z is $-N(R^2)_2$.

Alternatively, in this preferred embodiment, X is $-N(R^8)-$.

More preferably, Y is $-C(O)-$.

Alternatively, Y is $-S(O)_2-$.

Alternatively, Y is $-C(O)-$ and Z is $-N(R^2)_2$.

Alternatively, in this preferred embodiment, X is $-N(R^8)-$, wherein R^8 is $-C(O)R^{14}$ or $-S(O)_2R^{14}$.

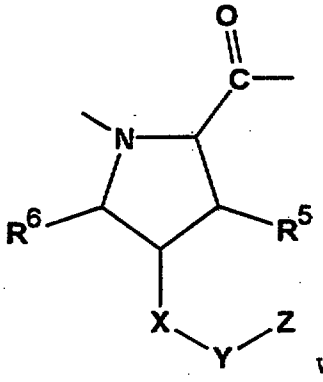
More preferably, when R^8 is $-C(O)R^{14}$, Y is $-C(O)-$.

Alternatively, Y is $-S(O)_2-$.

Alternatively, Y is -C(O)- and Z is $-N(R^2)_2$.

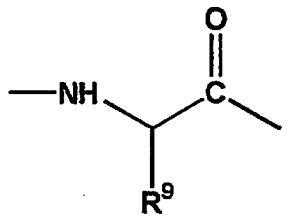
More preferably, when R^8 is $-S(O)_2R^{14}$, Y is -C(O)- and Z is $-N(R^2)_2$.

In a more preferred embodiment of this invention are compounds of formula (II), wherein A^1 is:



wherein, X is -O- and Y is $-CH_2-$;

A^2 is

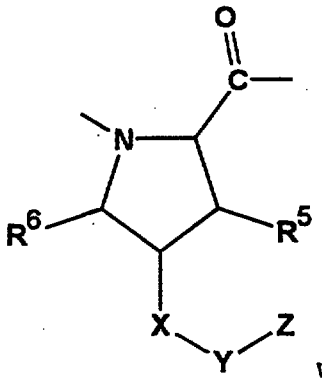


;

V is $-(NR^{11})-$, and

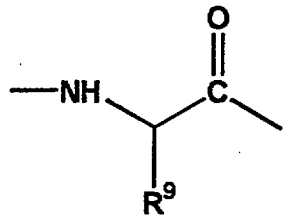
K is -C(O)-.

In another more preferred embodiment of this invention are compounds of formula (II), wherein A^1 is:



wherein, X is O and Y is CH_2,

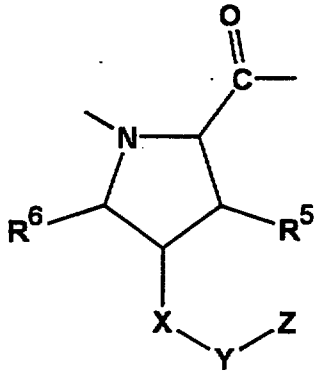
A^2 is:



V is $-N(R^{11})-$, and

K is $-S(O)_2-$

In another more preferred embodiment of this invention are compounds of formula (II), wherein A^1 is:



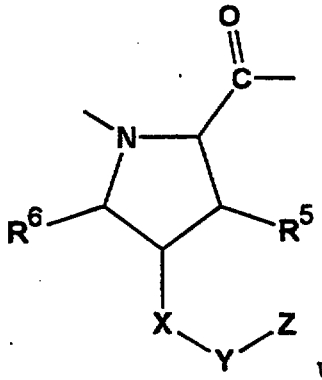
wherein, X is O and Y is a $-CH_2-$,

A^2 is a bond;

V is $-N(R^{11})-$, and

K is $-C(O)-$.

In another more preferred embodiment of this invention are compounds of formula (II), wherein A^1 is:



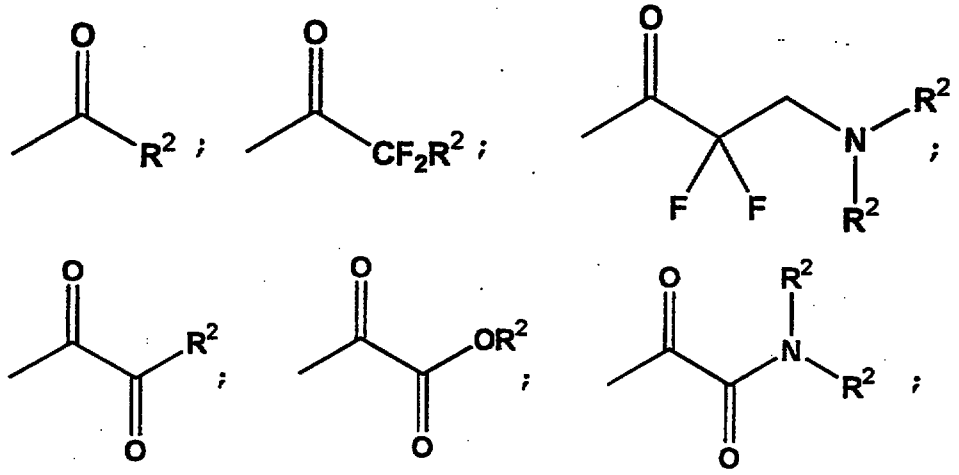
wherein, X is O and Y is $-CH_2-$,

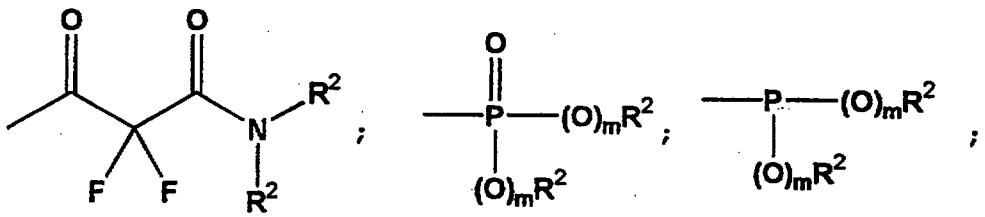
A^2 is a bond;

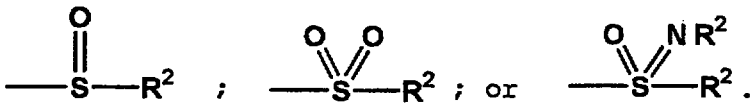
V is $-N(R^{11})-$, and

K is $-S(O)_2-$.

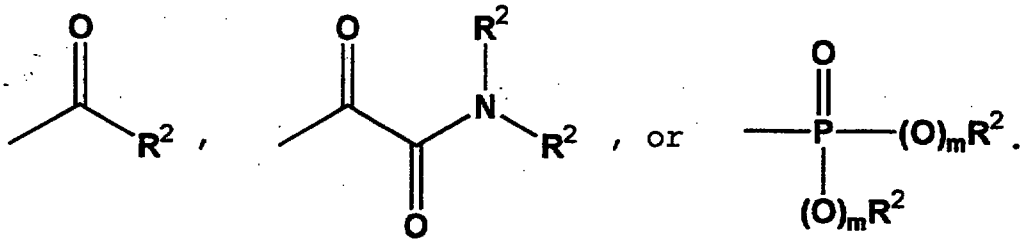
Preferably, in these more preferred embodiments, W is:



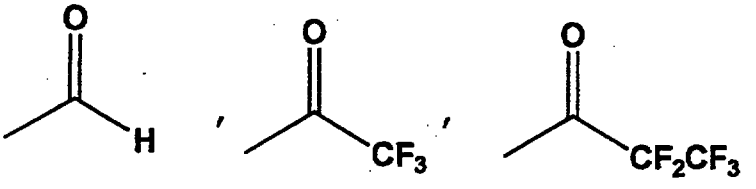


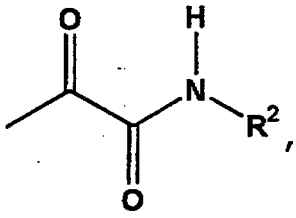
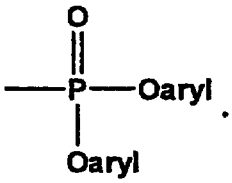


More preferably, W is



Most preferably, W is

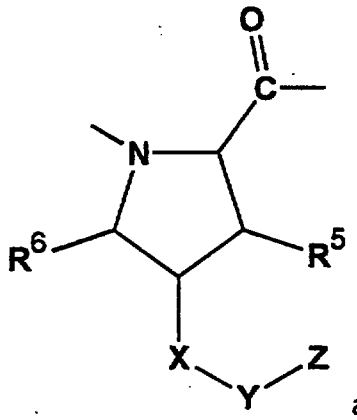


, wherein R^2 is aralkyl; or .

Preferably, in these more preferred embodiments, L is alkyl, alkenyl, allyl, or propargyl.

More preferably, L is trihalomethyl, sulfhydryl or alkyl substituted with trihalomethyl, sulfhydryl, or hydroxy.

In another preferred embodiment of formula (II), A^1 is

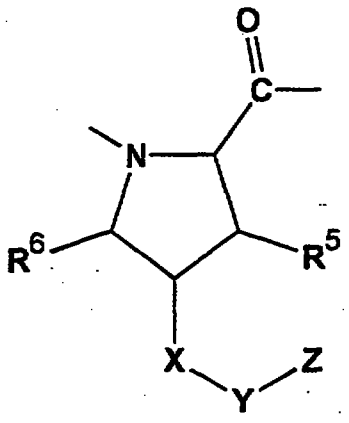


and

A^2 is a bond. Preferred groups in this preferred embodiment are as described above.

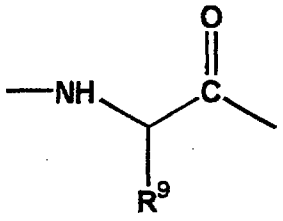
In another preferred embodiment of formula (II), A^1 is a bond. Preferred groups in this preferred embodiment are as described above.

In another preferred embodiment of formula (II), A^1 is



; and

A^2 is



The preferred, more preferred, and most preferred groups of this preferred embodiment are as described above.

This invention anticipates that many active-site directed inhibitors of the NS3 protease may be peptidomimetic in nature and thus may be designed from the natural substrate. Therefore, preferred substituents in peptidomimetic inhibitors of this invention include those which correspond to the backbone or side chains of naturally occurring substrates or synthetic subtrates with high affinity for the enzyme (low K_m).

In another preferred embodiment of formula (II), A^1 is a bond. The preferred, more preferred, and most preferred compounds of this preferred embodiment are as described above.

The skilled practitioner would realize that some certain groups could be classified either as

heterocycles or heteroaromatics, depending on the point of attachment.

The compounds of this invention may contain one or more asymmetric carbon atoms and thus may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a mammal or for use in affinity chromatography applications). Typically, such compounds are stable at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

The compounds of this invention may be synthesized using conventional techniques. Advantageously, these compounds are conveniently synthesized from readily available starting materials.

As used herein, the compounds of this invention, including the compounds of formulae (I) and (II), are defined to include pharmaceutically acceptable derivatives or prodrugs thereof. A "pharmaceutically acceptable derivative or prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention which, upon administration to a recipient, is

capable of providing (directly or indirectly) a compound of this invention.

Accordingly, this invention also provides prodrugs of the compounds of this invention, which are derivatives that are designed to enhance biological properties such as oral absorption, clearance, metabolism or compartmental distribution. Such derivations are well known in the art.

As the skilled practitioner realizes, the compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological compartment (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The term "protected" refers to when the designated functional group is attached to a suitable chemical group (protecting group). Examples of suitable amino protecting groups and protecting groups are described in T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); L. Paquette, ed. Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995) and are exemplified in certain of the specific compounds used in this invention.

Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally

administered compound to be more readily absorbed into the blood), have more favorable clearance rates or metabolic profiles, or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species. Preferred prodrugs include derivatives where a group which enhances aqueous solubility or active transport through the gut membrane is appended to the structure of formulae (I) and (II).

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., magnesium), ammonium and N-(C_{1-4} alkyl)$_4^+$ salts. This invention also envisions the quaternization

of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

In general, compounds of formulae (I) and (II) are obtained via methods illustrated in Examples 1-8. As can be appreciated by the skilled artisan however the synthetic schemes set forth herein are not intended to comprise a comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described above may be performed in an alternate sequence or order to give the desired compounds.

Without being bound by theory, we believe that the compounds of this invention interact either covalently or noncovalently with the active site of the HCV NS3 protease and other serine proteases, inhibiting the ability of such an enzyme to cleave natural or synthetic substrates. Noncovalent interactions are advantageous in that they impart relatively greater specificity of inhibition and will not inhibit other undesirable targets, e.g. cysteine proteases. These compounds will therefore have a greater therapeutic index when administered to mammals than covalent protease inhibitors, which can interact with a wide range of proteases and cause undesireable toxic effects. In contrast, covalent interactions are advantageous in that they impart greater inhibitory potency allowing lower doses may be administered and thus ameliorating any lack of specificity problems.

The novel compounds of the present invention are excellent inhibitors of proteases, particularly serine proteases, and more particularly HCV NS3 protease inhibitors. Accordingly, these compounds are capable of targeting and inhibiting proteases, particularly serine proteases, and more particularly HCV NS3 proteases. As such, these compounds interfere with the life cycle of viruses, including HCV and are thus useful as antiviral agents. Inhibition can be measured by various methods such as the methods of Example 11.

The term "antiviral agent" refers to a compound or drug which possesses viral inhibitory activity. Such agents include reverse transcriptase inhibitors (including nucleoside and non-nucleoside analogs) and protease inhbitors. Preferably the protease inhibitor is a HCV protease inhibitor.

The term "treating" as used herein refers to the alleviation of symptoms of a particular disorder in a patient or the improvement of an ascertainable measurement associated with a particular disorder. As used herein, the term "patient" refers to a mammal, including a human.

Thus, according to another embodiment this invention provides pharmaceutical compositions comprising a compound of formula (I) or (II) or a pharmaceutically acceptable salt thereof; an additional agent selected from, but not including, an immunomodulatory agent, such as α-, β-, or γ-interferon; other antiviral agents, such as ribavarin or amantadine; other inhibitors of HCV protease; inhibitors of other targets in the HCV life cycle such as helicase, polymerase, or metalloprotease; or combinations thereof and any pharmaceutically acceptable carrier, adjuvant or vehicle. An alternate

embodiment provides compositions comprising a compound of formula (I) or (II) or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier, adjuvant or vehicle. Such composition may optionally comprise an additional agent selected from an immunomodulatory agent, such as α-, β-, or γ-interferon; other antiviral agents, such as ribavarin; other inhibitors of HCV protease; inhibitors of the HCV helicase; or combinations thereof.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as dα-tocopherol, polyethyleneglycol 1000 succinate, surfactrants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes,

polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as "α-, β-, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-β-cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of formula (I) or (II).

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol,

water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as those described in Pharmacopeia Helvetica (Ph. Helv.) or a similar alcohol, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and/or suspensions. Other commonly used surfactants such as Tweens or Spans and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain

sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema

formulation. Topically-transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 0.5 and about 75 mg/kg body weight per day of the protease inhibitor compounds described herein are useful in a monotherapy for the prevention and treatment of antiviral, particularly anti-HCV mediated disease. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

When the compositions of this invention comprise a combination of a compound of formula (I) or (II) and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 to 80%

of the dosage normally administered in a monotherapy regimen.

According to one embodiment, the pharmaceutical compositions of this invention comprise an additional immunomodulatory agent. Examples of additional immunomodulatory agents include, but are not limited to, α-, β-, and δ-interferons.

According to an alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise an anti-viral agent. Examples of anti-viral agents include, ribavirin and amantadine.

According to another alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise other inhibitors of HCV protease.

According to yet another alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise an inhibitor of other targets in the HCV life cycle, such as helicase, polymerase, or metalloprotease.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age,

body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician.

When these compounds or their pharmaceutically acceptable salts are formulated together with a pharmaceutically acceptable carrier, the resulting composition may be administered in vivo to mammals, such as man, to inhibit serine proteases, particularly HCV NS3 protease or to treat or prevent viral infection, particularly HCV virus infection. Such treatment may also be achieved using the compounds of this invention in combination with agents which include, but are not limited to: immunomodulatory agents, such as α-, β-, or γ-interferons; other antiviral agents such as ribavirin, amantadine; other inhibitors of HCV NS3 protease; inhibitors of other targets in the HCV life cycle such as helicase, polymerase, metalloprotease, or internal ribosome entry; or combinations thereof. These additional agents may be combined with the compounds of this invention to create a single dosage form. Alternatively these additional agents may be separately administered to a mammal as part of a multiple dosage form.

Accordingly, another embodiment of this invention provides methods of inhibiting serine protease activity in mammals by administering a compound of the formula (I) or (II), wherein the substituents are as defined above. Preferably, the serine protease is HCV NS3.

In an alternate embodiment, the invention provides methods of inhibiting HCV or HCV NS3 activity in a mammal comprising the step of administering to said

mammal, a compound of formula (I) or (II), wherein the substituents are as defined above.

In an alternate embodiment, this invention provides methods of decreasing serine protease activity in a mammal comprising the step of administrating to said mammal any of the pharmaceutical compositions and combinations described above. If the pharmaceutical composition comprises only a compound of this invention as the active component, such methods may additionally comprise the step of administering to said mammal an agent selected from an immunomodulatory agent, an antiviral agent, a HCV protease inhibitor, or an inhibitor of other targets in the HCV life cycle. Such additional agent may be administered to the mammal prior to, concurrently with, or following the administration of the HCV inhibitor composition.

In a preferred embodiment, these methods are useful in decreasing HCV NS3 protease activity in a mammal. If the pharmaceutical composition comprises only a compound of this invention as the active component, such methods may additionally comprise the step of administering to said mammal an agent selected from an immunomodulatory agent, an antiviral agent, a HCV protease inhibitor, or an inhibitor of other targets in the HCV life cycle such as helicose, polymerase, or metallo protease. Such additional agent may be administered to the mammal prior to, concurrently with, or following the administration of the compositions of this invention.

In an alternate preferred embodiment, these methods are useful for inhibiting viral replication in a mammal. Such methods are useful in treating or preventing, for example, viral diseases, such as HCV. If the pharmaceutical composition comprises only a compound

of this invention as the active component, such methods may additionally comprise the step of administering to said mammal an agent selected from an immunomodulatory agent, an antiviral agent, a HCV protease inhibitor, or an inhibitor of other targets in the HCV life cycle. Such additional agent may be administered to the mammal prior to, concurrently with, or following the administration of the composition according to this invention.

The compounds set forth herein may also be used as laboratory reagents. The compounds of this invention may also be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials. These materials include, but are not limited to, biological materials, such as blood, tissue, etc; surgical instruments and garments; laboratory instruments and garments; and blood collection apparatuses and materials.

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

General Materials and Methods

A general synthetic methodology for preparing compounds of this invention is provided in Example 1. More specific methodologies for preparing compounds of this invention, including compounds 1-198, are provided in Examples 2-9.

The HPLC data reported in Tables 1-7 is expressed in terms of solvent gradient; retention time; and % purity. Deionized water was used in each method.

The correct $(M + H)^+$ and/or $(M + Na)^+$ molecular ions for all compounds were obtained by either matrix-assisted laser desorption mass spectrometry (Kratos MALDI I) or by electro spray mass spectromity (MICROMASS Quatro II).

