Title: GAMMA SECRETASE MODULATORS

Abstract: In its many embodiments, the present invention provides a novel class of heterocyclic compounds as modulators of gamma secretase, methods of preparing such compounds, pharmaceutical compositions containing one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition, or amelioration of one or more diseases associated with the central nervous system using such compounds or pharmaceutical compositions.
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GAMMA SECRETASE MODULATORS

Reference To Related Application
This application claims the benefit of U.S. Provisional Application No. 60/916458 filed on May 7, 2007.

Field of the Invention
The present invention relates to certain heterocyclic compounds useful as gamma secretase modulators (including inhibitors, antagonists and the like), pharmaceutical compositions containing the compounds, and methods of treatment using the compounds and compositions to treat various diseases including central nervous system disorders such as, for example, neurodegenerative diseases such as Alzheimer's disease and other diseases relating to the deposition of amyloid protein. They are especially useful for reducing Amyloid beta (hereinafter referred to as Aβ) production which is effective in the treatment of diseases caused by Aβ such as, for example, Alzheimer's and Down Syndrome.

Background of the Invention
Alzheimer's disease is a disease characterized by degeneration and loss of neurons and also by the formation of senile plaques and neurofibrillary change. Presently, treatment of Alzheimer's disease is limited to symptomatic therapies with a symptom-improving agent represented by an acetylcholinesterase inhibitor, and the basic remedy which prevents progress of the disease has not been developed. A method of controlling the cause of onset of pathologic conditions needs to be developed for creation of the basic remedy of Alzheimer's disease.

Aβ protein, which is a metabolite of amyloid precursor protein (hereinafter referred to as APP), is considered to be greatly involved in degeneration and loss of neurons as well as onset of demential conditions (for example, see Klein W L, et al Proceeding National Academy of Science USA,


suggest that the main components of Aβ protein are Aβ40 consisting of 40 amino acids and Aβ42 having two additional amino acids at the C-terminal. The Aβ40 and Aβ42 tend to aggregate (for example, see Jarrell J T et al, The carboxy terminus of the β amyloid protein is critical for the seeding of amyloid formation: implications for the pathogenesis of Alzheimer's disease, Biochemistry, May 11,1993, 32(18), p. 4693-4697) and constitute main components of senile plaques (for example, (Glenner GG, et al, Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein, Biochemical and Biophysical Research Communications, May 16, 1984, 120(3), p. 885-90. See also Masters C L, et al, Amyloid plaque core protein in Alzheimer disease and Down syndrome, Proceeding National Academy of Science USA, June 1985, 82(12), p. 4245-4249.).


These Aβs are produced when APP is cleaved by beta secretase and subsequently clipped by gamma secretase. In consideration of this, creation of inhibitors of γ secretase and β secretase has been attempted for the purpose of
reducing production of Aβs. Many of these secretase inhibitors already known are peptides or peptidomimetics such as L-685,458. L-685,458, an aspartyl protease transition state mimic, is a potent inhibitor of amyloid β-protein precursor γ-secretase activity, Biochemistry, Aug. 1, 2000, 39(30), p. 8698-8704).

Also of interest in connection with the present invention are: US 2006/0004013 (Eisai, published January 5, 2006); WO 2005/10422 (Boehringer Ingelheim, published November 24, 2005); WO 2006/045554 (CellZome AG, published May 4, 2006); WO 2004/10350 (Neurogenetics, published December 23, 2004); WO 2004/071431 (Myriad Genetics, published August 26, 2004); US 2005/0042284 (Myriad Genetics, published February 23, 2005) and WO 2006/001877 (Myriad Genetics, published January 5, 2006).

There is a need for new compounds, formulations, treatments and therapies to treat diseases and disorders associated with Aβ. It is, therefore, an object of this invention to provide compounds useful in the treatment or prevention or amelioration of such diseases and disorders.

**Summary of the Invention**

In its many embodiments, the present invention provides a novel class of heterocyclic compounds as gamma secretase modulators (including inhibitors, antagonists and the like), methods of preparing such compounds, pharmaceutical compositions comprising one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition or amelioration of one or more diseases associated with the Aβ using such compounds or pharmaceutical compositions.

The compounds of this invention (Formula I) can be useful as gamma secretase modulators and can be useful in the treatment and prevention of diseases such as, for example, Alzheimers disease, mild cognitive impairment (MCI), Downs Syndrome, Glaucoma (Guo et.al., Proc. Natl. Acad. Sci. USA 104,

In one embodiment, the present application discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in Formula I:

![Formula I](image)

wherein U, G, V, R¹, R², R⁶, R⁷, R⁸, R⁹, and R¹⁰ are as defined below.

In another embodiment, the present application discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in Formula IA:

![Formula IA](image)

wherein U, G, V, R¹, R², R⁶, R⁷, R⁸, R⁹, and R¹⁰ are as defined below.

The compounds of Formula I can be useful as gamma secretase modulators and can be useful in the treatment and prevention of diseases such as, for example, central nervous system disorders such as Alzheimers disease and Downs Syndrome.
This invention also provides compounds of formula I.
This invention also provides pharmaceutically acceptable salts of the compounds of formula I.
This invention also provides pharmaceutically acceptable esters of the compounds of formula I.
This invention also provides pharmaceutically solvates of the compounds of formula I.
This invention also provides compounds of formula I in pure and isolated form.
This invention also provides compounds of formula I in pure form.
This invention also provides compounds of formula I in isolated form.
This invention also provides compounds 1 to 164.
This invention also provides compounds 1 to 9.
This invention also provides compounds 10 to 164.
This invention also provides compounds 10 to 162.
This invention also provides pharmaceutical compositions comprising an effective amount of one or more (e.g., one) compounds of formula I, or a pharmaceutically acceptable salt, ester or solvate thereof, and a pharmaceutically acceptable carrier.
This invention also provides pharmaceutical compositions comprising an effective amount of one or more (e.g., one) compounds of formula I, or a pharmaceutically acceptable salt, ester or solvate thereof, and an effective amount of one or more (e.g., one) other pharmaceutically active ingredients (e.g., drugs), and a pharmaceutically acceptable carrier.
This invention also provides a method for modulating (including inhibiting, antagonizing and the like) gamma-secretase, comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula I to a patient in need of treatment.
This invention also provides a method for modulating (including inhibiting, antagonizing and the like) gamma-secretase, comprising administering an
effective (i.e., therapeutically effective) amount of a compound of formula I to a patient in need of treatment.

This invention also provides a method of treating one or more neurodegenerative diseases, comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula I to a patient in need of treatment.

This invention also provides a method of inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula I to a patient in need of treatment.

This invention also provides a method of inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula I to a patient in need of treatment.

This invention also provides a method of treating Alzheimer's disease, comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula I to a patient in need of treatment.

This invention also provides a method of treating Alzheimer's disease, comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula I to a patient in need of treatment.

This invention also provides a method of treating Alzheimer's disease, comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula I, in combination with an effective (i.e., therapeutically effective) amount of one or more cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-
piperidinyl]methyl]-1 H -inden-1-one hydrochloride, i.e, donepezil hydrochloride, available as the Aricept ® brand of donepezil hydrochloride), to a patient in need of treatment.

This invention also provides a method of treating Alzheimer’s disease, comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula I, in combination with an effective (i.e., therapeutically effective) amount of one or more compounds selected from the group consisting of Aβ antibody inhibitors, gamma secretase inhibitors and beta secretase inhibitors.

This invention also provides combinations comprising an effective (i.e., therapeutically effective) amount of one or more compounds of formula I, in combination with an effective (i.e., therapeutically effective) amount of one or more compounds selected from the group consisting of cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 H -inden-1-one hydrochloride, i.e, donepezil hydrochloride, available as the Aricept ® brand of donepezil hydrochloride), Aβ antibody inhibitors, gamma secretase inhibitors and beta secretase inhibitors.

This invention also provides a method of treating Alzheimer’s disease, comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula I, in combination with an effective (i.e., therapeutically effective) amount of one or more (e.g., one) cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 H -inden-1-one hydrochloride, i.e, donepezil hydrochloride, available as the Aricept ® brand of donepezil hydrochloride), to a patient in need of treatment.

This invention also provides a method of treating Downs syndrome, comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula I to a patient in need of treatment.
This invention also provides a method of treating Downs syndrome, comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of formula I, in combination with an effective (i.e., therapeutically effective) amount of one or more cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1\textsubscript{$\alpha$}-inden-1-one hydrochloride, i.e., donepezil hydrochloride, available as the Aricept \textsuperscript{®} brand of donepezil hydrochloride), to a patient in need of treatment.