Example 1

Numerous amino acids for use in the synthesis of peptidyl and peptidomimetic compounds of this invention may be purchased commercially from, for instance, Sigma Chemical Company or Bachem Feinchemikalien AG (Switzerland). Amino acids that are not commercially available can be made by known synthetic routes ("Kinetic Resolution of Unnatural and Rarely Occurring Amino Acids: Enantioselective Hydrolysis of N-Acyl Amino Acids Catalyzed by Acylase I", Chenault, H.K. et. al., J. Am. Chem. Soc. 111, 6354-6364 (1989) and references cited therein; "Synthesis of β-γ-Unsaturated Amino Acids by the Strecker Reaction, Greenlee, W.J., J. Org. Chem. 49, 2632-2634 (1984); "Recent Stereoselective Synthetic Approaches to Beta-amino Acids", Cole, D. Tetrahedron 50: 9517 (1994); "The Chemistry of Cyclic Alpha Imino Acids", Mauger, A.B; Volume 4 of "Chemistry

and Biochemistry of Amino Acids, Peptides, and Proteins", Weinstein, B. editor, Marcel Dekker (1977); "Recent Progress in the Synthesis and Reactions of Substituted Piperidines", Org. Prep. Procedure Int. 24, 585-621 (1992), all of which are incorporated herein by reference).

Certain compounds of formula (I) or (II) may be synthesized from amino acids by procedures which are well known in the art of peptide and organic chemical synthesis. Examples of such syntheses are generally set forth in Bodanszky and Bodanszky, "The Practice of Peptide Synthesis", Springer-Verlag, Berlin, Germany (1984), "The Peptides", Gross and Meinhofer, eds; Academic Press, 1979, Vols. I-III, and Stewart, J.M. and Young, J.D., "Solid Phase Peptide Synthesis, Second Edition", Pierce Chemical Company, Rockford, IL (1984); and "Recent Advances in the Generation of Molecular Diversity", Moos, W.H., Green, G.D. and Pavia, M.R. in "Annual Reports in Medicinal Chemistry, Vol. 28" pp. 315-324; Bristol, J.A., ed.; Academic Press, San Diego, CA (1993), all of which are incorporated herein by reference.

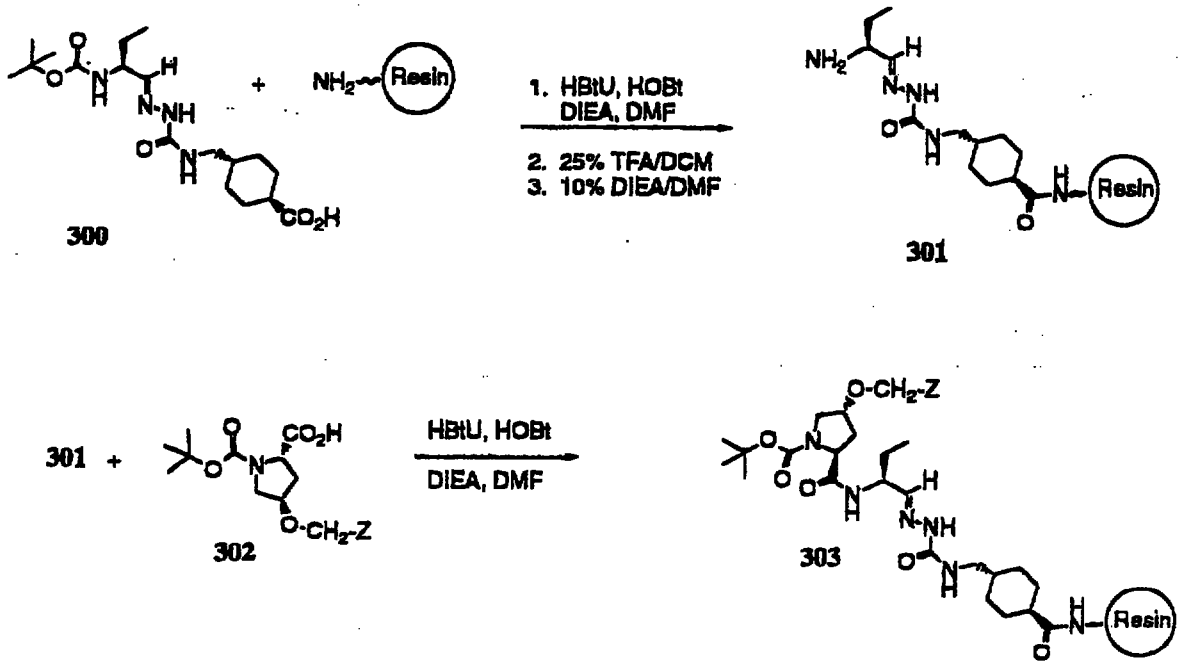
Typically, for solution phase synthesis of peptides, the α-amine of the amino acid to be coupled is protected by a urethane such as Boc, Cbz, Fmoc or Alloc while the free carboxyl is activated by reaction with a carbodiimide such as DCC, EDC, or DIC, optionally in the presence of a catalyst such as HOBT, HOAt, HOSu, or DMAP. Other methods, which proceed through the intermediacy of activated esters, acid halides, enzyme-activated amino acids and anhydrides including phosphonium reagents such as BOP, Py-BOP, N-carboxy-anhydrides, symmetrical anhydrides, mixed carbonic anhydrides, carbonic-phosphinic and carbonic-phosphoric anhydrides, are also

suitable. After the peptide has been formed, protecting groups may be removed by methods described in the references listed above, such as by hydrogenation in the presence of a palladium, platinum or rhodium catalyst, treatment with sodium in liquid ammonia, hydrochloric, hydrofluoric, hydrobromic, formic, trifluoromethanesulfonic, or trifluoroacetic acid, secondary amines, fluoride ion, trimethylsilyl halides including bromide and iodide, or alkali. Automation of the synthetic process, using techniques such as those set forth above, can be accomplished by use of commercially available instrumentation, including but not limited to the Advanced Chemtech 357 FBS and 496 MOS; Tecan CombiTec, and Applied Biosystems 433A among others. Specific application of these methods and their equivalents, depending upon the target compound, will be apparent to those skilled in the art. Modifications of chemical processes and choice of instrumentation is within the skill of the ordinary practitioner.

Example 2

Compounds 1-26 (Table 1) were prepared as described in scheme 1.

SCHEME 1


300
NH2 Resin
1. HBtU, HOBt DIEA, DMF
2. 25% TFA/DCM
3. 10% DIEA/DMF
301
301 +
302
HBtU, HOBt
DIEA, DMF
303
1. 25% TFA/DCM
2. 10% DIEA/DMF
304
1. Fmoc-Val, HBTU HOBt,DIEA,NMP
2. 25% pip/DMF
3. Fmoc-Val, HBTU HOBt,DIEA,NMP
4. 25% pip/DMF
5. Prz-OH, HBTU HOBt,DIEA,NMP
Prz-Val-Val-
305
95% TFA/5% H2O
or
THF/H2CO/1NHCl
306

Synthesis of 301-306

Step A. Synthesis of 301. 4-Methyl Benzhydrylamine resin (1.05 mmol/g, 20.0 g) was placed in a sintered glass funnel and washed with dimethylformamide (3 X 75 mL), 10% (v/v) diisopropylethylamine (DIEA) in dimethylformamide (2 X 75 mL) and finally with dimethylformamide (4 X 75 mL). Sufficient dimethylformamide was added to the resin to obtain a slurry followed by **300** (8.0 g, 20.8 mmol, prepared from (2S) 2-(t-Butyloxycarbonylamino)-butyraldehyde according to A.M. Murphy et. al. J. Am. Chem. Soc., 114, 3156-3157 (1992)), 1-hydroxybenzotriazole hydrate (HOBT·H_2O; 3.22 g, 21.0 mmol), O-benzotriazole-N,N,N,N'-tetramethyluronium hexafluorophosphate (HBTU; 8.0 g, 21.0 mmol), and DIEA (11.0 mL, 63 mmol). The reaction mixture was agitated overnight at room temperature using a wrist arm shaker. The resin was isolated on a sintered glass funnel by suction filtration and washed with dimethylformamide (3 X 75 mL). Unreacted amine groups were then capped by reacting the resin with 20% (v/v) acetic anhydride/dimethylformamide (2 X 50 mL) directly in the funnel (10 min/wash). The resin was washed with dimethylformamide (3 X 75 mL) and dichloromethane (3 X 75 mL) prior to drying overnight *in vacuo* to yield **300a** (26.3 g, 81% yield).

The t-Boc protecting group was removed from resin **300a** using the Advanced ChemTech 396 Multiple Peptide synthesizer by the following procedure. Resin **300a** (0.05 mmol) was swelled by washing with dichloromethane (3 X 1 mL) followed by cleavage of the t-

Boc protecting group with 50% (v/v) TFA/dichloromethane (1.0 mL) for 10 min (with shaking) followed by fresh reagent (1 mL) for 30 min. The resin was then washed with dichloromethane (3 X 1 ml), followed by DMF (3 X 1 mL), then 10% DIEA/dimethylformamide (v/v) (2 X 1 mL), and finally with N-methypyrrolidone (3 X 1 mL) to yield resin **301**.

Step B. Synthesis of 303. This compound was prepared from resin **301** (0.05 mmol) using an Advanced ChemTech 396 Multiple Peptide synthesizer. Resin **301** was acylated with a solution of 0.4M **302** and 0.4M HOBT in N-methypyrrolidone (0.5 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methypyrrolidone (0.35 mL) and the reaction was shaken for 4 hr at room temperature. The coupling reaction was repeated. The resin was then washed with dimethylformamide (3 X 1 ml), followed by dichloromethane (3 X 1 mL) to yield resin **303**.

Step C . Synthesis of 305. The synthesis of the resin-bound compound was completed using an Advanced ChemTech 396 Multiple Peptide synthesizer. Resin **303** was washed with dichloromethane (3 X 1 mL) followed by cleavage of the t-Boc protecting group with 50% (v/v) TFA/dichloromethane (1.0 mL) for 10 min (with shaking) followed by fresh reagent (1 mL) for 30 min. The resin was then washed with dichloromethane (3 X 1 ml), followed by DMF (3 X 1 mL), then 10% DIEA/dimethylformamide (v/v) (2 X 1 mL), and finally with N-methypyrrolidone (3 X 1 mL) to yeild resin **304**. This resin was then acylated with a solution of 0.4M Fmoc-Valine and 0.4M HOBT in N-methypyrrolidone (0.5 mL), a solution of 0.4M HBTU in N-

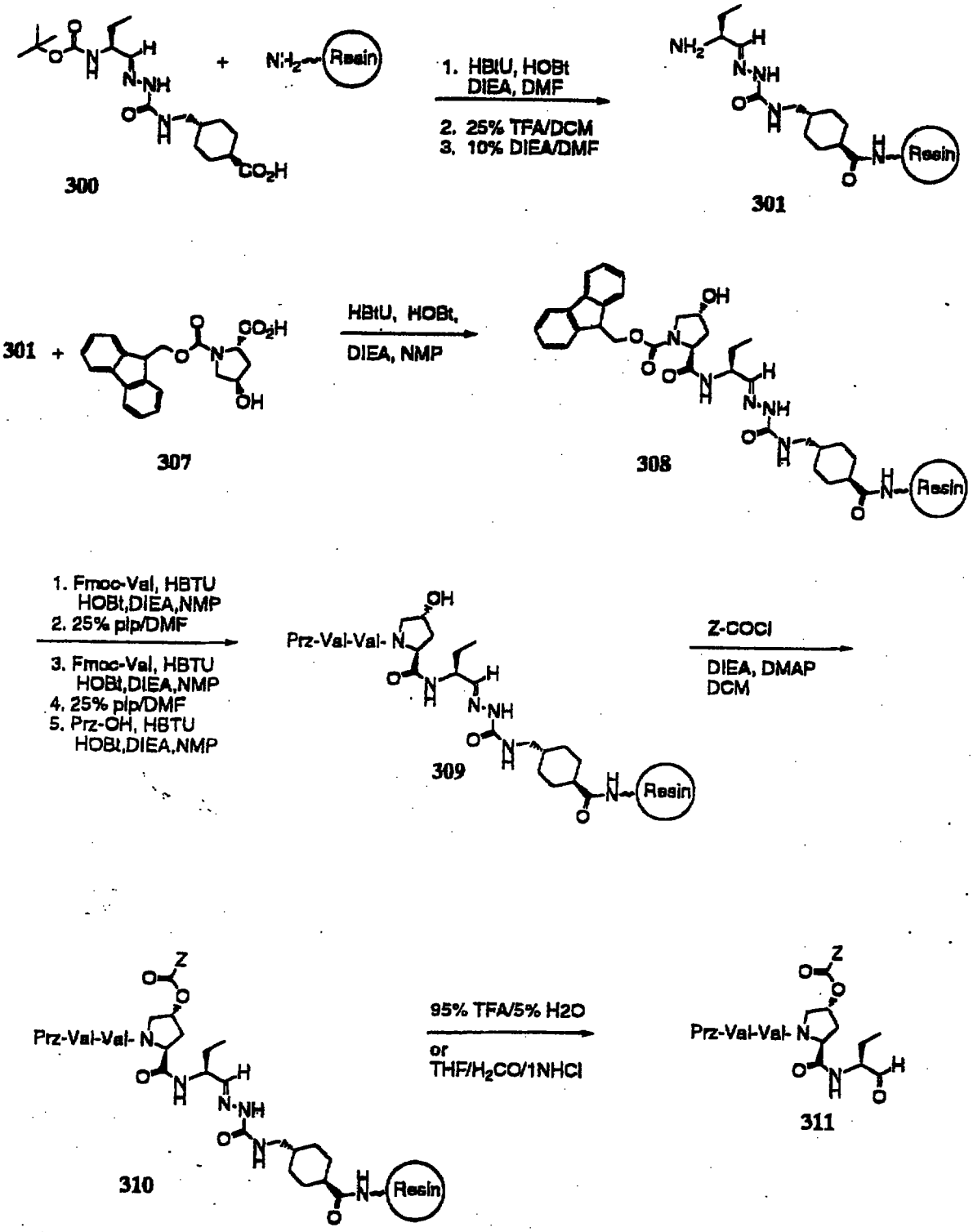
methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methypyrrolidone (0.35 mL) and the reaction was shaken for 4 hr at room temperature. The coupling reaction was repeated. The automated cycles consisted of: (1) a resin wash with dimethylformamide (3 X 1 mL); (2) deprotection with 25% (v/v) piperidine in dimethylformamide (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min.; (3) a resin wash with dimethylformamide (3 X 1 mL) and N-methypyrrolidone (3 X 1 mL) prior to coupling as described above. Fmoc-Valine and Pyrazine-2-carboxylic acid were coupled in this manner.

Step D. Synthesis of 306. Prior to cleavage, the resin was washed with 1:1 dichloromethane/methanol (3 X 1 mL) and then dried *in vacuo*. The aldehyde was cleaved from the resin by treatment with either 95% TFA/ 5% H_2O (v/v, 1.5 mL) for 30 min at room temperature or by treatment with tetrahydrofuran/30% formalin/1N HCl 9:1:1 (v:v:v) for 1 hr at room temperature. After washing the resin with cleavage reagent (1 mL), the combined filtrates were diluted with water and lyophilized to obtain crude **306** as a white powder. The compound was purified by semi-prep RP-HPLC with a Waters DeltaPak 300 Å C18 column (15 μ, 30 X 300 mm) eluting with a linear acetonitrile gradient containing 0.1% TFA (v/v) over 45 min at 20 mL/min. Fractions containing the desired product were pooled and lyophilized to provide **306**.

Example 3

Compounds 27-29 (Table 1) were prepared as described in scheme 2.

SCHEME 2


300
1. HBtU, HOBt
DIEA, DMF
2. 25% TFA/DCM
3. 10% DIEA/DMF
301
HBtU, HOBt,
DIEA, NMP
307
308
1. Fmoc-Val, HBTU
HOBt,DIEA,NMP
2. 25% pip/DMF
3. Fmoc-Val, HBTU
HOBt,DIEA,NMP
4. 25% pip/DMF
5. Prz-OH, HBTU
HOBt,DIEA,NMP
Prz-Val-Val-
309
Z-COCl
DIEA, DMAP
DCM
95% TFA/5% H2O
or
THF/H2CO/1NHCl
310
311
Resin

Step A. Synthesis of 301. See Step A, Scheme 1 methodology.

Step B. Synthesis of 308. Resin **301** (6.0 g, 0.65 mmol/g, 3.9 mmol) was swelled in a sintered glass funnel by washing with dichloromethane (3 X 50 mL). The Boc protecting group was then cleaved with 50% (v/v) TFA/dichloromethane (50 mL) for 10 min (intermittent stirring) and then for 30 min with fresh reagent (50 ml). The resin was then washed with dichloromethane (3 X 50 ml), dimethylformamide (2 X 50 mL), 10% DIEA/dimethylformamide (v/v) (2 X 50 mL), and finally N-methylpyrrolidone (3 X 50 mL). After transferring the resin to a 100 mL flask, N-methypyrrolidone was added to obtain a slurry followed by **307** (2.83 g, 8.0 mmol), HOBT·H_2O (1.22 g, 8.0 mmol), HBTU (3.03 g, 8.0 mmol) and DIEA (4.2 mL, 24 mmol). The reaction mixture was agitated overnight at room temperature using a wrist arm shaker. The resin work-up and capping with 20% (v/v) acetic anhydride in dimethylformamide were performed as described for **301** to yield **308** (6.86 g, quantitative yield).

Step C. Synthesis of 309. This compound was prepared from resin **308** (0.15 mmol) using a Tecan CombiTec synthesizer. Resin **308** (0.076 mmol) was washed with dimethylformamide (3 X 2 mL), deprotected with 25% (v/v) piperidine in dimethylformamide (2.5 mL) for 5 min followed by fresh reagent (2 mL) for 20 min . The resin was washed with dimethylformamide (3 X 2.5 mL) and N-methypyrrolidone (3 X 2.5 mL) prior to acylation with a solution of 0.4M Fmoc-Valine and 0.4M HOBT in N-methypyrrolidone (0.8 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.8 mL) and a solution of 1.6M DIEA in N-methypyrrolidone (0.6 mL) and the reaction was shaken for 8 hr at room temperature. The coupling reaction was repeated. The deprotection and coupling procedures were repeated to add the second Valine residue and to add the final pyrazine-2-carboxylic acid residue. The resin was then washed with dichloromethane (3 X 2.5 ml) to yield resin **309**.