This invention also provides a method of treating Downs syndrome, comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula I, in combination with an effective (i.e., therapeutically effective) amount of one or more (e.g., one) cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1\textsubscript{$\alpha$}-inden-1-one hydrochloride, i.e., donepezil hydrochloride, available as the Aricept \textsuperscript{®} brand of donepezil hydrochloride), to a patient in need of treatment.

This invention also provides combination therapies for (1) modulating gamma-secretase, or (2) treating one or more neurodegenerative diseases, or (3) inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), or (4) treating Alzheimer's disease.

The combination therapies are directed to methods comprising the administration of an effective amount of one or more (e.g., one) compounds of formula I and the administration of an effective amount of one or more (e.g., one) other pharmaceutical active ingredients (e.g., drugs).

This invention also provides a method of treating mild cognitive impairment, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

This invention also provides a method of treating glaucoma, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.
This invention also provides a method of treating cerebral amyloid angiopathy, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

This invention also provides a method of treating stroke, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

This invention also provides a method of treating dementia, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

This invention also provides a method of treating microgliosis, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

This invention also provides a method of treating brain inflammation, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

This invention also provides a method of treating olfactory function loss, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

This invention also provides pharmaceutical compositions comprising a combination of an effective amount of one or more (e.g., one) compounds of formula I, in combination with an effective amount of one or more compounds selected from the group consisting of cholinesterase inhibitors, Aβ antibody inhibitors, gamma secretase inhibitors and beta secretase inhibitors. The pharmaceutical compositions also comprise a pharmaceutically acceptable carrier.

This invention also provides a kit comprising, in separate containers, in a single package, pharmaceutical compositions for use in combination, wherein one container comprises an effective amount of a compound of formula I in a pharmaceutically acceptable carrier, and another container (i.e., a second container) comprises an effective amount of another pharmaceutically active 
ingredient, the combined quantities of the compound of formula I and the other pharmaceutically active ingredient being effective to: (a) treat Alzheimer's disease, or (b) inhibit the deposition of amyloid protein in, on or around neurological tissue (e.g., the brain), or (c) treat neurodegenerative diseases, or (d) modulate the activity of gamma-secretase.

This invention also provides a kit comprising, in separate containers, in a single package, pharmaceutical compositions for use in combination, wherein one container comprises an effective amount of a compound of formula I in a pharmaceutically acceptable carrier, and another container (i.e., a second container) comprises an effective amount of another pharmaceutically active ingredient (as described below), the combined quantities of the compound of formula I and the other pharmaceutically active ingredient being effective to: (a) treat Alzheimer's disease, or (b) inhibit the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), or (c) treat neurodegenerative diseases, or (d) modulate the activity of gamma-secretase.

This invention also provides any one of the methods disclosed above and below wherein the compound is selected from the group consisting of the compounds 1 to 164.

This invention also provides any one of the above mentioned methods of treatment wherein the compound is selected from the group consisting of compounds in Table 1 (i.e. compounds 1 to 9).

This invention also provides any one of the methods disclosed above and below wherein the compound of formula I is selected from the group consisting of the compounds 10 to 164.

This invention also provides any one of the methods disclosed above and below wherein the compound of formula I is selected from the group consisting of the compounds 10 to 162.

This invention also provides any one of the methods disclosed above and below wherein the compound is any one of the compounds 1 to 164.
This invention also provides any one of the pharmaceutical compositions disclosed above and below wherein the compound is selected from the group consisting of the compounds 1 to 164.

This invention also provides any one of the pharmaceutical compositions disclosed above and below wherein the compound is any one of the compounds 1 to 164.

This invention also provides any one of the methods disclosed above and below wherein the compound is selected from the group consisting of the compounds in Table 14.

This invention also provides any one of the methods disclosed above and below wherein the compound is any one of the compounds in Table 14.

Other embodiments of this invention are directed to any one of the embodiments above or below that are directed to formula I, or the use of formula I (e.g. the embodiments directed to methods of treatment, pharmaceutical compositions and kits), wherein the compound is a compound of formula IA instead of formula I. Those skilled in the art will appreciate that the compounds of formula I and formula IA are isomers of each other.

**Detailed Description**

In one embodiment, the present invention discloses compounds which are represented by structural Formula I, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

In one embodiment, the present application discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in Formula I:
wherein:

- $U$ is $\text{C} R^5$ or $N$;
- $G$ is $O$ or $S$;
- $V$ is selected from the group consisting of a bond, $O$, $-\text{C(O)}-$, and $N(R^{14})$;
- $R^1$ is selected from the group consisting of $H$, halo, alkyl-, alkenyl-, alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclylalkyl-, wherein each of said alkyl-, alkenyl- and alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclylalkyl- can be unsubstituted or optionally independently substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below;
- $R^2$ is selected from the group consisting of $H$, alkyl-, alkenyl-, alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclylalkyl-, wherein each of said alkyl-, alkenyl- and alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclylalkyl- can be unsubstituted or optionally independently substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below;

or, alternatively, $R^1$ and $R^2$ may be joined together to form a C5-C8 cycloalkyl or a 5-8 membered heterocyclyl moiety, with each of said cycloalkyl or heterocyclyl moiety being unsubstituted or optionally...
independently being substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below;

or, alternatively, R\(^1\) and R\(^8\) are taken together to form a bond (i.e., there is a triple bond between the carbon atom to which R\(^1\) was bonded to and the carbon to which R\(^8\) was bonded to, i.e., the compound of formula I is a compound of formula II:

\[
\begin{align*}
\text{formula II} \\
\end{align*}
\]

wherein G, U, V, R\(^2\), R\(^6\), R\(^7\), R\(^9\), and R\(^{10}\) are as defined for formula I);

R\(^5\), R\(^6\) and R\(^7\) can be the same or different, each being independently selected from the group consisting of H, -C(O)R\(^{15}\), -C(O)OR\(^{15}\), -C(O)N(R\(^{15}\))(R\(^{16}\)), -C(N=OR\(^{15}\))R\(^{16}\), alkyl-, alkenyl-, alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclylalkyl-, wherein each of said alkyl-, alkenyl- and alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclylalkyl- can be unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below;

or alternately, R\(^6\) and R\(^7\) can be joined together to form a carbocyclic spirocyclic moiety or a heterocyclic spirocyclic moiety wherein each of said carbocyclic spirocyclic moiety and heterocyclic spirocyclic moiety can be: (i) unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below, or (ii)
fused with an aryl, heteroaryl, cycloalkyl or heterocycloalkyl ring, wherein each of said carbocyclic spirocyclic moiety, heterocyclic spirocyclic moiety, aryl, heteroaryl, cycloalkyl and heterocycloalkyl ring can be unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below;

\[ R^8 \text{ is selected from the group consisting of H, halo, } -\text{CN}, -\text{OR}^{15}, -\text{C(O)R}^{15}, -\text{C(O)OR}^{15}, -\text{C(O)N(R}^{15})(\text{R}^{16}), -\text{SR}^{15}, -\text{S(O)N(R}^{15})(\text{R}^{16}), -\text{CH(R}^{15})(\text{R}^{16}), -\text{S(O)}_2\text{N(R}^{15})(\text{R}^{16}), -\text{C(=NOR}^{15})\text{R}^{16}, -\text{P(O)(OR}^{15})(\text{OR}^{16}), -\text{N(R}^{15})(\text{R}^{16}), -\text{alkyl-N(R}^{15})(\text{R}^{16}), -\text{N(R}^{15})\text{C(O)R}^{16}, -\text{CH}_2\text{-N(R}^{15})\text{C(O)R}^{16}, -\text{CH}_2\text{-N(R}^{15})\text{S(O)}_2\text{R}^{16}, -\text{N(R}^{15})\text{S(O)}_2\text{N(R}^{16})(\text{R}^{17}), -\text{N(R}^{15})\text{S(O)}\text{N(R}^{16})(\text{R}^{17}), -\text{N}(\text{R}^{15})\text{C(O)N(R}^{15})(\text{R}^{16}), -\text{CH}_2\text{-N(R}^{15})\text{C(O)N(R}^{15})(\text{R}^{16}), -\text{N}(\text{R}^{15})\text{S(O)}\text{S(O)}_2\text{R}^{16}, -\text{N}(\text{R}^{15})\text{S(O)}\text{S(O)}_2\text{N(R}^{16})(\text{R}^{17}), -\text{N}(\text{R}^{15})\text{C(O)OR}^{16}, -\text{CH}_2\text{-N(R}^{15})\text{C(O)OR}^{16}, -\text{S(O)R}^{15}, -\text{N}_3, -\text{NO}_2 \text{ and } -\text{S(O)}_2\text{R}^{15}, \text{alkyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl- with each of said alkyl-, alkenyl-, alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl- being unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below; \]

\[ R^{10} \text{ is selected from the group consisting of a bond, alkyl-, aryl-, arylalkyl-, arylalkenyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl-, heterocyclyalkyl- and the moieties:} \]
where $X$ is O, N($R^{14}$) or S;

wherein each of said alkyl-, aryl-, arylalkyl-, arylalkenyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- heterocyclylalkyl- and the above-noted moieties for $R^{10}$ can be unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each being independently selected from the group consisting of the moieties shown below;

or, alternatively, $R^8$ and $R^{10}$, together with the carbon atom to which they are bound, can form a C$_4$-C$_7$ carbocyclic (e.g., cycloalkyl) ring, or a 4-7 membered heterocyclyl ring, or a C$_4$-C$_7$ carbocyclyl ring, or a 4-7 membered heterocyclyl ring; and wherein said carbocyclic ring, heterocyclyl ring, carbocyclyl ring, or heterocyclyl ring is optionally substituted with 1-5 independently selected $R^{21}$ substituents;

$R^9$ is selected from the group consisting of alkyl-, alkenyl-, alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclylalkyl-, wherein each of said alkyl-, alkenyl- and alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclylalkyl-can be unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below,

$R^{14}$ is selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -CN, -C(O)R$^{15}$, -C(O)OR$^{15}$, -C(O)N(R$^{15}$)(R$^{16}$), -S(O)N(R$^{15}$)(R$^{16}$), -S(O)$_2$N(R$^{15}$)(R$^{16}$), -C(=NOR$^{15}$)R$^{16}$, and -P(O)(OR$^{15}$)(OR$^{16}$), and
wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, and heteroaryalkyl groups is optionally substituted with 1-5 substituents independently selected from the group consisting of the moieties shown below:

5  
R₁⁵, R₁⁶ and R₁⁷ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, R₁⁸-alkyl, R₁⁸-cycloalkyl, R₁⁸-cycloalkylalkyl, R₁⁸-heterocyclyl, R⁺₁⁸-aryl, R₁⁸-aryalkyl, R₁⁸-heteroaryl and R₁⁸-heteroaryalkyl;

10  
R₁⁸ is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, aryalkynyl, -NO₂, halo, heteroaryl, -CF₃, -CN, -C(O)R₁⁹, -C(O)OH, -C(O)OR₁⁹, -C(O)NHR₂⁰, -C(O)NH₂, -C(O)N(alkyl)(aryl), -C(O)N(alkyl)(acyl), -C(O)N(alkyl)(heteroaryl), -SR₁⁹, -S(O)₂R₂₀, -S(O)NH(aryl), -S(O)NH₂, -S(O)N(aryl)(alkyl), -S(O)NH(aryl), -S(O)NH₂, -S(O)₂N(aryl)₂, -S(O)₂N(alkyl)(aryl), -OOF₃, -OH, -OR₂₀, -O-heterocyclylalkyl, -O-heterocyclylalkyl, -NH₂, -NHR₂₀, -N(arylalkyl)₂, -N(arylalkyl)-heteroaryalkyl, -NHC(O)R₂₀, -NHC(O)NH₂, -NHC(O)NH(alkyl), -NHC(O)N(aryl)(alkyl), -N(arylalkyl)C(O)NH(aryl), -N(arylalkyl)C(O)NH(alkyl), -N(arylalkyl)C(O)N(aryl)(alkyl), -N(arylalkyl)S(O)₂N(aryl)(alkyl); and -N(arylalkyl)S(O)₂N(aryl)(alkyl);

15  
or, alternately, two R₁⁸ moieties on adjacent carbons can be linked together to form:

20  

R₁⁹ is alkyl, cycloalkyl, aryl, arylalkyl or heteroaryalkyl;

R₂₀⁻ is alkyl, cycloalkyl, aryl, halo substituted aryl, aryalkyl, heteroaryl or heteroaryalkyl;
wherein each of the carbocyclic spirocyclic, heterocyclic spirocyclic, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R¹, R², R⁶, R⁷, R⁸, R⁹, R¹⁰ and R¹⁴ are independently unsubstituted or substituted by 1 to 5 R²¹ groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R²¹ are independently unsubstituted or substituted by 1 to 5 R²² groups independently selected from the group consisting of alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, halo, -CF₃, -CN,

-OR¹⁵, -C(O)R¹⁵, -C(O)OR¹⁵, -alkyl-C(O)OR¹⁵, C(O)N(R¹⁵)(R¹⁶), -SR¹⁵, -S(O)N(R¹⁵)(R¹⁶), -C(=NOR¹⁵)R¹⁶, -P(O)(OR¹⁵)(OR¹⁶), -N(R¹⁵)(R¹⁶), -alkyl-N(R¹⁵)(R¹⁶),
-N(R¹⁵)C(O)R¹⁶, -CH₂-N(R¹⁵)C(O)R¹⁶, -CH₂-N(R¹⁵)C(O)N(R¹⁶)(R¹⁷), -CH₂-N(R¹⁵);
-N(R¹⁵)S(O)R¹⁶, -N(R¹⁵)S(O)₂R¹⁶, -CH₂-N(R¹⁵)S(O)₂R¹⁶,
-N(R¹⁵)S(O)₂N(R¹⁶)(R¹⁷), -N(R¹⁵)S(O)N(R¹⁶)(R¹⁷), -N(R¹⁵)C(O)N(R¹⁶)(R¹⁷),
-CH₂-N(R¹⁵)C(O)N(R¹⁶)(R¹⁷), -N(R¹⁵)C(O)OR¹⁶, -CH₂-N(R¹⁵)C(O)OR¹⁶, -S(O)R¹⁵, -N₃, -NO₂ and -S(O)₂R¹⁵;

Thus, one embodiment is directed to a compound of the formula I:
or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

- $U$ is $\text{\textgreaterCR}_5$ or $N$;
- $G$ is $O$ or $S$;
- $V$ is selected from the group consisting of a bond, $O$, $\text{-C(O)-}$, and $N(R^{14})$;
- $R^1$ is selected from the group consisting of: $H$, halo, alkyl-, alkenyl-, alkylnyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl-, wherein each of said alkyl-, alkenyl- and alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl- is optionally substituted with 1-5 substituents independently selected from the group consisting of the $R^{21}$ groups;
- $R^2$ is selected from the group consisting of: $H$, alkyl-, alkenyl-, alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl-, wherein each of said alkyl-, alkenyl- and alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl- is optionally substituted with 1-5 substituents independently selected from the group consisting of the $R^{21}$ groups;

or

$R^1$ and $R^2$ are joined together to form a C5-C8 cycloalkyl or a 5-8 membered heterocyclyl moiety, wherein each of said cycloalkyl or heterocyclyl moiety is optionally substituted with 1-5 substituents independently selected from the group consisting of the $R^{21}$ groups; or
R\textsuperscript{1} and R\textsuperscript{8} are taken together to form a bond (i.e., there is a triple bond between the carbon atom to which R\textsuperscript{1} was bonded to and the carbon to which R\textsuperscript{8} was bonded to, i.e., the compound of formula I is a compound of formula II:

![Diagram](image)

formula II

wherein G, U, V, R\textsuperscript{2}, R\textsuperscript{6}, R\textsuperscript{7}, R\textsuperscript{8}, and R\textsuperscript{10} are as defined for formula I;

R\textsuperscript{5}, R\textsuperscript{6} and R\textsuperscript{7} are each independently selected from the group consisting of H, -C(O)R\textsuperscript{15}, -C(O)OR\textsuperscript{15}, -C(O)N(R\textsuperscript{15})(R\textsuperscript{16}), -C(=NOR\textsuperscript{15})R\textsuperscript{16}, alkyl-, alkenyl-, alkynyl-, aryl-, arylalkyl-, alkyaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroaryalkyl-, heterocyclyl- and heterocyclyalkyl- and wherein each of said alkyl-, alkenyl- and alkynyl-, aryl-, arylalkyl-, alkyaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroaryalkyl-, heterocyclyl- and heterocyclyalkyl- is optionally substituted with 1-5 substituents independently selected from the group consisting of the R\textsuperscript{21} groups; or