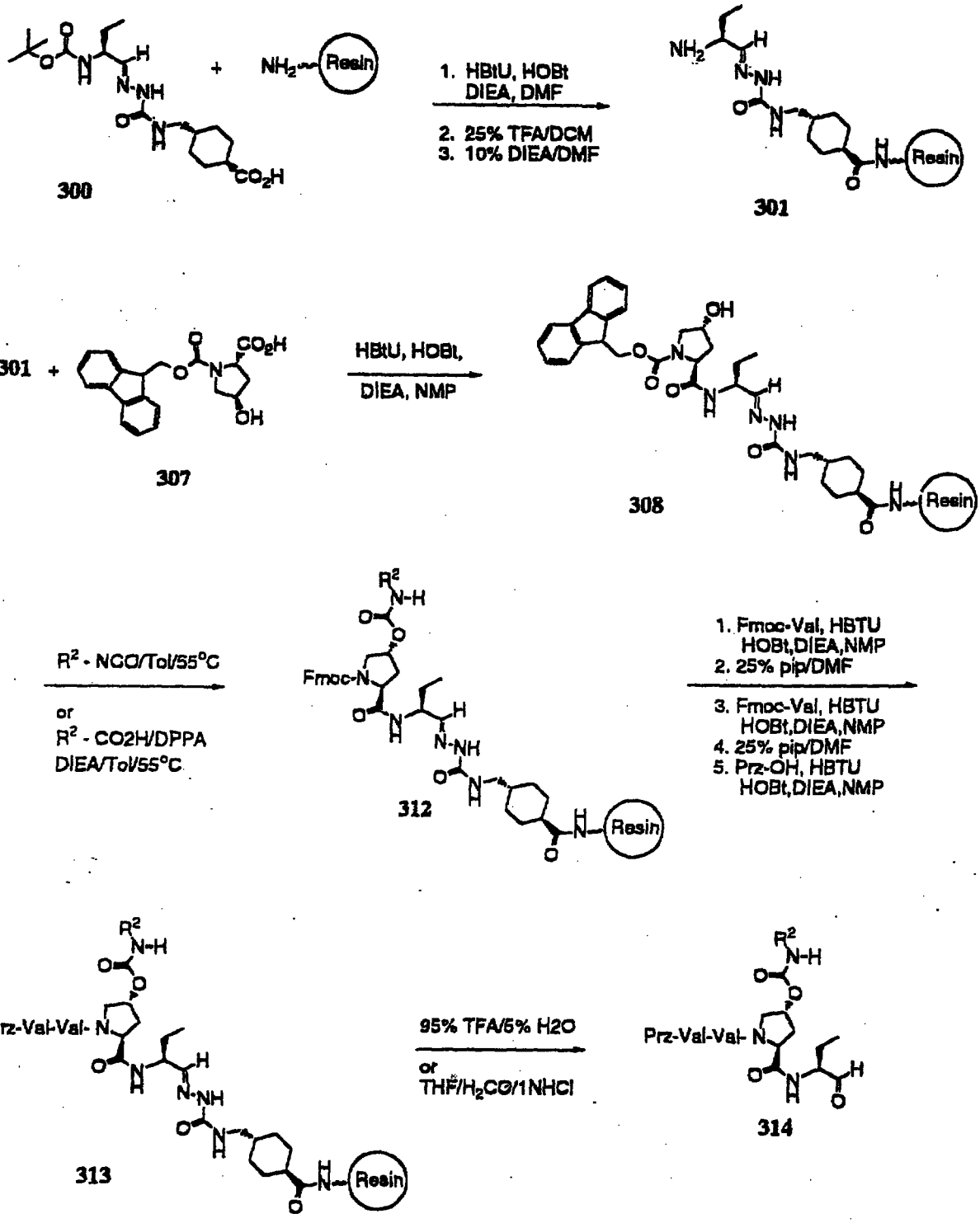
Step D. Synthesis of 310. To resin **309** was added 1:1 pyridine/dichloromethane (v/v) (1 mL), 0.8M dimethylaminopyridine in dimethylformamide (0.2 mL), and a solution of 0.2M **Z-COCl** in dichloromethane (1.5 mL) and the reaction was shaken for 8 hr at room temperature. The acylation reaction was repeated. The resin was washed with dichloromethane (3 X 2.5 mL), dimethylformamide (3 X 2.5 mL), dichloromethane (3 X 2.5 mL), and finally with 1:1 dichloromethane/methanol (3 X 2.5 mL) to yield resin **310**.

Step E. Synthesis of 311. Prior to cleavage, the resin was washed with 1:1 dichloromethane/methanol (3 X 1 mL) and then dried *in vacuo*. The aldehyde was cleaved from the resin by treatment with tetrahydrofuran/formalin/acetic acid/1N HCl 5:1:1:0.1 (v:v:v:v) for 1 hr at room temperature. After washing the resin with cleavage reagent (1 mL), the combined filtrates were diluted with water and lyophilized to obtain crude **311** as a white powder. The compound was purified by semi-prep RP-HPLC with a Waters DeltaPak 300 Å C18 column (15 μ, 30 X 300 mm) eluting with a linear acetonitrile gradient containing 0.1% TFA (v/v) over 45 min at 20 mL/min. Fractions containing the desired product were pooled and lyophilized to provide **311**.

Example 4

Compounds 30-56 (Table 1) were prepared as described in scheme 3.

SCHEME 3



300 301 307 308 312 313 314

Step A. Synthesis of 301. See Step A, Scheme 1 methodology.

Step B. Synthesis of 308. See Step B, Scheme 2 methodology.

Step C. Synthesis of 312. This compound was prepared from resin **308** (0.15 mmol) using a Tecan CombiTec synthesizer. Resin **308** was washed with toluene (3 X 2.5 mL) and then suspended in toluene (1.0 mL). To this was added either a solution of 0.8M R_3 δ-isocyanate in toluene (1.0 mL) followed by 0.8M DIEA in toluene (1.0 mL) or a solution of 0.8M R_3 δ-carboxylic acid with 0.8M DIEA in toluene (1.0 mL) followed by 0.8M diphenylphosphorylazide in toluene (1.0 mL). The reaction was shaken for 8 hr at 55°C. The resin was then washed with toluene (3 X 2.5 ml) and dimethylformamide (4 X 2.5 mL) to yield resin **312**.

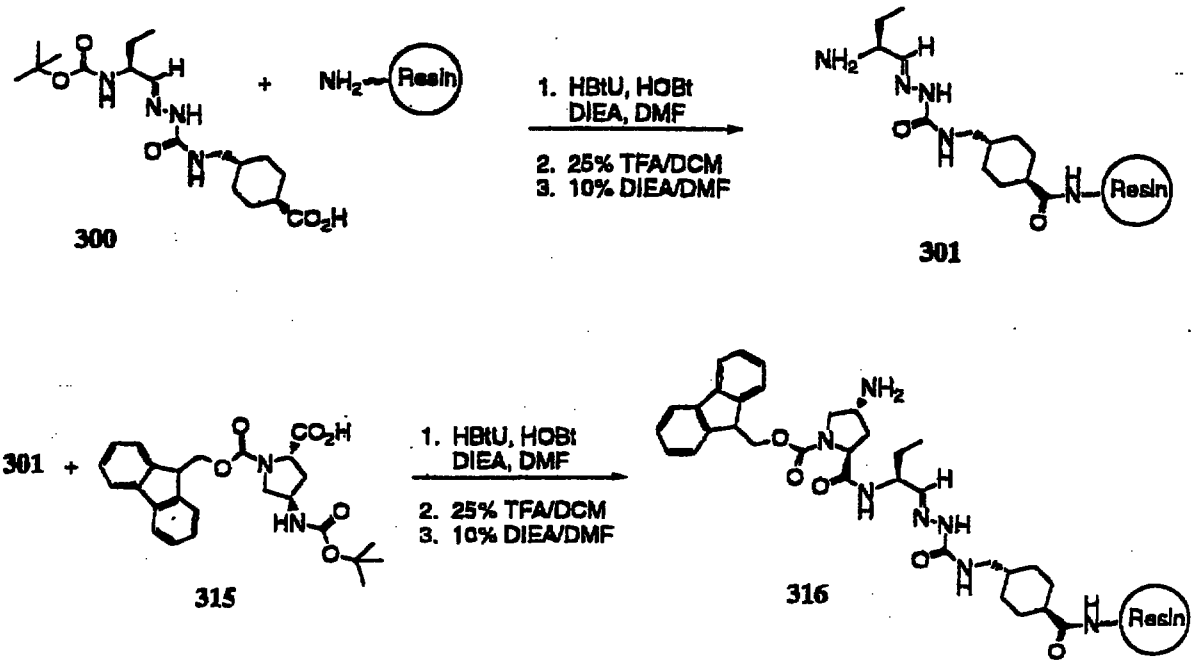
Step D. Synthesis of 313. See Step D, Scheme 2 methodology.

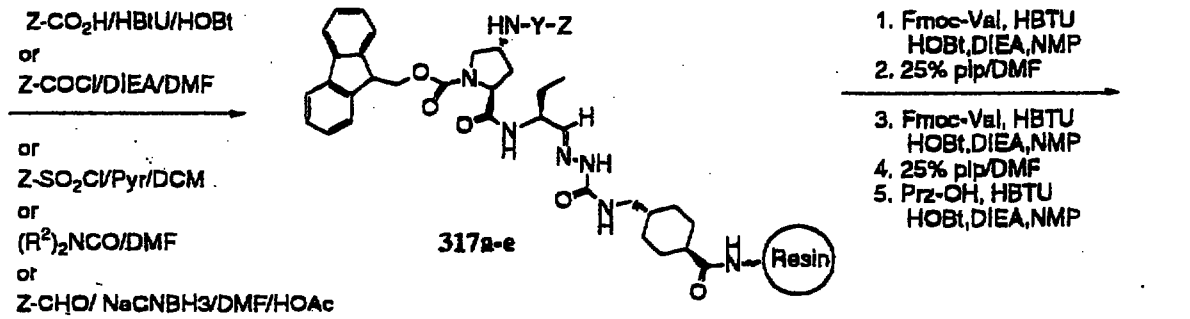
Step E. Synthesis of 314. See Step E, Scheme 2 methodology.

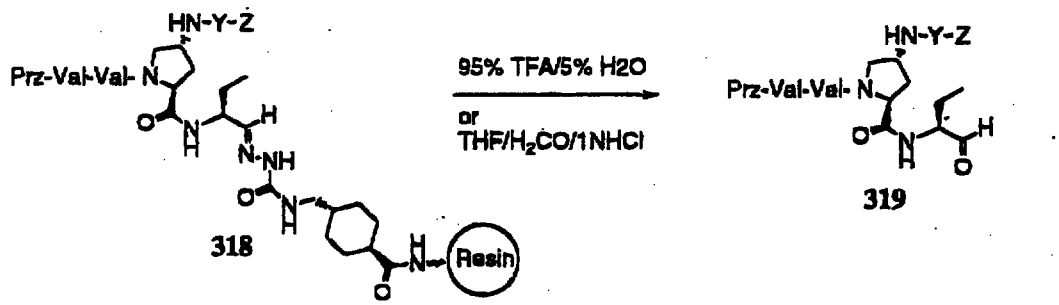
Example 5

Compounds 57-70 (Table 1) were prepared as described in scheme 4.

SCHEME 4


300
1. HBtU, HOBt
DIEA, DMF
2. 25% TFA/DCM
3. 10% DIEA/DMF
301
315
316
Resin


Z-CO2H/HBtU/HOBt
or
Z-COCl/DIEA/DMF
or
Z-SO2Cl/Pyr/DCM
or
(R2)2NCO/DMF
or
Z-CHO/ NaCNBH3/DMF/HOAc
317a-e
1. Fmoc-Val, HBTU
HOBt,DIEA,NMP
2. 25% pip/DMF
3. Fmoc-Val, HBTU
HOBt,DIEA,NMP
4. 25% pip/DMF
5. Prz-OH, HBTU
HOBt,DIEA,NMP


Prz-Val-Val-
95% TFA/5% H2O
or
THF/H2CO/1NHCl
318
319

Step A. Synthesis of 301. See Step A, Scheme 1 methodology.

Step B. Synthesis of 316. This compound was prepared from resin **301** (0.05 mmol) using an Advanced ChemTech 396 Multiple Peptide synthesizer. Resin **301** was acylated with a solution of 0.4M **315** and 0.4M HOBT in N-methypyrrolidone (0.5 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methypyrrolidone (0.35 mL) and the reaction was shaken for 4 hr at room temperature. The coupling reaction was repeated. The resin was then washed with dimethylformamide (3 X 1 ml), followed by dichloromethane (3 X 1 mL). The Boc protecting group was then cleaved with 50% (v/v) TFA/dichloromethane (1.0 mL) for 10 min with vortexing and then for 30 min with fresh reagent (1.0 ml). The resin was then washed with dichloromethane (3 X 1.0 ml), dimethylformamide (2 X 1.0 mL), 10% DIEA/dimethylformamide (v/v) (2 X 1.0 mL), dimethylformamide (3 X 1.0 ml), and finally dichloromethane (3 X 1.0 mL) to yield **316**.

Step C. Synthesis of 317a. Resin **316** was acylated with a solution of 0.4M **Z-CO_2H** and 0.4M HOBT in N-methypyrrolidone (0.5 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methypyrrolidone (0.35 mL) and the reaction was shaken for 4 hr at room temperature. The coupling reaction was repeated. The resin was then washed with dimethylformamide (3 X 1 ml) to yield resin **317a**.

Step C. Synthesis of 317b. Resin **316** was acylated with 0.5M **Z-COCl** in dimethylformamide (1 mL) and 1.6M DIEA in N-methypyrrolidone (0.35 mL) for 2 hr at room

temperature. The acylation step was repeated. The resin was washed with dimethylformamide (3 X 2.5 mL)to yield resin **317b**.

Step C. Synthesis of 317c. Resin **316** was reacted with 1.0M **Z-sulfonyl chloride** in dichloromethane (0.5 mL) and 1M pyridine in dichloromethane (0.60 mL) for 4 hr at room temperature The reaction was repeated. The resin was washed with dichloromethane (3 X 1.0 mL), and then dimethylformamide (3 X 1.0 mL)to yield resin **317c**.

Step C. Synthesis of 317d. Resin **316** was reacted with 0.5M **Z-isocyanate** in dimethylformamide (1.2 mL) for 8 hr at room temperature The reaction was repeated. The resin was washed with dimethylformamide (3 X 1.0 mL)to yield resin **317d**.

Step C. Synthesis of 317e. Resin **316** was reacted with 0.5M **Z-CHO** in dimethylformamide (1.2 mL) in the presence of acetic acid (0.1 mL) and sodium cyanoborohydride (200 mg) for 4 hr at room temperature. The reaction was repeated. The resin was washed with dimethylformamide (3 x 1.0 mL) to yield resin **317e**.

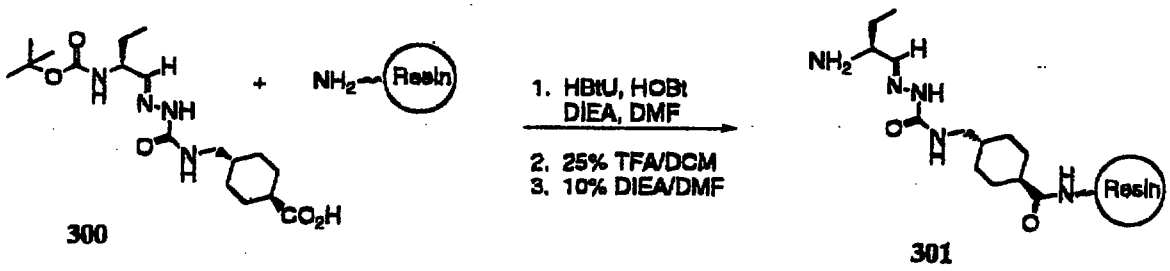
Step D. Synthesis of 318. The synthesis of the resin-bound compound was completed using an Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles described in Step C, Scheme 1, were used to add Fmoc-Valine, followed by another Fmoc-Valine, and finally pyrazine-2-carboxylic acid.

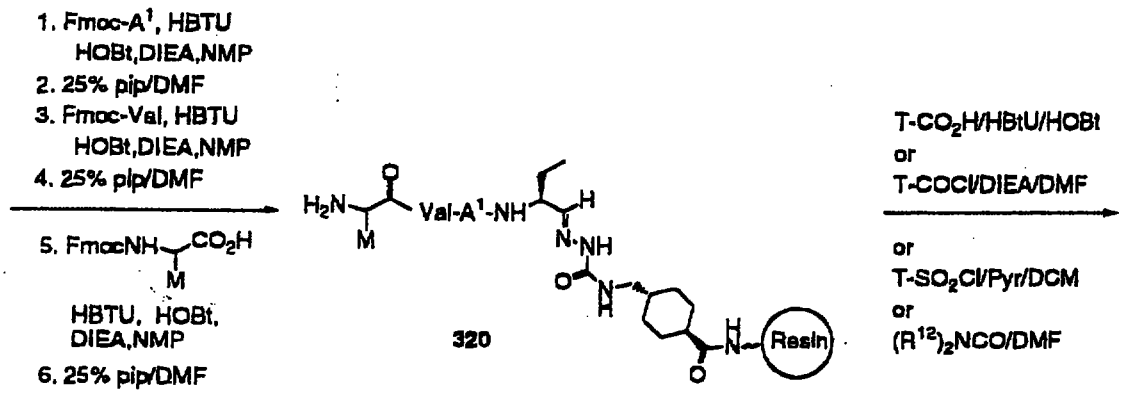
Step E. Synthesis of 319. See Step E, Scheme 2 methodology.

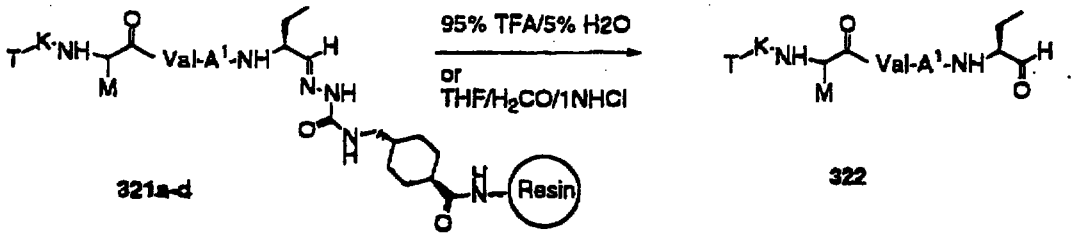
Example 6

Compounds 81-100 and 127-142 (Tables 3 and 4) were prepared as described in scheme 5.

SCHEME 5


1. HBtU, HOBt
DIEA, DMF
2. 25% TFA/DCM
3. 10% DIEA/DMF
Resin
300
301


1. Fmoc-A1, HBTU
HOBt,DIEA,NMP
2. 25% pip/DMF
3. Fmoc-Val, HBTU
HOBt,DIEA,NMP
4. 25% pip/DMF
5. FmocNH
HBTU, HOBt,
DIEA,NMP
6. 25% pip/DMF
Val-A1-NH
Resin
320
T-CO2H/HBtU/HOBt
or
T-COCl/DIEA/DMF
or
T-SO2Cl/Pyr/DCM
or
(R12)2NCO/DMF


95% TFA/5% H2O
or
THF/H2CO/1NHCl
Val-A1-NH
Resin
321a-d
322

Step A. Synthesis of 301. See Step A, Scheme 1 methodology.

Step B. Synthesis of 320. The synthesis of the resin-bound compound was accomplished using an Advanced ChemTech 396 Multiple Peptide synthesizer starting with resin **165** (0.05 mmol). The automated cycles described in Step C, Scheme 1, were used to add **Fmoc-A^1**, followed by **Fmoc-valine** and finally a terminal **Fmoc-amino acid.** The Fmoc group was removed as previously described with 25% piperidine/dimethylformamide (v:v) to yield resin **166.**

Step C. Synthesis of 321a. Resin **320** was acylated with a solution of 0.4M **T-CO_2H** and 0.4M HOBT in N-methypyrrolidone (0.5 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methypyrrolidone (0.35 mL) and the reaction was shaken for 4 hr at room temperature. The coupling reaction was repeated. The resin was then washed with dimethylformamide (3 X 1 ml), dichloromethane (3 X 1.0 mL), and 1:1 dichloromethane/methanol (v/v) (3 X 1 mL) to yield resin **321a.**

Step C. Synthesis of 321b. Resin **320** was acylated with 0.5M **T-COCl** in dimethylformamide (1 mL) and 1.6M DIEA in N-methypyrrolidone (0.35 mL) for 2 hr at room temperature. The acylation step was repeated. The resin was then washed with dimethylformamide (3 X 1 ml), dichloromethane (3 X 1.0 mL), and 1:1 dichloromethane/methanol (v/v) (3 X 1 mL) to yield resin **321b.**

Step C. Synthesis of 321c. Resin **320** was reacted with 1.0M **T-sulfonyl chloride** in dichloromethane (0.5 mL) and

1M pyridine in dichloromethane (0.60 mL) for 4 hr at room temperature The reaction was repeated. The resin was then washed with dimethylformamide (3 X 1.0 ml), dichloromethane (3 X 1.0 mL), and 1:1 dichloromethane/methanol (v/v) (3 X 1.0 mL) to yield resin **303c**.

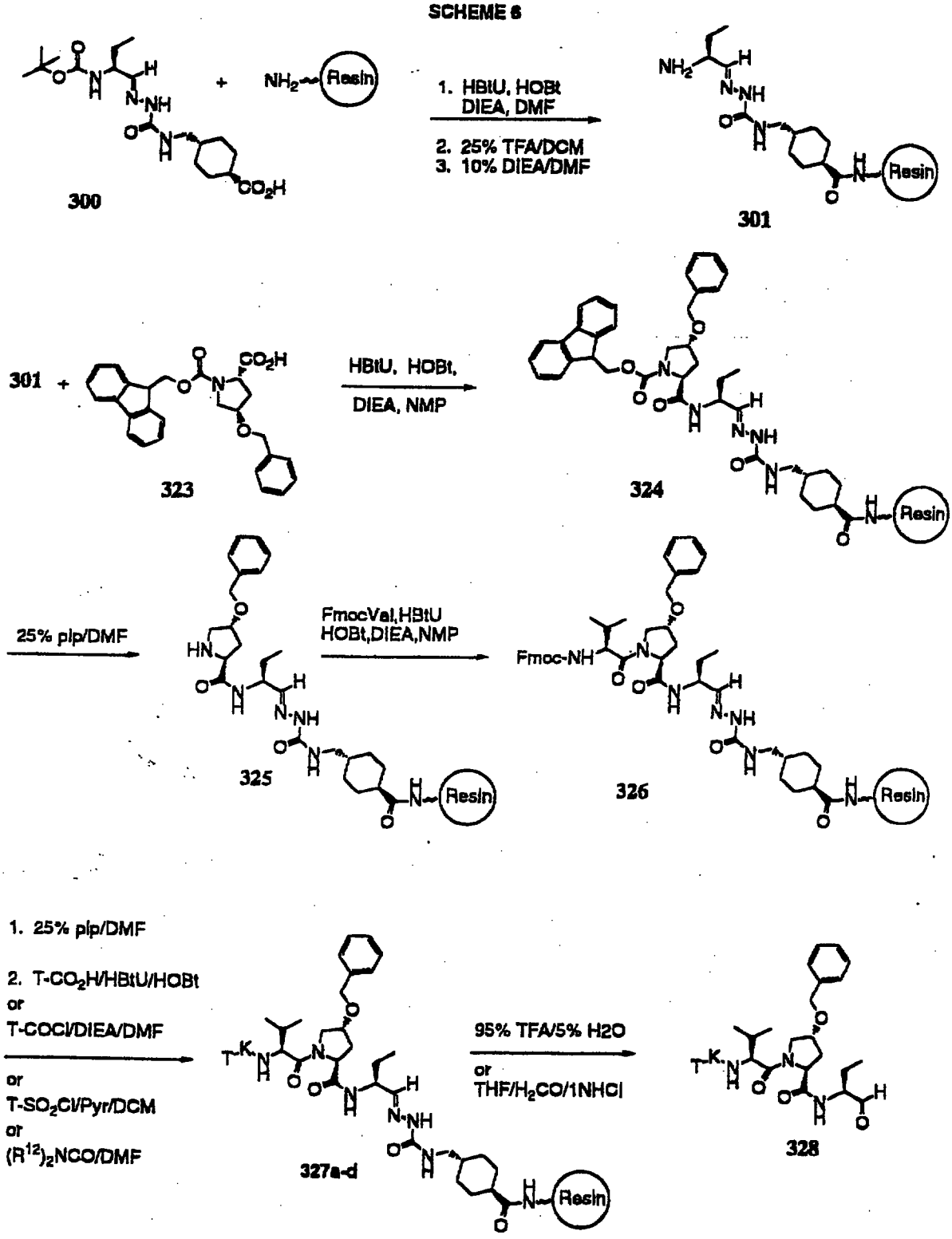
Step C. Synthesis of 321d. Resin **320** was reacted with 0.5M **T-isocyanate** in dimethylformamide (1.2 mL) for 8 hr at room temperature The reaction was repeated. The resin was then washed with dimethylformamide (3 X 1.0 ml), dichloromethane (3 X 1.0 mL), and 1:1 dichloromethane/methanol (v/v) (3 X 1.0 mL) to yield resin **321d**.

Step D. Synthesis of 322. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/5% H_2O (v/v, 1.5 mL) for 45 min at room temperature. After washing the resin with fresh cleavage reagent (1 mL), the combined filtrates were added to cold 1:1 ether:pentane (12 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% acetonitrile/90% H_2O/0.1% TFA (15 mL) and lyophilized to obtain crude **322** as a white powder. The compound was purified by semi-prep RP-HPLC with a Waters DeltaPak 300 Å C18 column (15 µ, 30 X 300 mm) eluting with a linear acetonitrile gradient containing 0.1% TFA (v/v) over 45 min at 20 mL/min. Fractions containing the desired product were pooled and lyophilized to provide **322**.

Example 7

Compounds 143-197 (Table 6) were prepared as described in scheme 6.

SCHEME 6


300
1. HBtU, HOBt
DIEA, DMF
2. 25% TFA/DCM
3. 10% DIEA/DMF
301
HBtU, HOBt,
DIEA, NMP
323
324
25% pip/DMF
FmocVal,HBtU
HOBt,DIEA,NMP
325
326
1. 25% pip/DMF
2. T-CO2H/HBtU/HOBt
or
T-COCl/DIEA/DMF
or
T-SO2Cl/Pyr/DCM
or
(R12)2NCO/DMF
327a-d
95% TFA/5% H2O
or
THF/H2CO/1NHCl
328
Resin

Step A. Synthesis of 301. See Step A, Scheme 1 methodology.

Step B. Synthesis of 326. This compound was prepared from resin **301** (0.50 mmol) using an Applied Biosystems Model 433A Peptide synthesizer. N^{α}-Fmoc-protected amino acids were added sequentially to resin **301** with standard coupling cycles using HBTU with HOBt as coupling agents in N-methylpyrrolidinone to yield resin **326**.

Step C. Synthesis of 327a. The synthesis was completed using an Advanced ChemTech 396 Multiple Peptide Synthesizer. Resin **326** (0.05 mmol) was deprotected with 25% (v/v) piperidine in dimethylformamide (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min. The resin was washed with dimethylformamide (3 X 1 mL) and N-methypyrrolidone (3 X 1 mL). The resin was acylated with a solution of 0.4M **T-CO_2H** and 0.4M HOBT in N-methypyrrolidone (0.5 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methypyrrolidone (0.35 mL) and the reaction was shaken for 4 hr at room temperature. The coupling reaction was repeated. The resin was then washed with dimethylformamide (3 X 1 ml), dichloromethane (3 X 1.0 mL), and 1:1 dichloromethane/methanol (v/v) (3 X 1 mL) to yield resin **327a**.

Step C. Synthesis of 327b. The synthesis was completed using an Advanced ChemTech 396 Multiple Peptide Synthesizer. Resin **326** (0.05 mmol) was deprotected with 25% (v/v) piperidine in dimethylformamide (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min. The resin was washed with dimethylformamide (3 X 1 mL) and N-methypyrrolidone (3 X 1 mL). The resin was acylated with 0.5M **T-COCl** in dimethylformamide (1 mL) and 1.6M DIEA in

N-methypyrrolidone (0.35 mL) for 2 hr at room temperature. The acylation step was repeated. The resin was then washed with dimethylformamide (3 X 1 ml), dichloromethane (3 X 1.0 mL), and 1:1 dichloromethane/methanol (v/v) (3 X 1 mL) to yield resin **327b**.

Step C. Synthesis of 327c. The synthesis was completed using an Advanced ChemTech 396 Multiple Peptide Synthesizer. Resin **326** (0.05 mmol) was deprotected with 25% (v/v) piperidine in dimethylformamide (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min. The resin was washed with dimethylformamide (3 X 1 mL) and dichloromethane (3 X 1 mL). The resin was reacted with 1.0M **T-sulfonyl chloride** in dichloromethane (0.5 mL) and 1M pyridine in dichloromethane (0.60 mL) for 4 hr at room temperature The reaction was repeated. The resin was then washed with dimethylformamide (3 X 1.0 ml), dichloromethane (3 X 1.0 mL), and 1:1 dichloromethane/methanol (v/v) (3 X 1.0 mL) to yield resin **327c**.

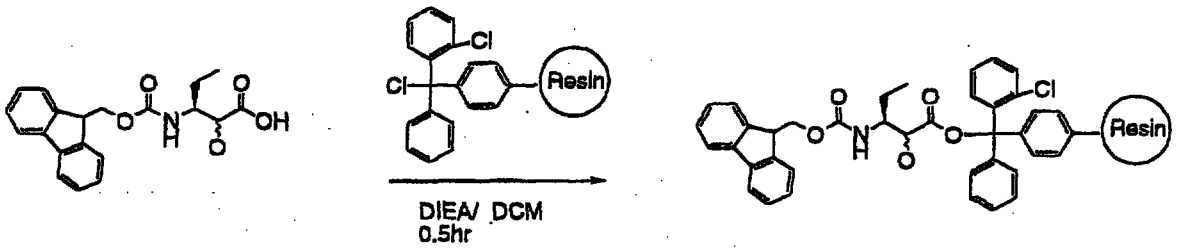
Step C. Synthesis of 327d. The synthesis was completed using an Advanced ChemTech 396 Multiple Peptide Synthesizer. Resin **326** (0.05 mmol) was deprotected with 25% (v/v) piperidine in dimethylformamide (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min. The resin was washed with dimethylformamide (3 X 1 mL). The resin was reacted with 0.5M **T-isocyanate** in dimethylformamide (1.2 mL) for 8 hr at room temperature The reaction was repeated. The resin was then washed with dimethylformamide (3 X 1.0 ml), dichloromethane (3 X 1.0 mL), and 1:1 dichloromethane/methanol (v/v) (3 X 1.0 mL) to yield resin **327d**.

Step D. Synthesis of 328. See Step D, Scheme 1 methodology.

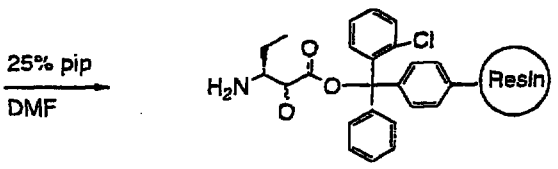
Example 8

Compounds 79-80 and 101-123 (Tables 2, 3 and 4) were prepared as described in scheme 7.

SCHEME 7

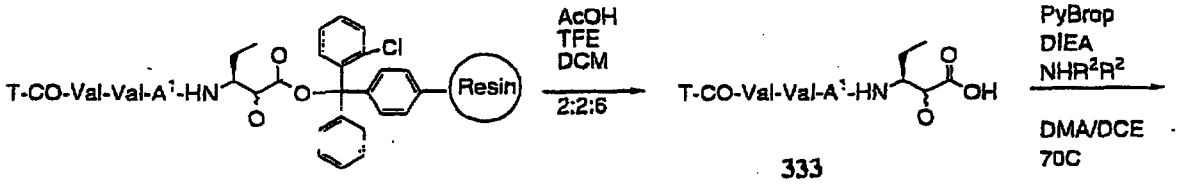


329 330

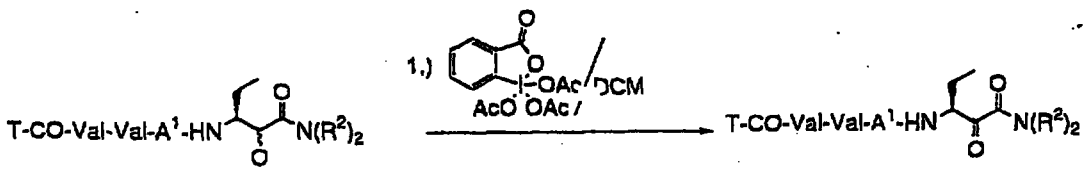


331

1. Fmoc-A^1, HBTU HOBt,DIEA,NMP
2. 25% pip/DMF
3. Fmoc-Val, HBTU HOBt,DIEA,NMP
4. 25% pip/DMF
5. Fmoc-Val, HBTU HOBt,DIEA,NMP
6. 25% pip/DMF
7. Cap with T-CO_2H



332 333



334 335

Step A. Synthesis of 330. 2-Chlorochlorotrityl resin (2.2 mmol/g, 1.69 g) was reacted with **329** (0.385 g, 1.1 mmol, prepared according to S. L. Harbeson et. al. J. Med. Chem., 37, 2918 (1994)) in dichloromethane in the presence of DIEA (0.47 mL, 2.7 mmol) at room temperature for 1 hour. The reaction was quenched by the addition of methanol and the resin was isolated on a sintered glass funnel by suction filtration and washed with dichloromethane (3 X 25 mL). The resin was dried overnight *in vacuo* to yield **330** (1.92 g, 0.49 meq/g).

Step B. Synthesis of 332. The synthesis of the resin-bound compound was accomplished using an Applied Biosystems Model 433A Peptide synthesizer starting with resin **330** (0.74 mmol). The automated cycles described in Step C, Scheme 1, were used to add **Fmoc-A^1**, followed by **Fmoc-A^2** and **Fmoc-A^3** . The Fmoc group was removed as previously described with 25% piperidine/dimethylformamide (v:v) to yield resin **332**.

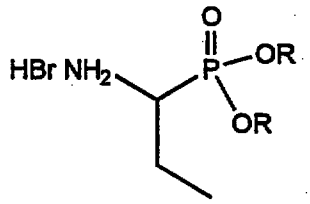
Step C. Synthesis of 333. Prior to cleavage, the resin was washed with 1:1 dichloromethane/methanol (3 X 1 mL) and then dried *in vacuo*. The peptide was cleaved from the resin by treatment with acetic acid: trifluoroethanol: dichloromethane (1:1:3) for 1 hr at room temperature. After washing the resin with dichloromethane, the combined filtrates were concentrated *in vacuo* to obtain crude **333** as a white powder (0.48 g, 76%).

Step D. Synthesis of 335. Compound **333** (0.05 g, 0.058 mmol) was dissolved in dimethylacetamide (1 mL) and to this was added DIEA (0.17 mmol), the appropriate amine (0.20 mmol), and PyBrop (0.12 mmol). The reaction was stirred for 2 hr at 70°C. The reaction was then diluted

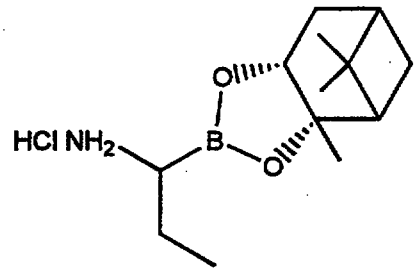
into H_2O(8 mL) followed by centrifugation to obtain the precipitate that was dried *in vacuo* to obtain crude **334**, which was then oxidized directly to compound **335**. Crude **334** was dissolved in N-methylpyrrolidone (3 mL) and reacted with Dess-Martin periodinane (110 mg, 0.26 mmol) at room temperature over night. Saturated aqueous sodium bicarbonate (5 mL) and 10% (w:v) aqueous sodium thiosulfate (5 mL) were added to the reaction and stirred prior to addition of H_2O (40 mL). The precipitate was isolated by centrifugation and the solid was dried *in vacuo*. When required, acid labile protecting groups were removed by treatment with 1:1 trifluoroacetic acid:dichloromethane at room temperature for 30 min. The solvent was removed in vacuo and the crude compound was purified by semi-prep RP-HPLC with a Waters DeltaPak 300 Å C18 column (15 μ, 30 X 300 mm) eluting with a linear acetonitrile gradient containing 0.1% TFA (v/v) over 45 min at 20 mL/min. Fractions containing the desired product were pooled and lyophilized to provide **335**.

Example 9

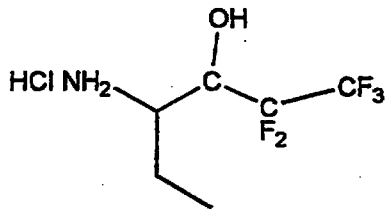
Compounds 71-78 and 124-126 were prepared from the appropriate protected peptide acids. Protected peptide acids were prepared as previously described in Scheme 7 using 2-Chloro-chlorotrityl resin. These peptide acids were then coupled to one of the following group using standard solution phase peptide coupling methodologies. The references for preparation of these groups are also given.



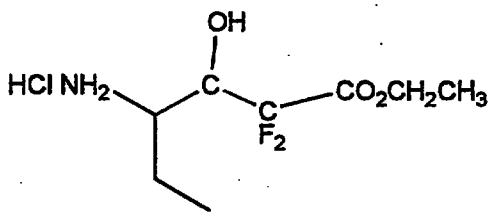
J. Oleksyszyn et. al., Synthesis, 985-986 (1979)



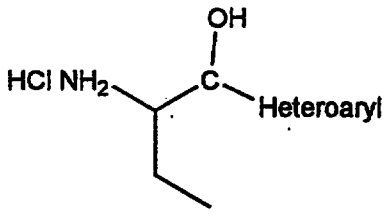
S. Elgendy et. al., Tetrahedron, 50, 3803-3812 (1994)



M. R. Angelestro et. al., Tetrahedron Letters, 33, 3265-3268 (1992)



T.T. Curran, J. Organic Chemistry, 58, 6360-6363 (1993)



E. Edwards, et. al., J. Medicinal Chemistry, 38, 3972-3982 (1995).

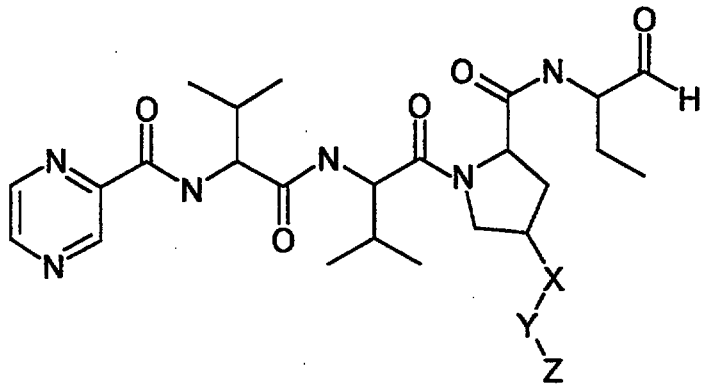
When required, the products obtained were oxidized to the ketones using Dess Martin Periodinane as described for Scheme 7. When required, acid labile protecting groups were removed by treatment with 1:1 trifluoroacetic

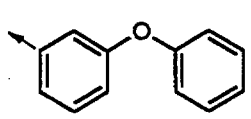
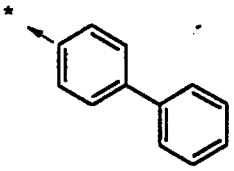
acid:dichloromethane at room temperature for 30 min. The solvent was removed in vacuo and the crude compound was purified by semi-prep RP-HPLC with a Waters DeltaPak 300 Å C18 column (15 μ, 30 X 300 mm) eluting with a linear acetonitrile gradient containing 0.1% TFA (v/v) over 45 min at 20 mL/min. Fractions containing the desired product were pooled and lyophilized to provide the final products 71-78 and 124-126.