R\textsuperscript{8} is selected from the group consisting of H, halo, -CN, -OR\textsuperscript{15}, -C(O)R\textsuperscript{15}, -C(O)OR\textsuperscript{15}, -C(O)N(R\textsuperscript{15})(R\textsuperscript{16}), -SR\textsuperscript{15}, -S(O)(O)(R\textsuperscript{15})(R\textsuperscript{16}), -CH(R\textsuperscript{15})(R\textsuperscript{16}), -S(O)\textsuperscript{2}N(R\textsuperscript{15})(R\textsuperscript{16}), -C(=NOR\textsuperscript{15})R\textsuperscript{16}, -P(O)(OR\textsuperscript{15})(OR\textsuperscript{16}), -N(R\textsuperscript{15})(R\textsuperscript{16}),
-alkyl-N(R\textsubscript{15})(R\textsubscript{16}), -N(R\textsubscript{15})C(O)R\textsubscript{16}, -CH\textsubscript{2}-N(R\textsubscript{15})C(O)R\textsubscript{16},

-CH\textsubscript{2}-N(R\textsubscript{15})C(O)N(R\textsubscript{16})(R\textsubscript{17}), -CH\textsubscript{2}-R\textsubscript{16}, -CH\textsubscript{2}N(R\textsubscript{15})(R\textsubscript{16}), -N(R\textsubscript{15})S(O)R\textsubscript{16},

-N(R\textsubscript{15})S(O)\textsubscript{2}R\textsubscript{16}, -CH\textsubscript{2}-N(R\textsubscript{15})S(O)\textsubscript{2}R\textsubscript{16}, -N(R\textsubscript{15})S(O)\textsubscript{2}N(R\textsubscript{16})(R\textsubscript{17}),

-N(R\textsubscript{15})S(O)N(R\textsubscript{16})(R\textsubscript{17}), -N(R\textsubscript{15})S(O)\textsubscript{2}N(R\textsubscript{16})(R\textsubscript{17}),

-R\textsubscript{16}, -R\textsubscript{15}, -R\textsubscript{17}; where each of said alkyl-, aryl-, arylalkyl-, arylalkenyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocycl- and heterocyclyalkyl- moieties is optionally substituted with 1-3 substituents independently selected from the group consisting of the the R\textsuperscript{11} groups;

R\textsuperscript{10} is selected from the group consisting of a bond, alkyl-, aryl-, arylalkyl-, arylalkenyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl-, heterocyclyalkyl- and the moieties:

where X is O, N(R\textsubscript{14}) or S;

wherein each of said alkyl-, aryl-, arylalkyl-, arylalkenyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl-, heterocyclyalkyl-,
is optionally substituted with 1-3 substituents independently selected from the
group consisting of the $R^{21}$ groups;

or, alternatively, $R^8$ and $R^{10}$, together with the carbon atom to which
they are bound, can form a $C_4$-$C_7$ carbocyclic (e.g., cycloalkyl) ring, or a 4-7
membered heterocyclyl ring, or a $C_4$-$C_7$ carbocyclenyl (e.g., cycloalkenyl)
ing, or a 4-7 membered heterocyclenyl ring; and wherein said carbocyclic
ring, heterocyclyl ring, carbocyclenylring, or heterocyclenyl ring is optionally
substituted with 1-5 independently selected $R^{21}$ substituents;

$R^9$ is selected from the group consisting of alkyl-, alkenyl-, alkynyl-, aryl-,
arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl,-
heterocyclyl- and heterocyclenyl-, and wherein each of said alkyl-, alkenyl-,
aldehyde-, aryl-, aryalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-,
heteroarylalkyl-, heterocyclyl- and heterocyclenyl- is optionally substituted with 1-3
substituents independently selected from the group consisting of the $R^{21}$ groups;

$R^{14}$ is selected from the group consisting of H, alkyl, cycloalkyl,
cycloalkylalkyl-, cycloalkenyl, heterocyclyl, heterocyclenylalkyl-, aryl, arylalkyl-,
heteroaryl, heteroarylalkyl-, -CN, -C(O)R^{15}, -C(O)OR^{15}, -C(O)N(R^{15})(R^{16}),
-S(O)N(R^{15})(R^{16}), -S(O)_2N(R^{15})(R^{16}), -C(N=NOR^{15})R^{16}, and -P(O)(OR^{15})(OR^{16}), and
wherein each of the alkyl, cycloalkyl, cycloalkylalkyl-, cycloalkenyl, heterocyclyl,
heterocyclenylalkyl-, aryl, arylalkyl-, heteroaryl, heteroarylalkyl- groups is optionally
substituted with 1-5 independently selected $R^{21}$ groups;
R\textsuperscript{15}, R\textsuperscript{16}, and R\textsuperscript{17} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl-, heterocyclyl, heterocyclylalkyl-, aryl, arylalkyl-, heteroaryl, heteroarylalkyl-, arylheterocyclyl-, (R\textsuperscript{18})\textsubscript{n}-alkyl-, (R\textsuperscript{18})\textsubscript{n}-cycloalkylalkyl-, (R\textsuperscript{18})\textsubscript{n}-heterocyclylalkyl-, (R\textsuperscript{18})\textsubscript{n}-heterocyclylalkyl-, (R\textsuperscript{18})\textsubscript{n}-arylated-, (R\textsuperscript{18})\textsubscript{n}-arylatedalkyl-, (R\textsuperscript{18})\textsubscript{n}-heteroaryl- and (R\textsuperscript{18})\textsubscript{n}-heteroarylalkyl-;

n is 1 to 5;

Each R\textsuperscript{18} is independently selected from the group consisting of: alkyl, alkenyl, alkynyl, aryl, arylalkyl-, arylalkenyl-, aryalkynyl-, -NU\textsubscript{2}, halo, heteroaryl, -CF\textsubscript{3}, -CN, -C(O)R\textsuperscript{19}, -C(O)OH, -C(O)OR\textsuperscript{19}, -C(O)NHR\textsuperscript{20}, -C(O)NH\textsubscript{2}, -C(O)NH\textsubscript{2}C(O)N(alkyl)\textsubscript{2}, -C(O)N(aryl)(aryl), -C(O)N(alkyl)(heteroaryl), -SR\textsuperscript{19}, -S(O)\textsubscript{2}R\textsuperscript{20}, -S(O)NH\textsubscript{2}, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl), -S(O)\textsubscript{2}NH\textsubscript{2}, -S(O)\textsubscript{2}NHR\textsuperscript{19}, -S(O)\textsubscript{2}NH(heterocyclyl), -S(O)\textsubscript{2}N(aryl)(alkyl), -S(O)\textsubscript{2}N(aryl)(aryl), -OCF\textsubscript{3}, -OH, -OR\textsuperscript{20}, -O-heterocyclylalkyl, -O-cycloalkylalkyl, -O-heterocyclylalkylalkyl, -NH\textsubscript{2}, -NHR\textsuperscript{20}, -N(alkyl)\textsubscript{2}, -N(arylalkyl)\textsubscript{2}, -N(arylatedalkyl)-, -(N(arylatedalkyl)), -NHC(O)R\textsuperscript{20}, -NHC(O)NH\textsubscript{2}, -NHC(O)NH(alkyl), -NHC(O)N(alkyl)(alkyl), -N(alkyl)C(O)NH(alkyl), -N(alkyl)C(O)N(alkyl)(alkyl), -NHS(O)\textsubscript{2}R\textsuperscript{20}, -NHS(O)\textsubscript{2}NH(alkyl), -NHS(O)\textsubscript{2}N(alkyl)(alkyl), -N(alkyl)S(O)\textsubscript{2}NH(alkyl) and -N(alkyl)S(O)\textsubscript{2}N(alkyl)(alkyl); or

two R\textsuperscript{18} moieties on adjacent carbons can be linked together to form:

\[
\begin{align*}
\text{R}\textsuperscript{19} & \text{ is selected from the group consisting of: alkyl, cycloalkyl, aryl, arylalkyl} \\
\text{and heteroarylalkyl;} \\
\text{R}\textsuperscript{20} & \text{ is selected from the group consisting of: alkyl, cycloalkyl, aryl, halo} \\
\text{substituted aryl, arylalkyl, heteroaryl and heteroarylalkyl;} \\
\text{Each R}\textsuperscript{21} & \text{ is independently selected from the group consisting of: alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl-, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl-, aryl, arylalkyl-, heteroaryl, heteroarylalkyl-, halo, -CN, -}
\end{align*}
\]
\[ \text{OR}^{15}, \text{-C(O)R}^{15}, \text{-C(O)OR}^{15}, \text{-C(O)N(R}^{15})(\text{R}^{16}), \text{-SR}^{15}, \text{-S(O)N(R}^{15})(\text{R}^{16}), \]
\[ \text{-CH(R}^{15})(\text{R}^{16}), \text{-S(O)}_{2}\text{N}(\text{R}^{15})(\text{R}^{16}), \text{-C(=\text{NOR})R}^{16}, \text{-P(O)(OR}^{15})(\text{OR}^{16}), \]
\[ \text{-N(R}^{15})(\text{R}^{16}), \text{-alkyl-N}(\text{R}^{15})(\text{R}^{16}), \text{-N}(\text{R}^{15})\text{C(O)R}^{16}, \text{-CH}_{2}\text{-N}(\text{R}^{15})\text{C(O)R}^{16}, \]
\[ \text{-CH}_{2}\text{-N}(\text{R}^{15})\text{C(O)N}(\text{R}^{16})(\text{R}^{17}), \text{-CH}_{2}\text{-R}^{15}, \text{-CH}_{2}\text{-N}(\text{R}^{15})(\text{R}^{16}), \text{-N}(\text{R}^{15})\text{S(O)R}^{16}, \]
\[ \text{-N}(\text{R}^{15})\text{S(O)}_{2}\text{R}^{16}, \text{-CH}_{2}\text{-N}(\text{R}^{15})\text{S(O)}_{2}\text{R}^{16}, \text{-N}(\text{R}^{15})\text{S(O)}_{2}\text{N}(\text{R}^{16})(\text{R}^{17}), \]
\[ \text{-N}(\text{R}^{15})\text{C(O)N}(\text{R}^{16})(\text{R}^{17}), \text{-N}(\text{R}^{15})\text{C(O)N}(\text{R}^{16})(\text{R}^{17}), \text{-CH}_{2}\text{-N}(\text{R}^{15})\text{C(O)N}(\text{R}^{16})(\text{R}^{17}), \]
\[ \text{-N}(\text{R}^{15})\text{C(O)OR}^{16}, \text{-CH}_{2}\text{-N}(\text{R}^{15})\text{C(O)OR}^{16}, \text{-S(O)R}^{15}, \text{-N}_{3}, \text{-NO}_{2} \text{ and } \text{-S(O)}_{2}\text{R}^{15}; \]
\[ \text{wherein each of the alkyl, cycloalkeny}, \text{cycloalkyl, cycloalkylalkyl-}, \text{heterocycloalkyl, heterocycloalkylalkyl-}, \text{aryl, aryalkyl-}, \text{heteroaryl, heteroarylalkyl-}, \text{alkenyl and alkynyl R}^{21} \text{ groups is optionally substituted with 1 to 5 independently selected R}^{22} \text{ groups; and} \]
\[ \text{Each R}^{22} \text{ is independently selected from the group consisting of alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, halo, -CF}_{3}, \text{-CN,} \]
\[ \text{-OR}^{15}, \text{-C(O)R}^{15}, \text{-C(O)OR}^{15}, \text{-alkyl-C(O)OR}^{15}, \text{C(O)N}(\text{R}^{15})(\text{R}^{16}), \text{-SR}^{15}, \]
\[ \text{-S(O)N}(\text{R}^{15})(\text{R}^{16}), \text{-S(O)}_{2}\text{N}(\text{R}^{15})(\text{R}^{16}), \text{-C(=\text{NOR})R}^{16}, \text{-P(O)(OR}^{15})(\text{OR}^{16}), \]
\[ \text{-N}(\text{R}^{15})(\text{R}^{16}), \text{-alkyl-N}(\text{R}^{15})(\text{R}^{16}), \text{-N}(\text{R}^{15})\text{C(O)R}^{16}, \text{-CH}_{2}\text{-N}(\text{R}^{15})\text{C(O)R}^{16}, \]
\[ \text{-N}(\text{R}^{15})\text{S(O)R}^{16}, \text{-N}(\text{R}^{15})\text{S(O)}_{2}\text{R}^{16}, \text{-CH}_{2}\text{-N}(\text{R}^{15})\text{S(O)}_{2}\text{R}^{16}, \text{-N}(\text{R}^{15})\text{S(O)}_{2}\text{N}(\text{R}^{16})(\text{R}^{17}), \]
\[ \text{-N}(\text{R}^{15})\text{S(O)N}(\text{R}^{16})(\text{R}^{17}), \text{-N}(\text{R}^{15})\text{C(O)N}(\text{R}^{16})(\text{R}^{17}), \text{-CH}_{2}\text{-N}(\text{R}^{15})\text{C(O)N}(\text{R}^{16})(\text{R}^{17}), \]
\[ \text{-N}(\text{R}^{15})\text{C(O)OR}^{16}, \text{-CH}_{2}\text{-N}(\text{R}^{15})\text{C(O)OR}^{16}, \text{-N}_{3}, \text{-NO}_{2}, \text{-S(O)R}^{15} \text{ and} \]
\[ \text{-S(O)}_{2}\text{R}^{15}. \]

In another embodiment, the present application discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

\[ \text{wherein:} \]
U is $\text{CR}^5$ or N;

G is O or S;

V is selected from the group consisting of a bond, O, -C(O)-, and N(R$^1$);

R$^1$ is selected from the group consisting of: H, halo, alkyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl-, wherein each of said alkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below;

R$^2$ is selected from the group consisting of: H, alkyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl-, wherein each of said alkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below;

or, alternatively, R$^1$ and R$^2$ may be joined together to form a C5-C8 cycloalkyl or a 5-8 membered heterocycly moiety, with each of said cycloalkyl or heterocycly moiety being unsubstituted or optionally independently being substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below;

or, alternatively, R$^1$ and R$^8$ are taken together to form a bond (i.e., there is a triple bond between the carbon atom to which R$^1$ was bonded to and the carbon to which R$^8$ was bonded to, i.e., the compound of formula I is a compound of formula II:}
wherein \( G \), \( U \), \( V \), \( R^2 \), \( R^6 \), \( R^7 \), \( R^9 \), and \( R^{10} \) are as defined for formula I;

\( R^5 \), \( R^6 \) and \( R^7 \) can be the same or different, each being independently selected from the group consisting of \( H \), -C(O)R\(^{15} \), -C(O)OR\(^{15} \), -C(O)N(R\(^{15}\))(R\(^{16} \)), -C(=NOR\(^{15}\))R\(^{16} \), alkyl-, aryl-, arylalkyl-, alkyaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroaryalkyl-, heterocyclyl- and heterocyclylalkyl-, wherein each of said alkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below;

or alternately, \( R^6 \) and \( R^7 \) can be joined together to form a carbocyclic spirocyclic moiety or a heterocyclic spirocyclic moiety wherein each of said carbocyclic spirocyclic moiety and heterocyclic spirocyclic moiety can be: (i) unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below, or (ii) fused with an aryl, heteroaryl, cycloalkyl or heterocycloalkyl ring, wherein each of said carbocyclic spirocyclic moiety, heterocyclic spirocyclic moiety, aryl, heteroaryl, cycloalkyl and heterocycloalkyl ring can be unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below;
R^8 is selected from the group consisting of H, halo, -CN, -OR^15, -C(O)R^15, -C(O)OR^15, -C(O)N(R^15)(R^16), -SR^15, -S(O)N(R^15)(R^16), -CH(R^15)(R^16), -S(O)_2N(R^15)(R^16), -C(=NOR^15)R^16, -P(O)(OR^15)(OR^16), -N(R^15)(R^16), -alkyl-N(R^15)(R^16), -N(R^15)C(O)R^16, -CH_{2}-N(R^15)C(O)R^16, -alkyl-N(R^15)(R^16), -N(R^15)C(O)OR^16, \text{ and } -N(R^15)S(O)R^16, alkyl, cycloalkyl, aryl and heteroaryl, with each of said alkyl, cycloalkyl, aryl and heteroaryl being unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group of the moieties shown below;

R^{10} is selected from the group consisting of a bond, aryl, heteroaryl, cycloalkyl, heterocyclic, arylalkyl-, alkyaryl-, heteroarylalkyl-, heterocyclylalkyl- and the moieties:

![Molecular structures](image)

where X is O, N(R^{14}) or S;

wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclic and the above-noted moieties for R^{10} can be unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each being independently selected from the group consisting of the moieties shown below;
or, alternatively, $R^8$ and $R^{10}$, together with the carbon atom to which they are bound, can form a $C_4$-$C_7$ carbocyclic (e.g., cycloalkyl) ring, or a 4-7 membered heterocyclyl ring, or a $C_4$-$C_7$ carbocyclyl (e.g., cycloalkenyln) ring, or a 4-7 membered heterocyclenyl ring; and wherein said carbocyclic ring, heterocyclyl ring, carbocyclylring, or heterocyclenyl ring is optionally substituted with 1-5 independently selected $R^{21}$ substituents;

$R^9$ is selected from the group consisting of alkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkyaryl, heteroaryllalkyl and heterocyclylalkyl wherein each of said alkyl, aryl, heteroaryl and heterocyclyl can be unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below;

$R^{14}$ is selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroaryllalkyl, -CN, -C(O)R, -C(O)OR, -C(O)N(R)(R), -S(O)N(R)(R), -S(O)NH(alkyl), -S(O)NH(aryl), -S(O)N(TM)(R)(R), -S(O)N(TM)(aryl), -S(O)N(TM2)(R)(R), -S(O)N(TM2)(aryl), -C(=NOR), P(O)(OR), and $R^{15}$, $R^{16}$ and $R^{17}$ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroaryllalkyl, arylcycloalkyl, arylheterocyclyl, $R^{18}$-alkyl, $R^{18}$-cycloalkyl, $R^{18}$-cycloalkylalkyl, $R^{18}$-heterocyclyl, $R^{18}$-heterocyclylalkyl, $R^{18}$-aryl, $R^{18}$-arylalkyl, $R^{18}$-heteroaryl and $R^{18}$-heteroaryllalkyl; or, alternately,

$R^{18}$ is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl-, arylalkenyl-, arylalkynyl-, -NO$_2$, halo, heteroaryl,

- CF$_3$, -CN, -C(O)R, -C(O)OH, -C(O)OR, -C(O)NHR, -C(O)NH$_2$,
- C(O)NH$_2$-C(O)N(alkyl)$_2$, -C(O)N(alkyl)(aryl), -C(O)N(alkyl)(heteroaryl), -SR, -S(O)$_2$R, -S(O)NH$_2$, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl),
- S(O)$_2$N(alkyl)(aryl), -OCF$_3$, -OH, -OR, -O-heterocyclyl, -O-cycloalkylalkyl,
- O-heterocyclylalkyl, -NH$_2$, -NHR, -N(aryl)$_2$, -N(aryalkyl)$_2$,
-N(arylalkylMheteroarylalkyl), -NHC(O)R²₀, -NHC(O)NH₂, -NHC(O)NH(alkyl),
-NHC(O)N(alkyl)(alkyl), -NHC(O)NH(alkyl), -NHC(O)N(alkyl)(alkyl),
-NHS(O)₂R²₀, -NHS(O)₂NH(alkyl), -NHS(O)₂N(alkyl)(alkyl), -N(alkyl)S(O)₂NH(alkyl)
and -N(alkyl)S(O)₂N(alkyl)(alkyl);

or, alternately, two R¹⁸ moieties on adjacent carbons can be linked together
to form:

R¹⁹ is alkyl, cycloalkyl, aryl, arylalkyl or heteroarylalkyl;
R²⁰ is alkyl, cycloalkyl, aryl, halo substituted aryl, arylalkyl, heteroaryl or
heteroarylalkyl;

wherein each of the carbocyclic spirocyclic, heterocyclic spirocyclic, alkyl,
cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl,
heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R¹, R², R⁵, R⁶, R⁷, R⁸, R⁹,
R¹⁰ and R¹⁴ are independently unsubstituted or substituted by 1 to 5 R²¹ groups
independently selected from the group consisting of alkyl, alkenyl, alkynyl,
cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl,
aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, -OR¹⁵, -C(O)R¹⁵, -C(O)OR¹⁵,
-C(O)N(R¹⁵)(R¹⁶), -SR¹⁵, -S(O)N(R¹⁵)(R¹⁶), -CH(R¹⁵)(R¹⁶), -S(O)₂N(R¹⁵)(R¹⁶),
-C(\(-\text{NOR}¹⁵\))(R¹⁶), -P(O)(OR¹⁵)(OR¹⁶), -N(R¹⁵)(R¹⁶), -alkyl-N(R¹⁵)(R¹⁶),

-N(R¹⁵)C(O)R¹⁶, -CH₂-N(R¹⁵)C(O)R¹⁶, -CH₂-N(R¹⁵)C(O)N(R¹⁵)(R¹⁷), -CH₂-R¹⁵,

wherein each of the alkyl, cycloalkenyl, cycloalkyl, cycloalkylalkyl,
heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl,
alkenyl and alkynyl groups in R²¹ are independently unsubstituted or substituted
by 1 to 5 R²² groups independently selected from the group consisting of alkyl,
cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, halo, -CF₃, -CN, -OR₁⁵, -C(O)R₁⁵, -C(O)OR₁⁵, C(O)N(R¹⁵)(R₁⁶), -SR¹⁵, -S(O)N(R¹⁵)(R₁⁶), -S(O)₂N(R¹⁵)(R₁⁶), -C(=NOR¹⁵)R₁⁶, -P(O)(OR¹⁵)(OR₁⁶), -N(R¹⁵)(R₁⁶), -alkyl-N(R¹⁵)(R₁⁶), -N(R¹⁵)C(O)R₁⁶, -CH₂-N(R¹⁵)C(O)R₁⁶, -N(R¹⁵)S(O)R₁⁶, -N(R¹⁵)S(O)₂R₁⁶, -N(R¹⁵)S(O)₂N(R₁⁶)(R₁⁷), -N(R¹⁵)S(O)N(R₁⁶)(R₁⁷), -N(R¹⁵)C(O)N(R₁⁶)(R₁⁷), -CH₂-N(R¹⁵)C(O)N(R₁⁶)(R₁⁷), -N(R¹⁵)C(O)OR₁⁶, -CH₂-N(R¹⁵)C(O)OR₁⁶, -N₃, -NO₂, -S(O)R₁⁵ and -S(O)₂R₁⁵;

In another embodiment, the present application discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

\[
\text{\begin{tikzpicture}
\node (U) at (0,0) {U};
\node (V) at (1,1) {V};
\node (R²) at (2,0) {R²};
\node (R¹) at (1,1.5) {R¹};
\node (R⁹) at (0,0.5) {R⁹};
\node (R⁸) at (0.5,0.5) {R⁸};
\node (R¹⁰) at (0.5,-0.5) {R¹⁰};
\node (R⁶) at (2.5,0) {R⁶};
\node (R⁷) at (2.5,-0.5) {R⁷};
\node (N) at (0.5,0) {N};
\node (G) at (1.5,0) {G};
\end{tikzpicture}}
\]

wherein:

- **U** is \( -\text{CR}⁵ \) or \( N \);
- **V** is selected from the group consisting of a bond, -C(O)-, O and -N(R¹⁴);
- **R¹** is selected from the group consisting of H, halo, alkyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl wherein each of said alkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy and alkoxy groups;
- **R²** is selected from the group consisting of H, alkyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl wherein each of said alkyl, aryl, heteroaryl, cycloalkyl and
heterocyclyl can be unsubstituted or optionally independently substituted with 1-5
substituents which can be the same or different, each substituent being
independently selected from the group consisting of halo, -CN, -NH2, -NH(alkyl), -N(alkyl)2, hydroxy and
alkoxy groups;
or, alternatively, R1 and R2 may be joined together to form a C5-C8
cycloalkyl or a 5-8 membered heterocyclyl moiety, with each of said cycloalkyl or
cycloalkyl moiety being unsubstituted or optionally independently being
substituted with 1-5 substituents which can be the same or different, each
substituent being independently selected from the group consisting of halo, -CN,
-NH2, -NH(alkyl), -N(alkyl)2, hydroxy and alkoxy groups;
or, alternatively, R1 and R8 are taken together to form a bond (i.e.,
there is a triple bond between the carbon atom to which R1 was bonded to and the
carbon to which R8 was bonded to, i.e., the compound of formula I is a compound
of formula II:

wherein G, U, V, R2, R6, R7, R9, and R10 are as defined for formula I;