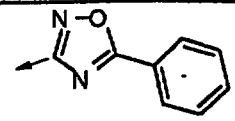
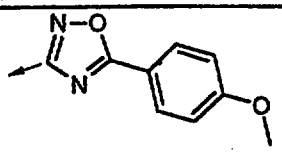
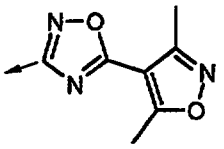
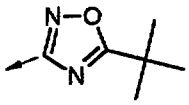
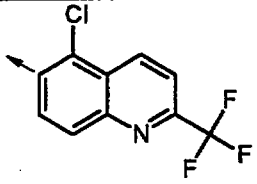
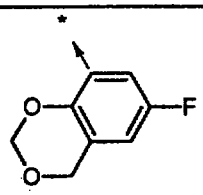
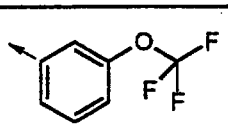
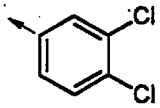
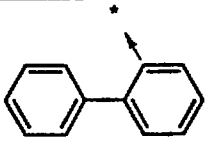
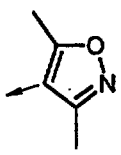
Example 10

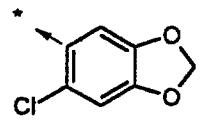
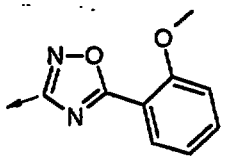
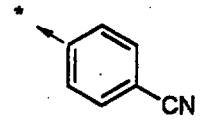
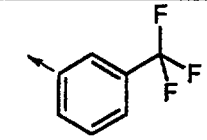
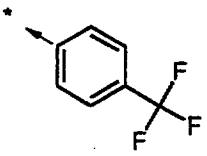
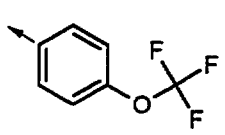
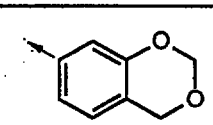
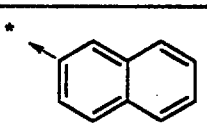
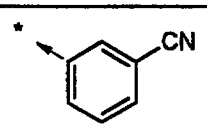
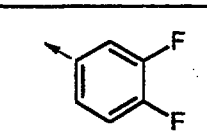
Compound 198 was prepared by modification of the general methodology described in Example 1.

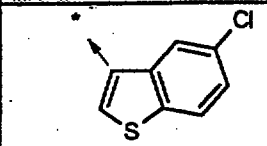
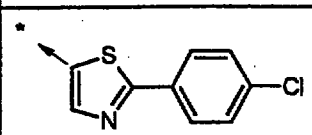
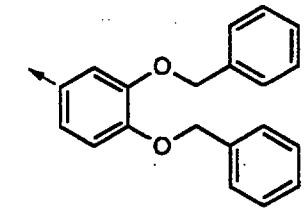
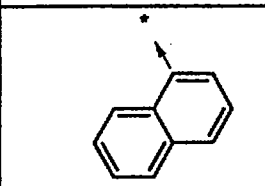
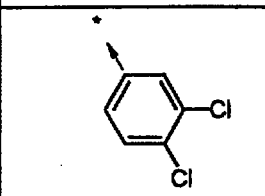
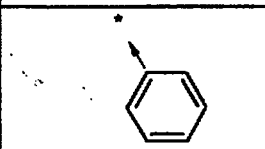
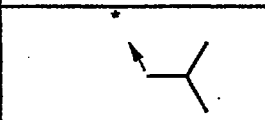
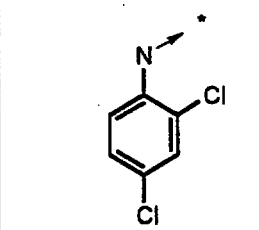
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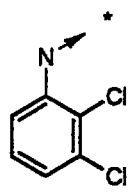
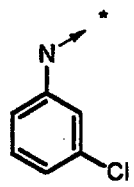
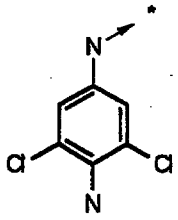
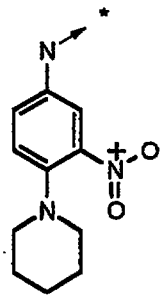
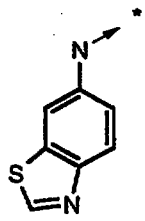
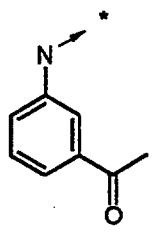


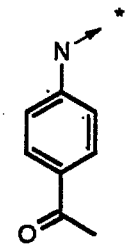
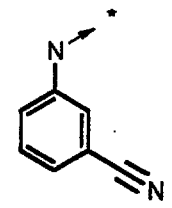
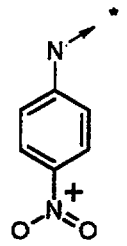
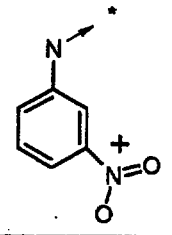
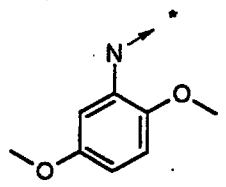
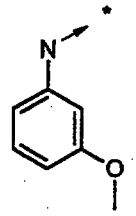
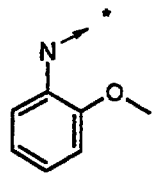
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2		O	CH_2	(M+Na)= 693.2	40-80%B; 5.376 min; 95%

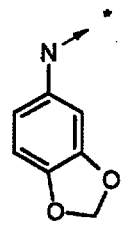
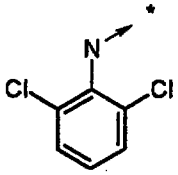
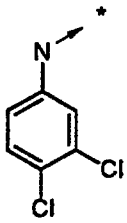
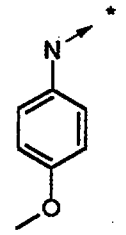
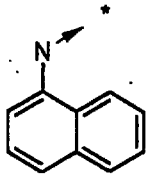
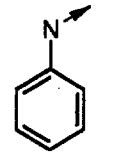
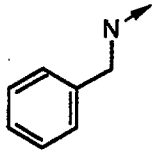
	Z	X	Y	MS Data	HPLC
3		O	CH_2	(M+H)= 664.0 (M+Na)= 685.2	20-60%B; 8.527 min.; 100%
4		O	CH_2	(M+Na)= 714.3	20-60%B; 8.885 min.; 100%
5		O	CH_2	(M+H)= 682.9 , (M+Na)= 704.0	20-60%B; 7.541 min.; 95.6%
6		O	CH_2	(M+H)= 644.0 , (M+Na)= 664.0	20-60%B; 7.822 min.; 100%
7		O	CH_2	(M+H)= 746.7 , (M+Na)= 765.7	40-80%B; 4.228 min.; 92%
8		O	CH_2	(M+H)= 671.5 , (M+Na)= 694.0	20-60%B; 8.554 min.; 98%
9		O	CH_2	(M+Na)= 700.9	40-80%B; 4.688 min.; 100%
10		O	CH_2	(M+Na)= 686.3	40-80%B; 4.630 min.; 94%
11		O	CH_2	(M+H)= 671.1, (M+Na)= 693.2	40-80%B; 5.323 min.; 6.435 min.; 88:12, fast:slow
12		O	CH_2	(M+H)= 613.7, (M+Na)= 636.2	20-60%B; 5.696 min.; 100%

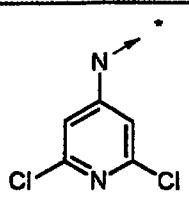
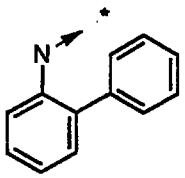
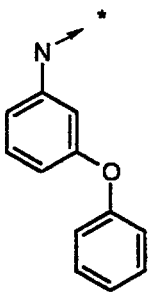
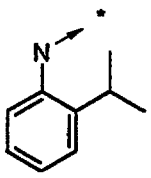
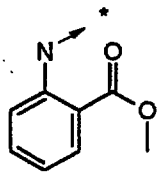
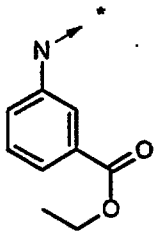
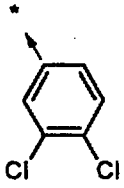
	Z	X	Y	MS Data	HPLC
13		O	CH_2	(M+Na)=695.3	20-60%B; 9.046 min.; 100%
14		O	CH_2	(M+Na)=714.9	20-60%B; 7.729 min.; 100%
15		O	CH_2	(M+Na)= 642.72	20-60%B; 7.133 min.; 100%
16		O	CH_2	(M+Na)= 685.6	20-60%B; 10.177 min.; 100%
17		O	CH_2	(M+Na)= 685.6	20-60%B; 10.265 min.; 100%
18		O	CH_2	(M+Na)= 700.9	20-60%B; 10.696 min.; 100%
19		O	CH_2	(M+Na)= 709.4	30-70%B; 9.216 min.; 100%
20		O	CH_2	(M+Na)= 667.3	20-60%B; 10.225 min; 100%
21		O	CH_2	(M+Na)= 641.8	20-60%B; 7.15 min.; 100%
22		O	CH_2	(M+Na)= 653.1	20-60%B; 8.822 min.; 100%

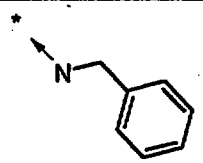
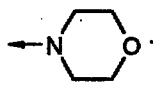
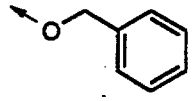
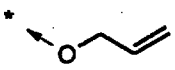
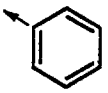
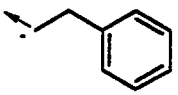
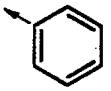
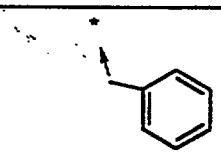
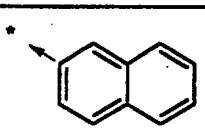
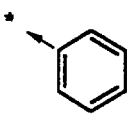
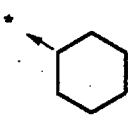
	Z	X	Y	MS Data	HPLC
23		O	CH_2	(M+Na)= 707.3	20-60%B; 11.362 min.; 100%
24		O	CH_2	(M+Na)= 733.9	20-60%B; 10.964 min.; 100%
25		O	CH_2	(M+Na)= 828.2	40-80%B; 7.040 min.; 100%
26		O	CH_2	(M+Na)= 667.5	30-70%B; 8.907 min.; 96%
27		O	C(O)	(M+H) = 677.3	10-60%B; 10.83 min; 80%
28		O	C(O)	(M+H) = 609.3	10-60%B; 9.65 min; 98%
29		O	C(O)	(M+H) = 589.6	10-60%B; 9.52 min; 98%
30		O	C(O)	(M+H) = 692.3	10-60% B; 11.52 min; 98% (slow RT); 10-60%B; 10.73 min; 90% (fast RT)

#	Z	X	Y	MS Data	HPLC
31		O	C(O)	(M+H) = 692.3	10-60%B; 11.21 min; 98% (slow RT); 10-60%B; 10.23 min; 98%
32		O	C(O)	(M+H) = 658.4	10-60% B; 10.72 min; 98%
33		O	C(O)	(M+H) = 707.48	10-60%B; 9.9 min; 98%
34		O	C(O)	(M+H) = 752.6	10-60%B; 10.37 min; 98%
35		O	C(O)	(M+H) = 681.5	10-60%B; 8.40 min; 98%
36		O	C(O)	(M+H) = 666.6	10-60%B; 8.57 min; 86%

	Z	X	Y	MS Data	HPLC
37		O	C(O)	(M+H) = 666.6	10-60%B; 8.70 min; 86%
38		O	C(O)	(M+H) = 649.6	10-60%; 9.44 min; 98%
39		O	C(O)	(M+H) = 669.6	10-60%B; 10.06 min; 94%
40		O	C(O)	(M+H) = 669.6	10-60%B; 11.0 min; 96% (slow RT); 10-60%B; 10.12 min; 98% (fast RT)
41		O	C(O)	(M+H) = 684.6	10-60%B; 9.81 min; 95%
42		O	C(O)	(M+H) = 654.6	10-60%B; 9.52 min; 98%
43		O	C(O)	(M+H) = 654.6	10-60%B; 9.73 min; 93%

	Z	X	Y	MS Data	HPLC
44		O	C(O)	(M+H) = 668.56	10-60%B; 8.35 min; 92%
45		O	C(O)	(M+Na) = 716.5	10-60%B; 8.86 min; 80%
46		O	C(O)	(M+Na) = 716.1	10-60%B; 11.26/11.58 min (1:7); 98%; 10-60%B; 11.27/11.56 min (2:1); 98%
47		O	C(O)	(M+Na) = 678.1	10-60%B; 8.33 min; 96%
48		O	C(O)	(M+Na) = 697.8	10-60%B; 9.73 min; 90%
49		O	C(O)	(M+Na) = 647.2	10-60%B; 8.59 min; 90%
50		O	C(O)	(M+Na) = 660.6	10-60%B; 8.36 min; 94%

	Z	X	Y	MS Data	HPLC
51		O	C(O)	(M+H) = 693.3	10-60%B; 9.42 min/10.37 min; 85%
52		O	C(O)	(M+H) = 700.4	10-60%B; 10.59 min; 98%
53		O	C(O)	(M+H) = 716.3	10-60%B; 11.24/12.18 min; 95%
54		O	C(O)	(M+H) = 666.4	10-60%B; 9.97 min; 98%
55		O	C(O)	(M+H) = 682.3	10-60%B; 9.89 min; 98%
56		O	C(O)	(M+H) = 696.3	10-60%B; 10.34 min; 98%
57		NH	C(O)	(M+H) = 676.31	20-60%B; 9.023 min.; 100%

	Z	X	Y	MS Data	HPLC
58		NH	C(O)	(M+H)= 637.5	20-80%B; 5.152 min.; 100%
59		NH	C(O)	(M+H)= 617.5	20-80%B; 3.216 min.; 100%
60		NH	C(O)	(M+H)= 638.5	20-80%B; 6.221 min.; 100%
61		NH	C(O)	(M+H)= 588.4	20-80%B; 4.503 min.; 100%
62		NH	C(O)	(M+H)= 608.5	20-80%B; 5.055 min.; 100%
63		NH	C(O)	(M+H)= 636.5	20-80%B; 5.697 min.; 100%
64		NH	C(O) C(O)	(M+H)= 636.5	20-80%B; 5.548 min.; 100%
65		NH	$S(O)_2$	(M+H)= 658.4	20-80%B; 5.632 min.; 100%
66		NH	C(O)	(M+H)= 658.5	20-80%B; 6.690 min.; 100%
67		NH	CH_2	(M+H)= 594.5	20-80%B; 5.114 min.; 100%
68		NH	C(O)	(M+H)= 614.5	20-80%B; 5.559 min.; 100%

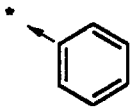
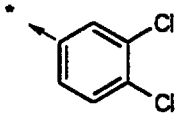
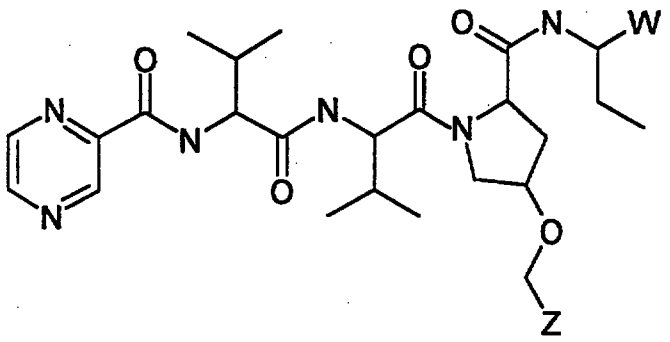
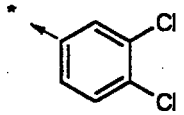
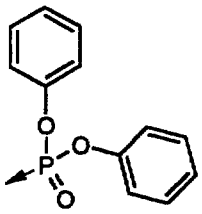
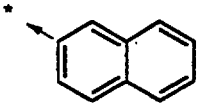
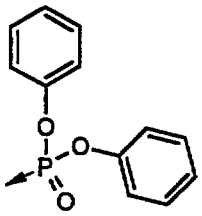
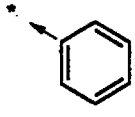
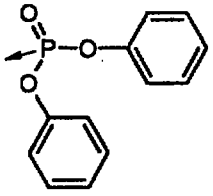
	Z	X	Y	MS Data	HPLC
69		O	CH_2	(M+H)=560.4	20-80%B; 8.062 min.; 100%
70		O	CH_2	(M+H)= 628.3	20-80%B; 9.990 min.; 100%

Table 2 Structures and analytical data - compounds 71-79



	Z	W	MS Data	HPLC
71			(M+H)= 869.3	40-80%B; 8.812:8.920 min.; 2:1 mix at Abu; 100%
72			(M+H)= 849.4	40-80%B; 8.380:8.539 min.; 2:1 mix at Abu; 100%
73			(M+H)= 799.5	20-60%B; 12.519 min.; 95%

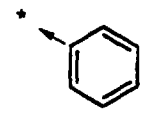
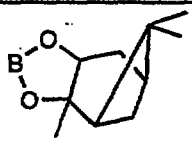
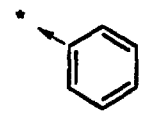
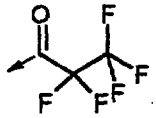
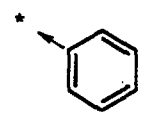
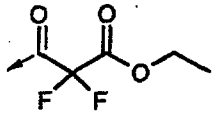
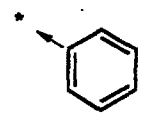
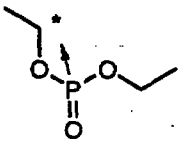
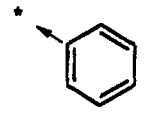
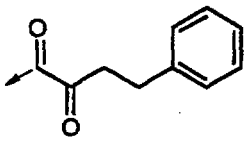
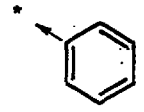
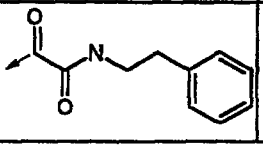
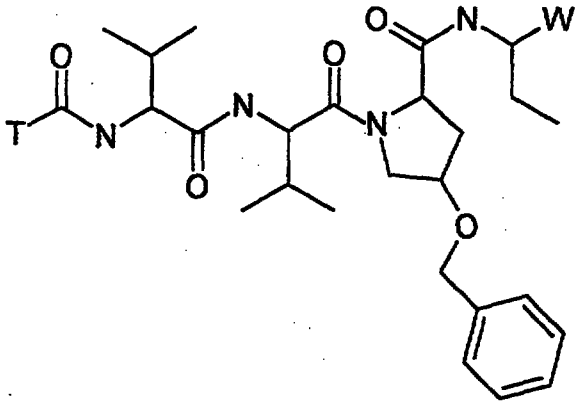
	Z	W	MS Data	HPLC
74			(M+H)= 716	15.62 min.; >95%
75			(M+H)=713	13.47 min.
76			(M+H)=717	13.05 min.; >90%
77			(M+H)= 703	10-90%B; 8.5 min.; 8.6 min (2:1); >95%
78			(M+H)= 727	8.7 min.; 10 min. (2:1); 95%
79			(M+H)= 743	10-80%B; 5.4 min.; 95%

Table 3 Structures and analytical data - compounds 80-88



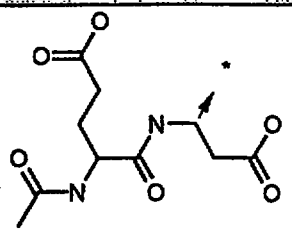
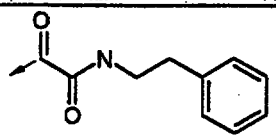
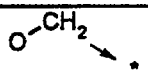
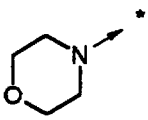
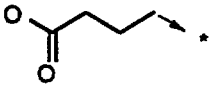
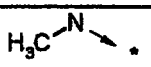
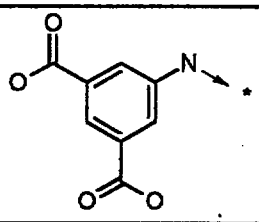
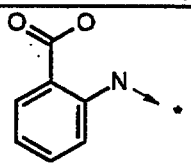
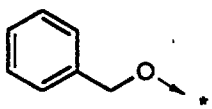
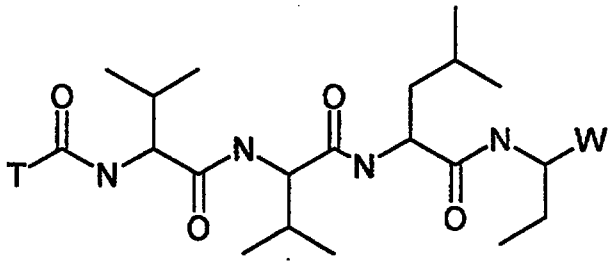
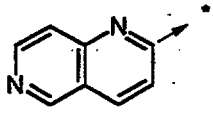
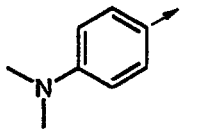
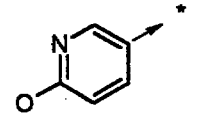
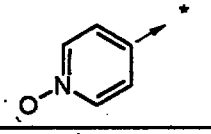
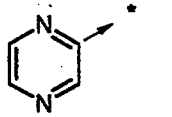
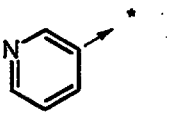
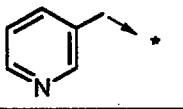
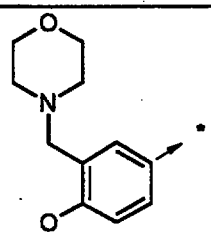
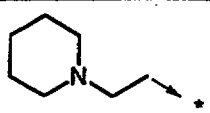
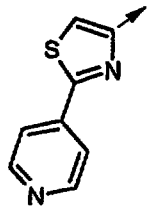
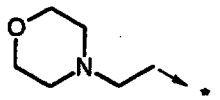
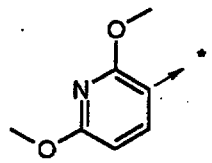
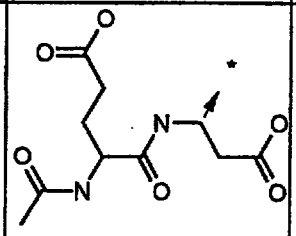
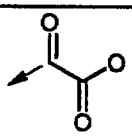
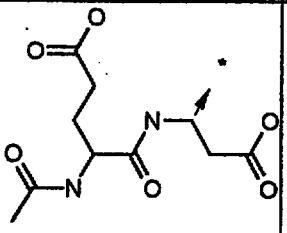
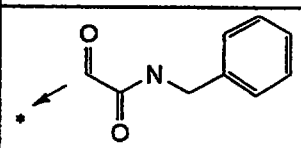
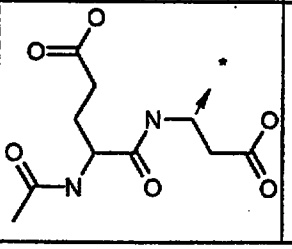
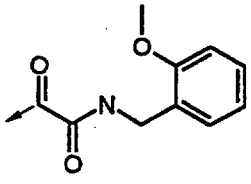
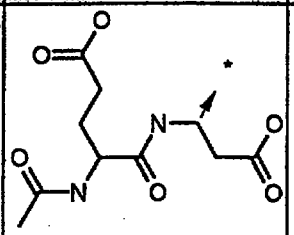
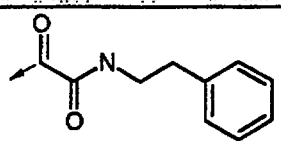
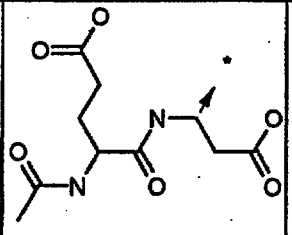
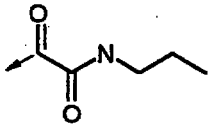
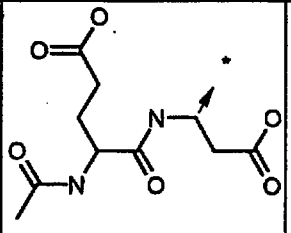
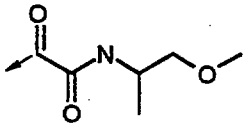
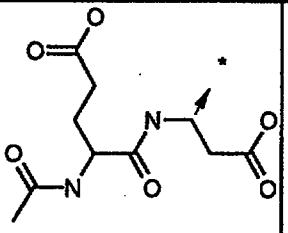
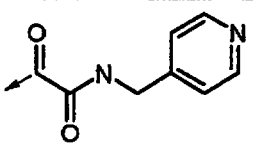
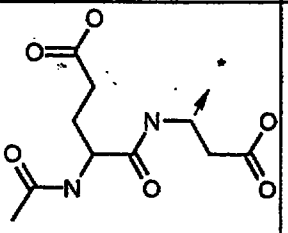
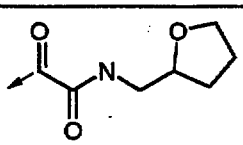
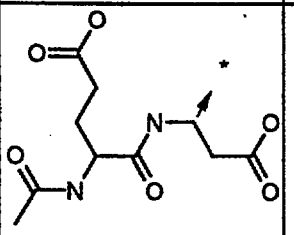
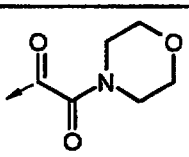
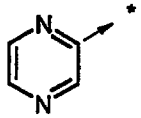
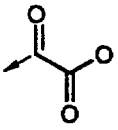
	T	W	MS Data	HPLC
80			(M+H)= 947	20-70%B; 6.15 min.; 95%
81		C(O)H	(M+Na)= 553.60	5-45%B; 11.699 min.; 100%
82		C(O)H	(M+H)= 547.4	5-45%B; 11.083 min.; 100%
83		C(O)H	(M+Na)= 625.3	5-45%B; 12.258 min.; 100%
84		C(O)H	(M+Na)= 626.5	5-45%B; 11.083 min.; 100%
85		C(O)H	(M+Na)= 569.5	5-45%B; 11.606 min.; 100%
86		C(O)H	(M+Na)= 717.2	5-45%B; 7.942 min.; 100%
87		C(O)H	(M+H)= 655.3	15-55%B; 10.735 min.; 100%
88		C(O)H	(M+Na)= 644.1	20-60%B; 11.360 min.; 98%

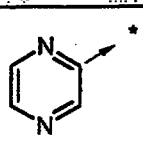
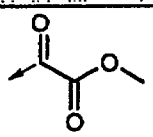
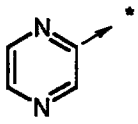
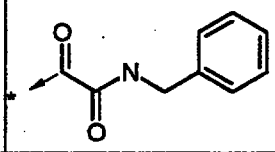
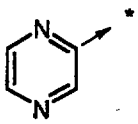
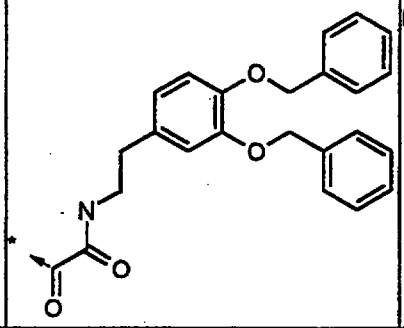
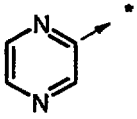
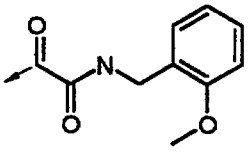
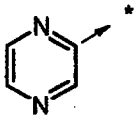
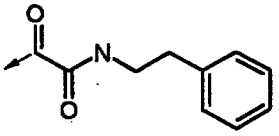
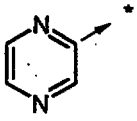
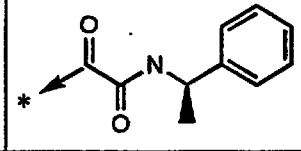
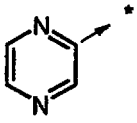
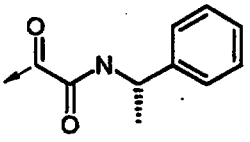
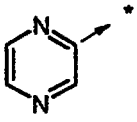
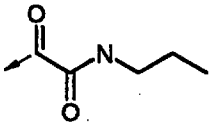
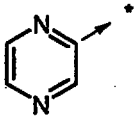
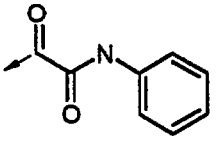
Table 4 Structures and analytical data - compounds 89-126



	T	W	MS Data	HPLC
89		C(O)H	(M+H)= 555.9	5-45% B; 10.771 min.; 99%
90		C(O)H	(M+H)= 556.0	5-45% B; 13.055 min.;95%
91		C(O)H	(M+H)= 522.4	5-45%B; 9.485 min.; 97%
92		C(O)H	(M+H)= 522.55	5-45%B; 9.072 min.; 100%
93		C(O)H	(M+H)= 506.33	5-45%B; 11.775 min.; 97%
94		C(O)H	(M+Na)= 526.6	5-45%B; 8.822 min.; 100%
95		C(O)H	(M+H)= 518.	5-45%B; 8.484 min.; 100%
96		C(O)H	(M+H)= 619.6	5-45%B; 9.944 min.; 90%

	T	W	MS Data	HPLC
97		C(O)H	(M+H)= 538.7	5-45%B; 9.099 min.; 100%
98		C(O)H	(M+H)= 588.6	5-45%B; 10.388 min.; 95%
99		C(O)H	(M+H)= 541.1	5-45%B; 8.326 min.; 100%
100		C(O)H	(M+Na)= 587.3	35-75%B; 6.763 min.; 95%
101			(M+H)= 729	10-80%B; 3.0 min; 95%
102			(M+H)= 819; (M+Na)= 840	20-70%B; 6.9 min; 95%
103			(M+H)=848; (M+Na)= 870	20-70%B; 6.3 min; 95%

	T	W	MS Data	HPLC
104			(M+H)= 833	20-70%B; 7.3 min; 95%
105			(M+H)=770; (M+Na)=792	20-70%B; 6.0 min; 95%
106			(M+H)= 801; (M+Na)= 822	20-70%; 5.9 min; 95%
107			(M+H)=819; (M+Na)= 841	20-70%B; 3.24 min; 95%
108			(M+H)=812; (M+Na)=834	20-70%B; 4.9 min; 95%
109			(M+H)=798; (M+Na)=820	20-70%B; 4.21 min; 95%
110			(M+H)= 550	10-40%B; 7.0 min; 95%

	T	W	MS Data	HPLC
111			(M+Na)= 886	10-50%B; 7.5 min; 95%
112			(M+H)= 638	10-80%B; 6.5 min; 95%
113			(M+H)= 865	40-80%B; 5.7 min; 95%
114			(M+H)= 669; (M+Na)= 693	25-40%B; 11.6 min; 95%
115			(M+H)= 653	10-80%B; 6.80 min; 95%
116			(M+H)= 653	10-80%B; 6.7 min; 95%
117			(M+H)= 653	10-80%B; 6.7 min; 95%
118			(M+Na)= 611	10-80%B; 5.62 min; 95%
119			(M+H)= 624	10-80%B; 12.1 min; 95%

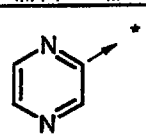
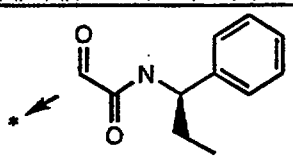
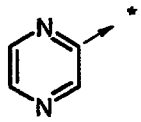
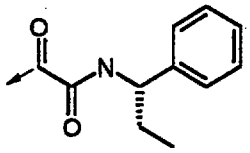
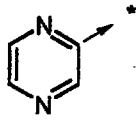
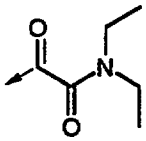
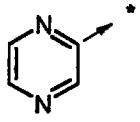
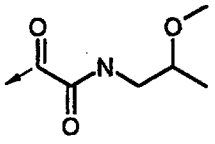
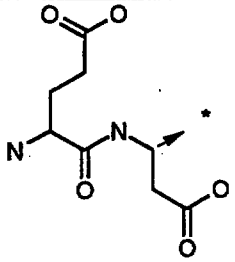
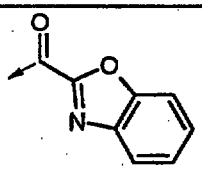
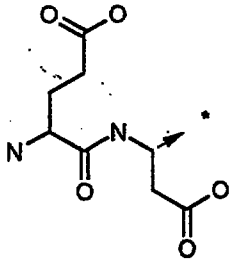
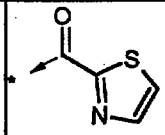
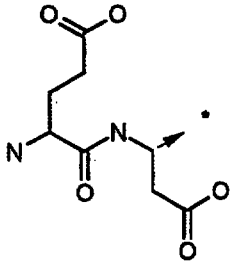
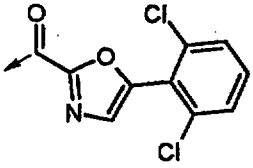
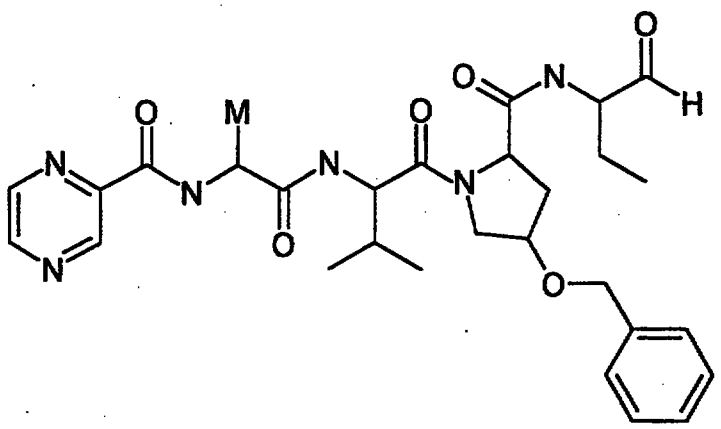
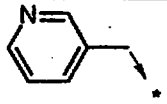
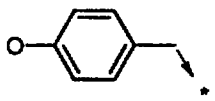
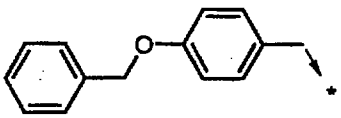
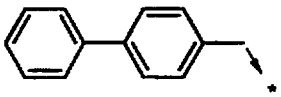
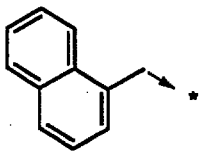
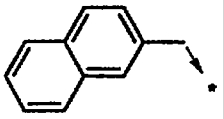
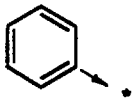
	T	W	MS Data	HPLC
120			(M+H)= 667	10-80%B; 13.4 min; 95%
121			(M+H)= 667	10-80%B; 13.3 min; 95%
122			(M+H)= 605	10-80%B; 11.0 min; 95%
123			(M+H)= 621	10-80%B; 9.7 min; 95%
124			(M+H)= 761	13.65 min.; 90%
125			(M+H)= 727	ND
126			(M+H)= 856	ND

Table 5 Structures and analytical data - compounds 127-142



	M	MS Data	HPLC
127		(M+H)= 644.30	15-55%B; 6.08 min; 100%
128		(M+H)= 681.3	20-60%B; 8.11 min; 100%
129		(M+H)= 750.6	30-70%B; 6.99 min; 100%
130		(M+H)= 720.2	30-70%B; 6.71 min; 100%
131		(M+Na)= 715.4	30-70%B; 5.64 min; 100%
132		(M+Na)= 715.2	30-70%B; 5.58 min; 100%
133		(M+H)= 630.9	30-70%B; 3.78 min; 100%