R5, R6 and R7 can be the same or different, each being independently
selected from the group consisting of H, -C(O)R15, -C(O)OR15, -C(O)N(R15)(R16),
-C(=NOR15)R16, alkyl-, aryl-, arylalkyl-, allylalkyl-, alkyaryl-, cycloalkyl-, cycloalkylalkyl-
heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl-, wherein each of
said alkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl can be unsubstituted or
optionally independently substituted with 1-5 substituents which can be the same
or different, each substituent being independently selected from the group
consisting of halo, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy, alkoxy, -aryl and heteroaryl groups;
or alternately, R⁶ and R⁷ can be joined together to form a carbocyclic spirocyclic moiety or a heterocyclic spirocyclic moiety wherein each of said carbocyclic spirocyclic moiety and heterocyclic spirocyclic moiety can be: (i) unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy, alkoxy, aryl and heteroaryl groups, or (ii) fused with an aryl, heteroaryl, cycloalkyl or heterocycloalkyl ring, wherein each of said carbocyclic spirocyclic moiety, heterocyclic spirocyclic moiety, aryl, heteroaryl, cycloalkyl and heterocycloalkyl ring can be unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy, alkoxy, aryl and heteroaryl groups;
R⁸ is selected from the group consisting of H, halo, -CN, -OR₁⁵, -C(O)R₁⁵, -C(O)OR₁⁵, -C(O)N(R¹⁵)(R₁⁶), -SR₁⁵, -S(O)N(R¹⁵)(R₁⁶), -CH(R¹⁵)(R₁⁶), -S(O)₂N(R¹⁵)(R₁⁶), -C(=NOR₁⁵)R₁⁶, -P(O)(OR₁⁵)(OR₁⁶), -N(R¹⁵)(R₁⁶), -alkyl-N(R¹⁵)(R₁⁶), -N(R¹⁵)C(O)R₁⁶, -CH₂-N(R¹⁵)C(O)R₁⁶, -CH₂-N(R¹⁵)C(O)N(R¹⁶)(R₁⁷), -CH₂-N(R¹⁵)C(O)N(R¹⁶)(R₁⁷), -N(R¹⁵)S(O)R₁⁶, -N(R¹⁵)S(O)₂R₁⁶, -CH₂-N(R¹⁵)S(O)₂R₁⁶, -N(R¹⁵)S(O)₂N(R¹⁶)(R₁⁷), -N(R¹⁵)C(O)OR₁⁶, -CH₂-N(R¹⁵)C(O)OR₁⁶, -S(O)R₁⁵, -N₃, -NO₂ and -S(O)₂R₁⁵, alkyl, cycloalkyl, aryl and heteroaryl, with each of said alkyl, cycloalkyl, aryl and heteroaryl being unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy and alkoxy groups;
\( R^{10} \) is selected from the group consisting of a bond, aryl, heteroaryl, cycloalkyl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl, heterocyclylalkyl and the moieties:

where \( X \) is O, NH or S;

wherein each of said aryl, heteroaryl, cycloalkyl, heterocyclyl and the above-noted moieties for \( R^{10} \) can be unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each being independently selected from the group consisting of halo, alkyl, -CN, -NH\(_2\), -NH(alkyl), -N(alkyl)\(_2\), hydroxy and alkoxy groups; and

\( R^9 \) is selected from the group consisting of alkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, alkylaryl, heteroarylalkyl and heterocyclylalkyl wherein each of said alkyl, aryl, heteroaryl and heterocyclyl can be unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH\(_2\), -NH(alkyl), -N(alkyl)\(_2\), hydroxy and alkoxy groups.

In another embodiment \( R^1 \) and \( R^2 \) can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclylalkyl-, wherein each of said alkyl-, alkenyl- and
alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl- can be unsubstituted or optionally independently substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below; or, alternatively, \( R^1 \) and \( R^2 \) may be joined together to form a C5-C8 cycloalkyl or a 5-8 membered heterocyclyl moiety, with each of said cycloalkyl or heterocyclyl moiety being unsubstituted or optionally independently being substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of the \( R^{21} \) moieties.

In another embodiment \( R^5 \), \( R^6 \) and \( R^7 \) can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl-, wherein each of said alkyl-, alkenyl- and alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl- can be unsubstituted or optionally independently substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below; or alternately, \( R^6 \) and \( R^7 \) can be joined together to form a carbocyclic spirocyclic moiety or a heterocyclic spirocyclic moiety wherein each of said carbocyclic spirocyclic moiety and heterocyclic spirocyclic moiety can be: (i) unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below, or (ii) fused with an aryl or heteroaryl ring, wherein each of said carbocyclic spirocyclic moiety, heterocyclic spirocyclic moiety, aryl and heteroaryl ring can be unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of the \( R^{21} \) moieties.
In another embodiment each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R<sup>1</sup>, R<sup>2</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> and R<sup>14</sup> are independently unsubstiuted or substituted by 1 to 5 R<sup>2</sup> groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, -OR<sup>15</sup>, -C(O)R<sup>15</sup>, -C(O)OR<sup>15</sup>, -C(O)N(R<sup>15</sup>)(R<sup>16</sup>), -SR<sup>15</sup>, -S(O)N(R<sup>15</sup>)(R<sup>16</sup>), -CH(R<sup>15</sup>)(R<sup>16</sup>), -S(O)R<sup>15</sup>, -N(R<sup>15</sup>)<sub>2</sub>N(R<sup>15</sup>)(R<sup>16</sup>), -C(NOR<sup>15</sup>)R<sup>16</sup>, -P(O)(OR<sup>15</sup>)(OR<sup>16</sup>), -N(R<sup>15</sup>)(R<sup>16</sup>), -alkyl-N(R<sup>15</sup>)(R<sup>16</sup>), -N(R<sup>15</sup>)C(O)R<sup>16</sup>, -CH<sub>2</sub>N(R<sup>15</sup>)C(O)R<sup>16</sup>, -CH<sub>2</sub>N(R<sup>15</sup>)C(O)N(R<sup>15</sup>)(R<sup>16</sup>)(R<sup>17</sup>), -CH<sub>2</sub>-R<sup>15</sup>; -CH<sub>2</sub>N(R<sup>15</sup>)(R<sup>16</sup>), -N(R<sup>15</sup>)S(O)R<sup>16</sup>, -N(R<sup>15</sup>)S(O)<sub>2</sub>R<sup>16</sup>, -CH<sub>2</sub>N(R<sup>15</sup>)S(O)<sub>2</sub>R<sup>16</sup>, -N(R<sup>15</sup>)S(O)<sub>2</sub>N(R<sup>16</sup>)(R<sup>17</sup>), -N(R<sup>15</sup>)S(O)N(R<sup>16</sup>)(R<sup>17</sup>), -N(R<sup>15</sup>)C(O)N(R<sup>16</sup>)(R<sup>17</sup>), -CH<sub>2</sub>N(R<sup>15</sup>)C(O)N(R<sup>16</sup>)(R<sup>17</sup>), -N(R<sup>15</sup>)C(O)OR<sup>16</sup>, -CH<sub>2</sub>N(R<sup>15</sup>)C(O)OR<sup>16</sup>, -S(O)R<sup>15</sup>, -N<sub>3</sub>, -NO<sub>2</sub> and -S(O)<sub>2</sub>R<sup>15</sup>; wherein each of the alkyl, cycloalkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R<sup>2</sup> are independently unsubstiuted or substituted by 1 to 5 R<sup>22</sup> groups independently selected from the group consisting of alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, halo, -CF<sub>3</sub>, -CN, -OR<sup>15</sup>, -C(O)R<sup>15</sup>, -C(O)OR<sup>15</sup>, -alkyl-C(O)OR<sup>15</sup>, C(O)N(R<sup>15</sup>)(R<sup>16</sup>), -SR<sup>15</sup>, -S(O)N(R<sup>15</sup>)(R<sup>16</sup>), -S(O)<sub>2</sub>N(R<sup>15</sup>)(R<sup>16</sup>), -C(N=NR<sup>15</sup>)(R<sup>16</sup>), -P(O)(OR<sup>15</sup>)(OR<sup>16</sup>), -N(R<sup>15</sup>)(R<sup>16</sup>), -alkyl-N(R<sup>15</sup>)(R<sup>16</sup>), -N(R<sup>15</sup>)C(O)R<sup>16</sup>, -CH<sub>2</sub>N(R<sup>15</sup>)C(O)R<sup>16</sup>, -N(R<sup>15</sup>)S(O)R<sup>16</sup>, -N(R<sup>15</sup>)S(O)<sub>2</sub>R<sup>16</sup>, -CH<sub>2</sub>N(R<sup>15</sup>)S(O)<sub>2</sub>R<sup>16</sup>, -N(R<sup>15</sup>)S(O)N(R<sup>16</sup>)(R<sup>17</sup>), -N(R<sup>15</sup>)S(O)N(R<sup>16</sup>)(R<sup>17</sup>), -N(R<sup>15</sup>)S(O)N(R<sup>16</sup>)(R<sup>17</sup>), -N(R<sup>15</sup>)C(O)N(R<sup>16</sup>)(R<sup>17</sup>), -N(R<sup>15</sup>)C(O)OR<sup>16</sup>, -CH<sub>2</sub>N(R<sup>15</sup>)C(O)OR<sup>16</sup>, -S(O)R<sup>15</sup> and -S(O)<sub>2</sub>R<sup>15</sup>.