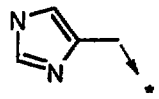
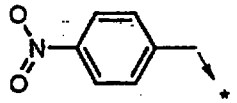
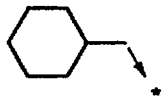
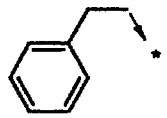
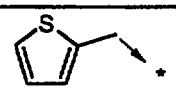
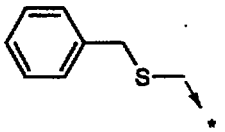
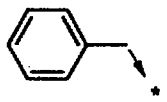
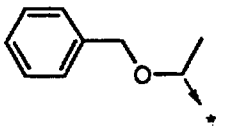
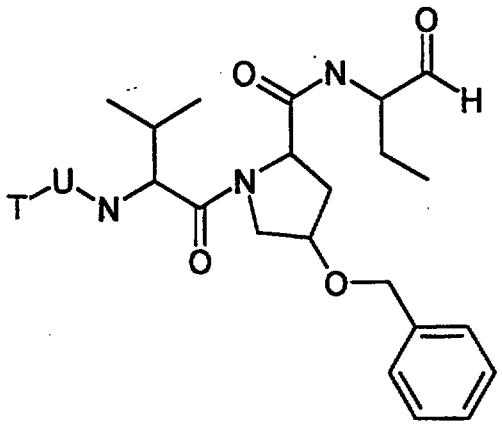
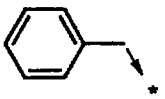
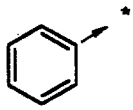
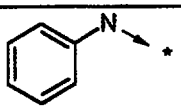
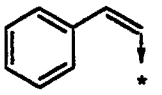
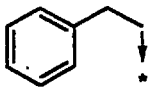
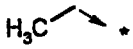
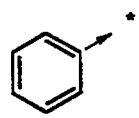
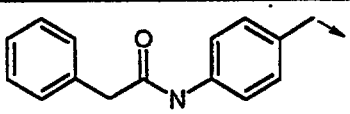
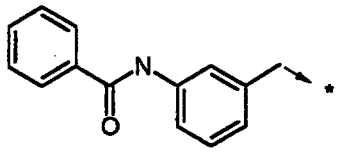
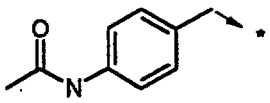
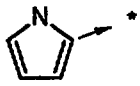
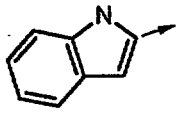
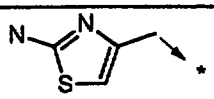
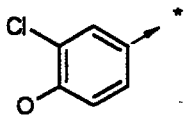
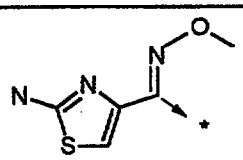
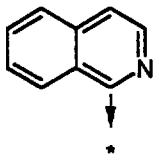
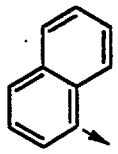
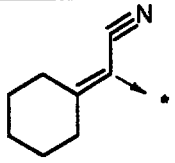
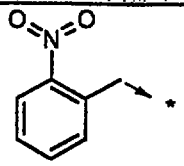
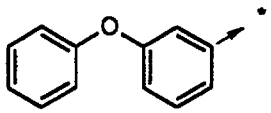
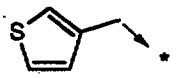
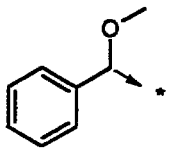
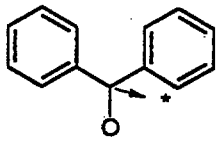
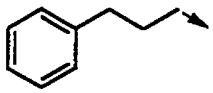
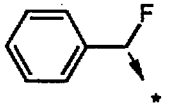
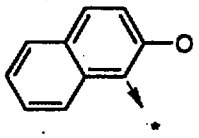
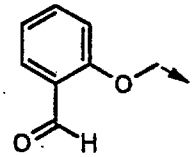
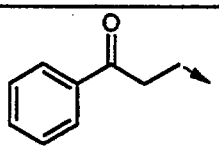
	M	MS Data	HPLC
134		(M+H)= 634.0	15-55%B; 5.90 min; 100%
135		(M+H)= 691.60	30-70%B; 4.22 min; 100%
136		(M+H)= 651.20	40-80%B; 5.59 min; 100%
137		(M+H)= 659.10	40-80%B; 4.65 min; 100%
138		(M+H)= 651.70	40-80%B; 3.83 min; 100%
139		(M+H)= 582.90	40-80%B; 2.34 min; 100%
140		(M+H)= 690.70	40-80%B; 5.15 min; 100%
141		(M+Na)= 664.80	40-80%B; 3.93 min; 100%
142		(M+Na)= 708.80	40-80%B; 5.398 min; 100%

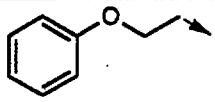
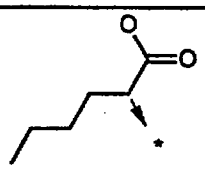
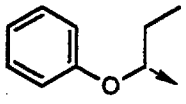
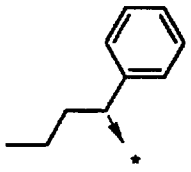
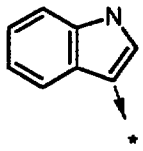
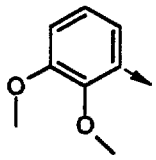
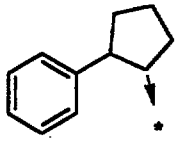
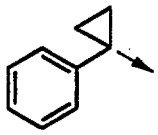
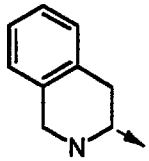
Table 6 Structures and analytical data - compounds 143-197

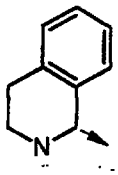
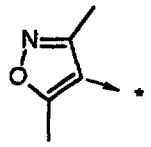
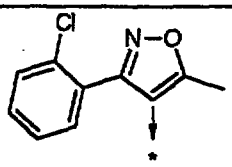
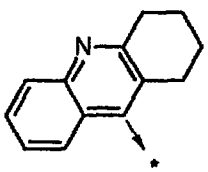
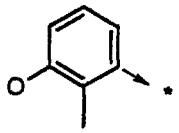
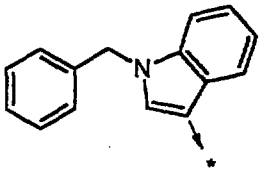
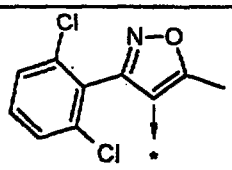
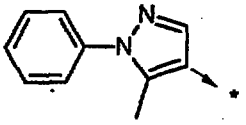
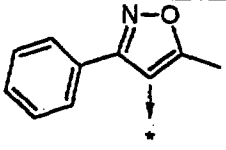


	T	U	MS Data	HPLC
143		$S(O_2)$	(M+Na)= 566.71	20-80%B; 10.186 min.; >95%
144		$S(O_2)$	(M+Na)= 552.26	20-80%B; 9.985 min.; 90%
145		C(O)	(M+Na)= 531.60	20-80%B; 9.978 min; 95%
146		C(O)	(M+Na)= 542.37	20-80%B; 10.404 min; 95%
147		C(O)	(M+Na)= 544.42	20-80%B; 10.246 min; 95%
148		C(O)	(M+Na)= 454.26	20-80%B; 7.109 min; 95%
149		C(O)	(M+Na)= 516.05	20-80%B; 9.668 min; 95%
150		C(O)	(M+Na)= 649.17	20-80%B; 9.880 min; 95%

	T	U	MS Data	HPLC
151		C(O)	(M+Na)= 648.45	20-80%B; 10.030 min; 95%
152		C(O)	(M+Na)= 587.08	20-80%B; 7.892 min; 95%
153		C(O)	(M+Na)= 505.47	20-80%B; 8.583 min; 95%
154		C(O)	(M+Na)= 554.96	20-80%B; 10.411 min; 95%
155		C(O)	(M+Na)= 551.90	20-80%B; 6.737 min; 95%
156		C(O)	(M+Na)= 566.11	20-80%B; 9.227 min; 95%
157		C(O)	(M+Na)= 594.59	20-80% B; 7.567 min; 95%
158		C(O)	(M+Na)= 567.00	20-80%B; 10.409 min; 95%
159		C(O)	(M+Na)= 566.10	20-80%B; 10.716 min; 95%
160		C(O)	(M+Na)= 559.27	20-80%B; 10.597 min; 95%

	T	U	MS Data	HPLC
161		C(O)	(M+Na)= 574.66	20-80%B; 9.723 min; 95%
162		C(O)	(M+Na)= 607.43	20-80%B; 12.019 min; 95%
163		C(O)	(M+H)= 514.83	20-80%B; 6.170 min; 95%
164		C(O)	(M+H)= 538.87	20-80%B; 7.094 min; 99%; 20-80%B; 6.712 min; 99%
165		C(O)	(M+Na)= 620.77	20-80%B; 8.390 min; 99%
166		C(O)	(M+H)= 536.44	20-80%B; 7.787 min; 99%
167		C(O)	(M+H)= 525.58	20-80%B; 7.023 min; 99%
168		C(O)	(M+Na)= 582.25	20-80%B; 7.220 min; 98%
169		C(O)	(M+H)= 552.32	20-80%B; 6.410 min; 99%
170		C(O)	(M+H)= 550.77	20-80%B; 6.663 min; 99%

	T	U	MS Data	HPLC
171		C(O)	(M+H)= 538.87	20-80%B; 7.101 min; 99%
172		C(O)	(M+Na)= 554.79	20-80%B; 7.011 min; 99%
173		C(O)	(M+H)= 551.59	20-80%B; 8.029 min; 96%
174		C(O)	(M+H)= 549.86	20-80%B; 7.320 min; 99%
175		C(O)	(M+Na)= 554.79	20-80%B; 6.413 min; 99%
176		C(O)	(M+H)= 555.05	20-80%B; 7.065 min; 99%
177		C(O)	(M+Na)= 584.55	20-80%B; 9.099 min; 99%
178		C(O)	(M+H)= 535.23	20-80%B; 8.038 min; 99%
179		C(O)	(M+Na)= 569.07	10-80%B; 5.885; 98%

	T	U	MS Data	HPLC
180		C(O)	(M+H)= 548.03	10-80% B; 5.991; 99%
181		C(O)	(M+Na)= 533.91	10-80%B; 7.237; 99%
182		C(O)	(M+Na)= 630.91	10-80%B; 9.382; 95%
183		C(O)	(M+H)= 599.4	10-80% B; 7.0 min; 99%
184		C(O)	(M+Na)= 545.27	10-80%B; 6.89 min; 99%
185		C(O)	(M+Na)= 643.91	10-80%B; 10.43 min; 99%
186		C(O)	(M+Na)= 664.69	10-80%B; 9.95 min; 99%
187		C(O)	(M+Na)= 595.53	10-80%B; 8.61 min; 99%
188		C(O)	(M+Na)= 596.45	10-80%B; 9.0 min; 92%

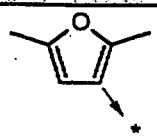
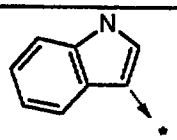
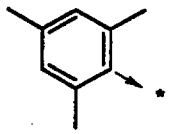
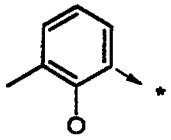
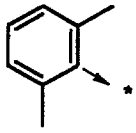
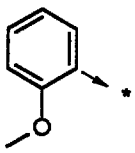
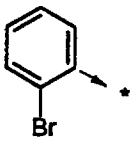
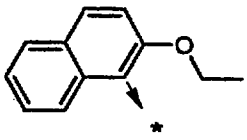
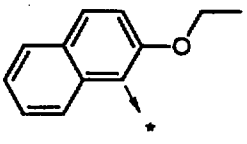
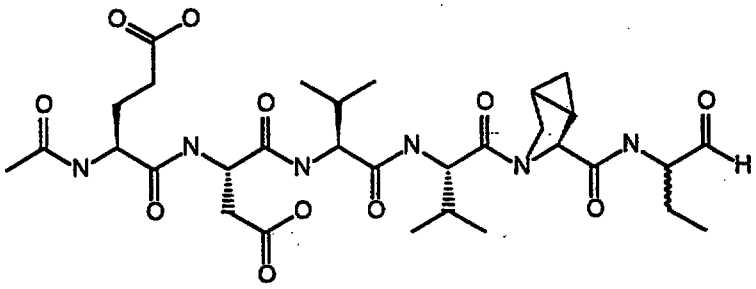
	T	U	MS Data	HPLC
189		C(O)	(M+Na)= 533.73	10-80%B; 8.438; 99%
190		C(O)	(M+Na)= 554.20	10-80%B; 7.990; 99%
191		C(O)	(M+Na)= 557.74	10-80%B; 9.06 min; 99%
192		C(O)	(M+Na)= 545.70	10-80%B; 10.11 min; 99%
193		C(O)	(M+Na)= 544.06	10-80%B; 8.41 min; 99%
194		C(O)	(M+Na)= 545.49	10-80%B; 8.41 min; 96%
195		C(O)	(M+Na)= 594.05	10-80%B; 8.3 min; 99%
196		C(O)	(M+H)= 574.3	10-80%B; 8.84 min; 98%
197		C(O)	(M+H)= 588.4	10-80%B; 9.37 min; 99%

Table 7 Structure and analytical data - compound 198.



	MS Data	HPLC
198	(M+Na)= 702.4	10-60%B; 4.2 min.; >95%

Example 11

Insofar as compounds of formula (I) or (II) are able to inhibit NS3 serine protease, they are of evident clinical utility for the treatment of viral diseases, including HCV. These tests are predictive of the compounds ability to inhibit HCV in vivo.

Peptides and Assays.

Peptides EDVV abuCSMSY (Abu designates - aminobutyric acid), DEMEECSQHLPYI, ECTTPCSGSWLRD and EDVV AbuC-p-nitroanilide was purchased from AnaSpec Inc. (San Jose, CA).

Peptide content of purified, lyophilized peptides and in-house peptides was determined by quantitative nitrogen analysis and the appropriate values were used in preparing stock peptide solutions (Galbreath). pKa determinations were determined by Robertson Microlit Laboratories, Inc. (Madison, NJ).

HPLC cleavage assays were performed using 25 nM to 3.0 µM enzyme in 100 µL volumes at 30 C containing 50 mM HEPES-KOH (pH 7.8), 100 mM NaCl, 20% glycerol, 5 mM DTT and the appropriate amount of substrate (in DMSO),

with or without NS4A peptide, such that the final concentration of DMSO did not exceed 4%. Separate control experiments verified that this percentage of DMSO did not effect enzymatic activity. Cleavage reactions were quenched by the addition of an equal volume of a mixture of 10% TFA: acetonitrile (1:1) and activity was assessed on a reversed phase HPLC column (Rainin C18 Microsorb-MV, 5mm, 4.6 x 250mm; 0-50% acetonitrile, 0.1% TFA @ 3.33% min) using a Hewlett Packard 1050 instrument with auto-injection and diode array detection at 210 nm and 280 nm (where appropriate). Peptide elution fragments were collected and identified by mass spectrometry and N-terminal sequence analysis. Fragment identity and concentration was further verified by authentic, synthesized products. Initial rates of cleaveage were determined at < 20% substrate conversion and catalytic parameters were determined assuming Michaelis-Menten kinetics using the MultiFit program (Day Computing, Cambridge, MA).

Spectrophotometric assays were run in a 96-well microtiter plate at 30 C, using a SpectraMax 250 reader (Molecular Devices, Sunnyvale, CA) with kinetic capability. Cleavage of EDVV AbuC-p-nitroanilide (5A-pNA) substrate was performed with or without NS44 in the same buffer used for HPLC assays at 30 C, and pNA release was monitored at 405 nm. The extinction coefficient of p-nitroaniline is independent of pH at values of 5.5. and above [Tuppy , H., et al., Hoppe-Seyler's Z. Physiol. Chem., 329, pp. 278-288 (1962)]; Raybuck and Luong, unpublished obervations). The percentage of DMSO did not exceed 4% in these assays.

Determination of the pH dependence of Vmax, K_m and V_{max}/K_m was performed using a series of constant ionic strength buffers containing 50 mM MES, 25 Nm Tris, 25 mM ethanolamine and 0.1 M NaCl [Morrison, J.F. and Stone,

R.F., Biochemistry, 27, pp. 5499-5506 (1988)]. The inflection point for log V data was calculated by nonlinear least squares fit of the data to the equation.

$$\log v = \log[Vmax/(1 + H/K_a)]$$

[Dixon, M. and Webb, E. C. Enzymes; Academic Press: New York; Vol., pp. 138-164 (1979)]. The inflection points for log (V/K) data were calculated by nonlinear least squares fit of the data to the equation

$\log v = \log[Vmax/(1 + H/K_a + K_b/H)]$ [Dixon, M. and Webb, E. C. Enzymes; Academic Press: New York; Vol., pp. 138-164 (1979)]. The program KineTic (BioKin Ltd) was used in both cases.

Kinetic constants for the rapid equilibrium ordered bisubstrate reaction were determined from rate *vs* [4A], [EDVV AbuC-pNA] data by non-linear least squares fitting to equation 1 [Morrison, J.F. Biochim. Biophys. Acta., 185, pp. 269-286 (1969)] as described in the text. K_{ii} and K_{is} values for peptidyl inhibitors were determined from rate *vs* [inhibitor], [substrate] data and fitting to the equation for mixed inhibition:

$$rate = Vmax[S]/\{Km(1+[I]/Kis) + [S] (1 + [I]/Kii)\}$$

The commercial program KinetAsyst (StateCollege, PA) was used for both procedures. Ki values were calculated from rate *vs* [inhibitor] plots by a nonlinear least squares fit of the data to the equation of Morrison for tight binding competitive inhibition [Morrison, J.F. Biochim. Biophys. Acta., 185, pp. 269-286 (1969)]. The KineTic program (BioKin Ltd) was used for this procedure.

The results are shown in Table 9. K_i values are expressed in μM. Category "A" indicates < 1 μM inhibition; category "B" indicates 1-100 μM inhibition; category "C" indicates > 100 μM. The designation "ND" indicates that the compound was not tested.

Table 9. Enzyme inhibition data for compounds 1-198.

Cmpd. No.	Ki (μM)	Cmpd. No.	Ki (μM)	Cmpd. No.	Ki (μM)
1	B	42	B	83	B
2	B	43	B	84	B
3	B	44	B	85	B
4	B	45	B	86	B
5	B	46	B	87	B
6	B	47	B	88	B
7	B	48	B	89	B
8	B	49	B	90	B
9	B	50	B	91	B
10	B	51	B	92	B
11	B	52	B	93	B
12	B	53	B	94	B
13	B	54	B	95	B
14	B	55	B	96	B
15	B	56	C	97	B
16	B	57	B	98	B
17	B	58	B	99	B
18	B	59	B	100	B
19	B	60	C	101	A
20	B	61	C	102	A
21	B	62	B	103	A
22	B	63	B	104	A
23	B	64	B	105	A
24	B	65	B	106	A
25	B	66	B	107	A
26	B	67	C	108	A
27	B	68	C	109	B
28	B	69	B	110	B
29	B	70	B	111	C
30	B	71	A	112	B
31	B	72	B	113	B
32	B	73	B	114	C
33	C	74	B	115	B
34	B	75	B	116	B
35	B	76	C	117	B
36	C	77	C	118	B
37	B	78	B	119	C
38	B	79	B	120	B
39	B	80	A	121	C
40	B	81	B	122	C
41	B	82	B		

Cmpd. No.	Ki (μM)	Cmpnd. No.	Ki (μM)	Cmpnd No.	Ki (μM)
123	B	149	B	174	B
124	B	150	B	175	B
125	B	151	C	176	C
126	C	152	C	177	C
127	C	153	B	178	C
128	B	154	B	179	B
129	B	155	B	180	C
130	C	156	B	181	C
131	B	157	B	182	C
132	B	158	B	183	B
133	B	159	B	184	B
134	C	160	B	185	B
135	B	161	C	186	C
136	B	162	B	187	C
137	B	163	C	188	C
138	B	164	C	189	C
139	C	165	C	190	C
140	B	166	C	191	C
141	B	167	C	192	C
142	B	168	B	193	C
143	C	169	C	194	C
144	C	170	C	195	B
145	B	171	C	196	B
146	B	172	C	197	B
147	C	173	C	198	A
148	C				

While we have hereinbefore presented a number of embodiments of this invention, it is apparent that my basic construction can be altered to provide other embodiments which utilize the methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the claims appended hereto rather than the specific embodiments which have been presented hereinbefore by way of example.

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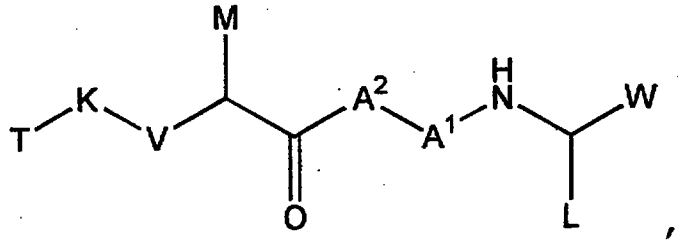
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☐ Description : paged ..... to paged .....
☒ Claim(s) : paged 109 to paged 120
☐ Drawing(s) : paged ..... to paged .....
☐ Abstract : paged ..... to paged .....

CLAIMS

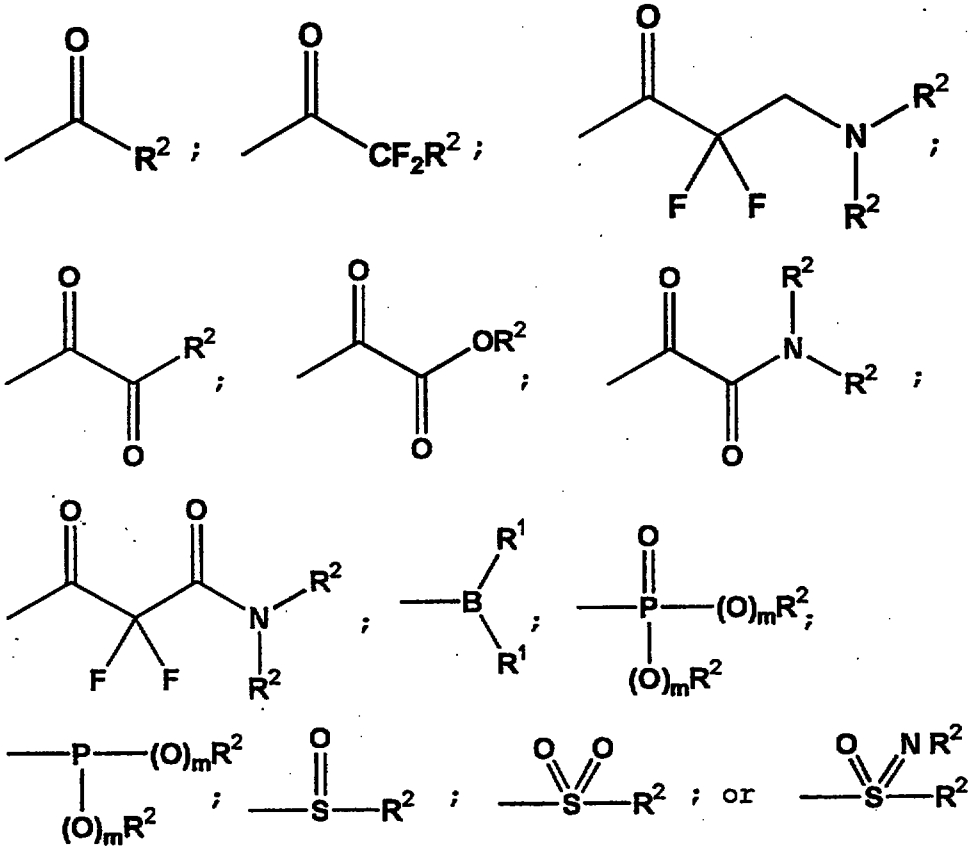
What is claimed is:

1. A compound of the formula (II):

(II) 

, wherein

W is:



m is 0 or 1;

each R^1 is hydroxy, alkoxy, or aryloxy, or each R^1 is an oxygen atom and together with the boron, to which they are each bound, form a 5-7 membered ring, wherein the ring atoms are carbon, nitrogen, or oxygen;

each R^2 is independently hydrogen, alkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heteroaryl, or heteroaralkyl, or two R^2 groups, which are bound to the same nitrogen atom, form together with that nitrogen atom, a 5-7 membered monocyclic heterocyclic ring system; wherein any R^2 carbon atom is optionally substituted with J;

J is alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, cycloalkyl, cycloalkoxy, heterocyclyl, heterocyclyloxy, heterocyclylalkyl, keto, hydroxy, amino, alkylamino, alkanoylamino, aroylamino, aralkanoylamino, carboxy, carboxyalkyl, carboxamidoalkyl, halo, cyano, nitro, formyl, acyl, sulfonyl, or sulfonamido and is optionally substituted with 1-3 J^1 groups;

J^1 is alkyl, aryl, aralkyl, alkoxy, aryloxy, heterocyclyl, heterocyclyloxy, keto, hydroxy, amino, alkanoylamino, aroylamino, carboxy, carboxyalkyl, carboxamidoalkyl, halo, cyano, nitro, formyl, sulfonyl, or sulfonamido;

L is alkyl, alkenyl, or alkynyl, wherein any hydrogen is optionally substituted with halogen, and wherein any hydrogen or halogen atom bound to any terminal carbon atom is optionally substituted with sulfhydryl or hydroxy;

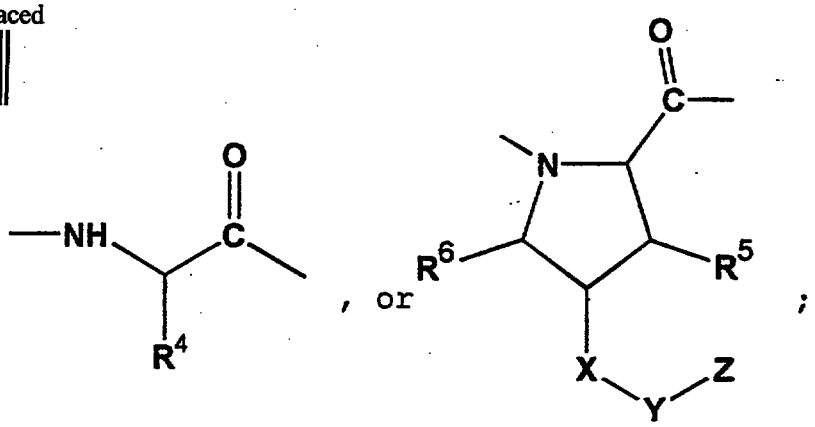
A^1 is a bond,

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R^4 is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups;

R^5 and R^6 are independently hydrogen, alkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroaralkyl, and is optionally substituted with 1-3 J groups;

X is a bond, $-C(H)(R^7)-$, $-O-$, $-S-$, or $-N(R^8)-$;

R^7 is hydrogen, alkyl, alkenyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroaralkyl, and is optionally substitituted with 1-3 J groups;

R^8 is hydrogen alkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, aralkanoyl, heterocyclanoyl, heteroaralkanoyl, $-C(O)R^{14}$, $-SO_2R^{14}$, or carboxamido, and is optionally substitituted with 1-3 J groups; or R^8 and Z, together with the atoms to which they are bound, form a nitrogen containing mono- or bicyclic ring system optionally substituted with 1-3 J groups;

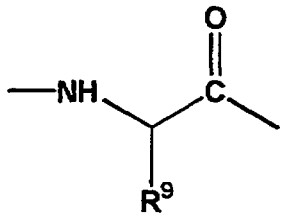
* C L M S *

R^{14} is alkyl, aryl, aralkyl, heterocyclyl, heterocyclyalkyl, heteroaryl, or heteroaralkyl;

Y is a bond, $-CH_2-$, $-C(O)-$, $-C(O)C(O)-$, $-S(O)-$, $-S(O)_2-$, or $-S(O)(NR^7)-$, wherein R^7 is as defined above;

Z is alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-OR^2$, or $-N(R^2)_2$, wherein any carbon atom is optionally substituted with J, wherein R^2 is as defined above;

A^2 is a bond or



;

R^9 is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups;

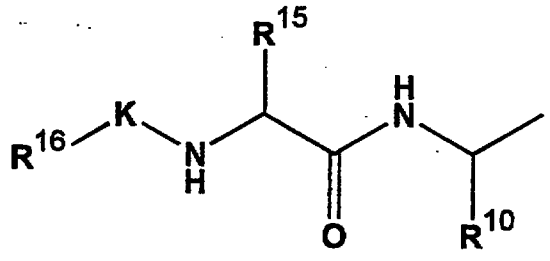
M is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroaralkyl, optionally substituted by 1-3 J groups, wherein any alkyl carbon atom may be replaced by a heteroatom;

V is a bond, $-CH_2-$, $-C(H)(R^{11})-$, $-O-$, $-S-$, or $-N(R^{11})-$;

R^{11} is hydrogen or C_{1-3} alkyl;

K is a bond, $-O-$, $-S-$, $-C(O)-$, $-S(O)-$, $-S(O)_2-$, or $-S(O)(NR^{11})-$, wherein R^{11} is as defined above;

T is $-R^{12}$, $-alkyl-R^{12}$, $-alkenyl-R^{12}$, $-alkynyl-R^{12}$, $-OR^{12}$, $-N(R^{12})_2$, $-C(O)R^{12}$, $-C(=NOalkyl)R^{12}$, or



;

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R^{12} is hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkylidenyl, or heterocycloalkylidenyl, and is optionally substituted with 1-3 J groups, or a first R^{12} and a second R^{12}, together with the nitrogen to which they are bound, form a mono- or bicyclic ring system optionally substituted by 1-3 J groups;

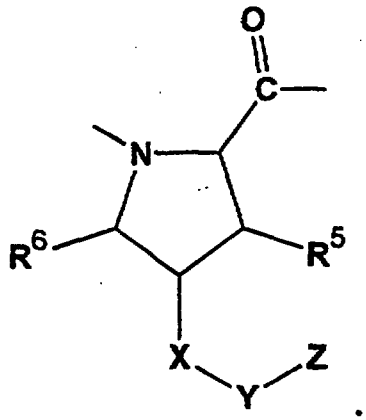
R^{10} is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 hydrogens J groups;

R^{15} is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups; and

R^{16} is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl.

2. The compound according to claim 1, wherein A1 is:

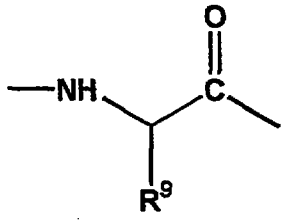
* C L M S *



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3. The compound according to claim 2, wherein R^5 and R^6 are hydrogen.

4. The compound according to claim 3, wherein A^2 is:



and R^9 is alkyl.

5. The compound according to claim 4, wherein R^9 is isopropyl.

6. The compound according to claim 5, wherein L is alkyl, alkenyl, or alkynyl, wherein any hydrogen is optionally substituted with halogen, and wherein any hydrogen or halogen atom bound to any terminal carbon atom is optionally substituted with sulfhydryl or hydroxy.

* C L M S *

7. The compound according to claim 6, wherein L is trihalomethyl, sulfhydryl, or alkyl substituted with trihalomethyl, sulfhydryl, or hydroxy.

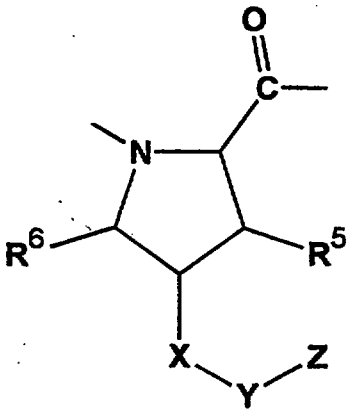
8. The compound according to claim 7, wherein:

X is -O- or -N(H)-; and

Y is $-CH_2-$, -C(O)-, or $-S(O)_2-$.

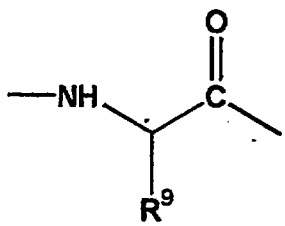
9. The compound according to claim 8, wherein V is -N(H)- and K is -C(O)- or $-S(O)_2-$.

10. The compound according to claim 1, wherein A^1 is:



, and R^5 and R^6 are hydrogen;

A^2 is:



and R^9 is isopropyl;

L is ethyl;

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* C L M S *

X is -O- or -N(H)-;

Y is $-CH_2-$, -C(O)-, or $-S(O)_2-$;

V is -N(H)-; and

K is -C(O)-.

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11. The compound according to claim 10, wherein M is isopropyl.

12. The compound according to claim 11, wherein Z is aryl or heteroaryl.

13. The compound according to claim 12, wherein T is aryl or heteroaryl.

14. The compound according to claim 13, wherein T is pyrazine.

15. The compound according to claim 10, wherein X is -O- and Y is $-CH_2-$.

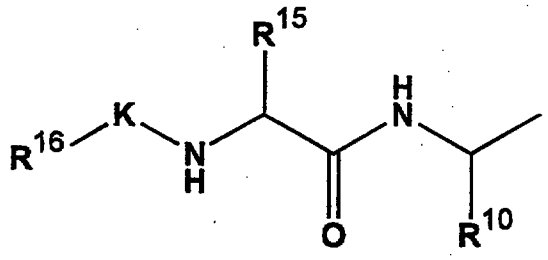
16. The compound according to claim 15, wherein Z is aryl or heteroaryl.

17. The compound according to claim 16, wherein Z is aryl.

18. The compound according to claim 10, wherein M is isopropyl.

19. The compound according to claim 18, wherein T is $-R^{12}$, $-OR^{12}$, $-N(R^{12})_2$, or





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20. The compound according to claim 19, wherein M is alkyl, heteroaralkyl, aryl, cycloalkylalkyl, aralkyl, or aralkyl, wherein one of the alkyl carbon atoms is replaced by O or S.

21. The compound according to claim 20, wherein said heteroatom is S or O.

22. The compound according to claim 21, wherein T is aryl or heteroaryl.

23. The compound according to claim 22, wherein T is pyrazine.

24. The compound according to claim 3, wherein

A^2 is a bond;

L is ethyl;

X is -O-;

Y is $-CH_2-$;

V is -N(H)-; and

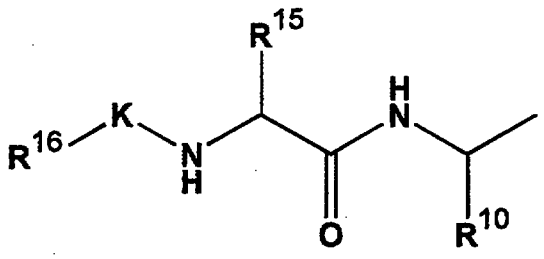
K is -C(O)- or $-S(O)_2-$.

25. The compound according to claim 24, wherein M is isopropyl.

26. The compound according to claim 25, wherein Z is aryl or heteroaryl.

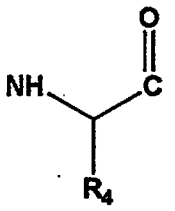
27. The compound according to claim 26, wherein Z is phenyl.

28. The compound according to claim 27, wherein T is $-R^{12}$, $-alkyl-R^{12}$, $-alkenyl-R^{12}$, $-OR^{12}$, $-N(R^{12})_2$, $-C(=NOalkyl)R^{12}$, or

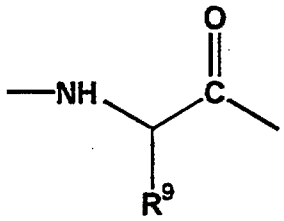


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29. The compound according to claim 1, wherein

A^1 is  ; and

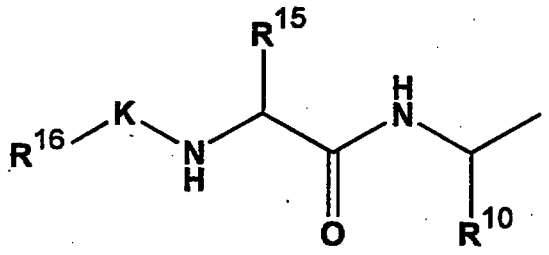
A^2 is



* C L M S *

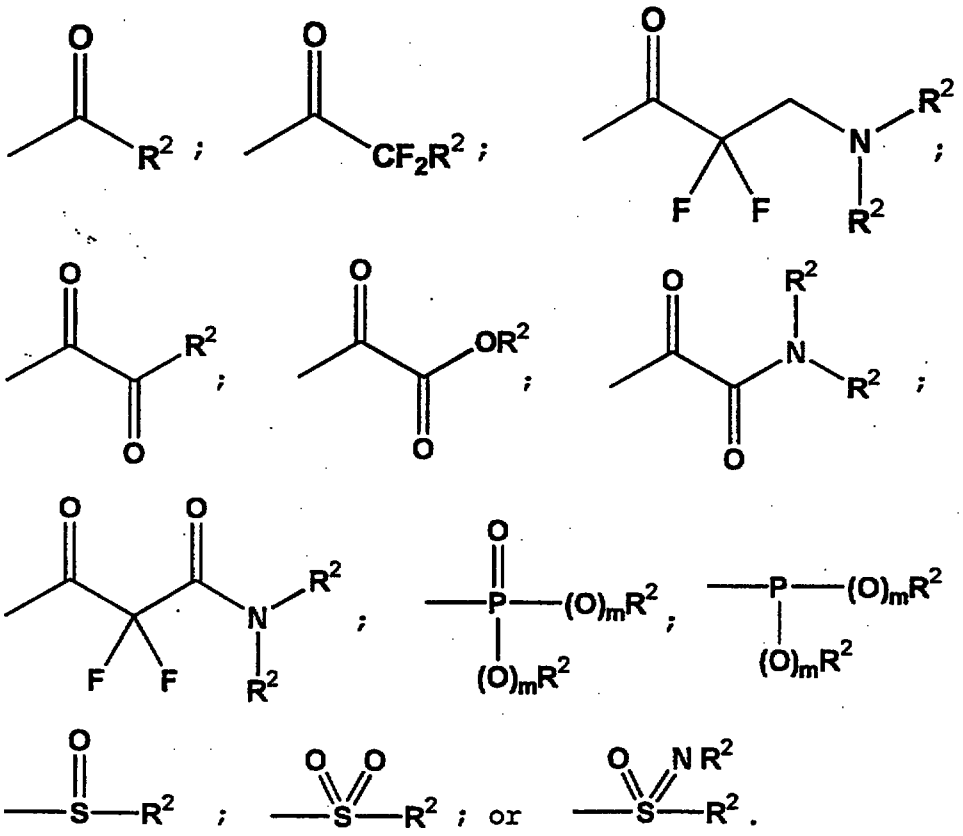
30. The compound according to claim 29, wherein M is isopropyl and K is -C(O)-.

31. The compound according to claim 30, wherein T is $-R^{12}$, -alkyl-R^{12}, -alkenyl-R^{12}, $-OR^{12}$, $-N(R^{12})_2$, $-C(=NOalkyl)R^{12}$, or



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32. The compound according to any one of claims 1-31, wherein W is



CLMS

33. A pharmaceutically acceptable composition comprising:

a) a compound according to claims 1-32 in an amount effective to inhibit HCV NS3 protease; and

b) a pharmaceutically suitable carrier.

34. A method for inhibiting serine protease activity comprising the step of administering to said patient a compound according to any one of claims 1-32.

35. The method according to claim 34, wherein the serine protease is HCV NS3 protease.

36. A method for treating or preventing a hepatitis C viral infection in a patient comprising the step of administering to said patient/mammal a compound according to any one of claims 1-32.

37. The method according to claim 36, wherein said compound is administered to a patient and is formulated together with a pharmaceutically suitable carrier into a pharmaceutically acceptable composition.

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