In another embodiment the compounds of formula I are compounds of formula II:
wherein G, U, V, R², R⁶, R⁷, R⁹, and R¹⁰ are as defined for formula I.

In another embodiment the compounds of formula I are compounds of formula III:

wherein R⁶, R⁷, R⁹, R¹⁰ and R²¹ are as defined in formula I.

In another embodiment the compounds of formula I are compounds of formula IV:

wherein R⁶, R⁷, R⁹, R¹⁰ and R²¹ are as defined in formula I.

In another embodiment the compounds of formula I are compounds of formula V:

wherein R⁶, R⁷, R⁹, R¹⁰ and R²¹ are as defined in formula I.

Examples of formula V include:
In another embodiment the compounds of formula I are compounds of formula VI:

wherein R⁶, R⁷, R⁹, R¹⁰ and R²¹ are as defined in formula I.

In another embodiment the compounds of formula I are compounds of formula VII:

wherein R⁶, R⁷, R⁹, R¹⁰ and R²¹ are as defined in formula I.

In another embodiment the compounds of formula I are compounds of formula VIII:

wherein R⁶, R⁷, R⁹, R¹⁰ and R²¹ are as defined in formula I.
In another embodiment the compounds of formula I are compounds of formula IX:

\[
\begin{align*}
\text{IX} & \quad R^9, R^{10}, R^7, R^{21} & \quad \text{as defined in formula I.}
\end{align*}
\]

In another embodiment the compounds of formula I are compounds of formula X:

\[
\begin{align*}
\text{X} & \quad R^9, R^{10}, R^7, R^{21} & \quad \text{as defined in formula I.}
\end{align*}
\]

Those skilled in the art will appreciate that for the compounds of the invention:

\[
\begin{align*}
\text{id} & \quad R^6 & \quad \text{can be:}
\end{align*}
\]

Those skilled in the art will appreciate that in the compounds of the invention R^7 can be:

Thus, for example, in embodiments of this invention R^6 and R^7 can be:
In other embodiments of this invention $R^6$ and $R^7$ can be:

$\textcircled{_{R^6}}$ and $\textcircled{_{R^7}}$

In another embodiment $G$ is $O$.

In another embodiment $G$ is $S$.

In another embodiment $V$ is selected from the group consisting of a bond, $O$, and $N(R^{14})$.

In another embodiment $V$ is a bond.

In another embodiment $V$ is $-C(O)-$.

In another embodiment $V$ is $-N(R^{14})$.

In another embodiment $R^8$ is selected from the group consisting of $H$, alkyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroaryalkyl-, heterocyclyl- and heterocyclylalkyl-, with each of said alkyl-, alkenyl- and alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroaryalkyl-, heterocyclyl- and heterocyclylalkyl- being unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of the $R^{21}$ moieties.

In another embodiment $R^8$ is selected from the group consisting of $H$, alkyl, cycloalkyl, aryl and heteroaryl, with each of said alkyl, cycloalkyl, aryl and heteroaryl being unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of the $R^{21}$ moieties.

In another embodiment $R^8$ is selected from the group consisting of $H$, alkyl, cycloalkyl, aryl and heteroaryl, with each of said alkyl, cycloalkyl, aryl and heteroaryl being unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each substituent being
independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy and alkoxy groups.

In another embodiment, R₈ and R₁₀, together with the carbon atom to which they are bound, form a C₄-C₇ carbocyclic (e.g., cycloalkyl) ring, or a 4-7 membered heterocyclyl ring, or a C₄-C₇ carbocyclenyl (e.g., cycloalkeny) ring, or a 4-7 membered heterocyclenyl ring; and wherein said carbocyclic ring, heterocyclyl ring, carbocyclenyl ring, or heterocyclenyl ring is optionally substituted with 1-5 independently selected R²¹ substituents.

In another embodiment, R₈ and R₁₀, together with the carbon atom to which they are bound, form a C₄-C₇ carbocyclic (e.g., cycloalkyl) ring; and wherein said carbocyclic ring is optionally substituted with 1-5 independently selected R²¹ substituents.

In another embodiment, R₈ and R₁₀, together with the carbon atom to which they are bound, form a 4-7 membered heterocyclyl ring; and wherein said heterocyclyl ring is optionally substituted with 1-5 independently selected R²¹ substituents.

In another embodiment, R₈ and R₁₀, together with the carbon atom to which they are bound, form a C₄-C₇ carbocyclenyl (e.g., cycloalkeny) ring; and wherein said carbocyclenyl ring is optionally substituted with 1-5 independently selected R²¹ substituents.

In another embodiment, R₈ and R₁₀, together with the carbon atom to which they are bound, form a 4-7 membered heterocyclenyl ring; and wherein said heterocyclenyl ring is optionally substituted with 1-5 independently selected R²¹ substituents.

In another embodiment, U is C(R⁵).

In another embodiment, U is N.

In another embodiment R¹ is H.

In another embodiment R¹ is halo (e.g., Br).

In another embodiment, R² is H.

In another embodiment, R² is alkyl.
In another embodiment, R² is methyl.
In another embodiment, R² is alkoxyalkyl
In another embodiment, R² is 3-methoxypropyl
In another embodiment, U is N and R² is 3-methoxypropyl

In another embodiment, R² is arylalkyl
In another embodiment, R² is selected from the group consisting of:
(a) alkyl, (b) alkyl substituted with an -OR¹⁵ group (e.g., -Oalkyl, such as, for example, -OCH₃) or a halo group (e.g., Cl), (c) arylalkyl- substituted with an -OR¹⁵ group (e.g., -Oalkyl, such as, for example, -OCH₃) or a halo group (e.g. F), (d) cycloalkyl (e.g., cyclopropyl), (e) heterocycloalkyl (e.g.,

\[
\text{and} \quad \text{and}
\]

(e) cycloalkylalkyl- substituted with a halo substituted alkyl (e.g. wherein the halo substituted alkyl is -CH₂Cl).

In another embodiment R² is selected from the group consisting of: H,

\[-(\text{CH}_2)_3\text{OCH}_3, \text{CH}_3, \text{CH}_2\text{CH}_3, -(\text{CH}_2)_2\text{OCH}_3, -(\text{CH}_2)_2\text{CH(CH}_3)_2,\]
\[\text{CH}_2\text{CH(CH}_3)_2\text{CH}_2\text{CH}_3, \text{CH}_2\text{CH}_2\text{CH}_3,\]

\[\text{and} \quad \text{and} \quad \text{and}
\]

In another embodiment R² is selected from the group consisting of: H,

\[-(\text{CH}_5)_3\text{OCH}_3, \text{CH}_3, \text{CH}_2\text{CH}_3, -(\text{CH}_2)_2\text{OCH}_3, -(\text{CH}_2)_2\text{CH(CH}_3)_2,\]
\[\text{CH}_2\text{CH(CH}_3)_2\text{CH}_2\text{CH}_3, \text{CH}_2\text{CH}_2\text{CH}_3,\]
In another embodiment, \( R_2 \) is phenylmethyl-.

In another embodiment, \( R_2 \) is (4-alkoxy)phenylmethyl-.

In another embodiment, \( R_2 \) is (4-methoxy)phenylmethyl-.

In another embodiment, \( R_1 \) is H.

In another embodiment, \( R_1 \) is alkyl.

In another embodiment, \( R_1 \) is methyl.

In another embodiment, \( R_1 \) and \( R_2 \) are joined together to form a cyclopentyl ring, which is unsubstituted.

In another embodiment, \( R_1 \) and \( R_2 \) are joined together to form a cyclopentyl ring, which is substituted with 1-3 substituents which can be the same or different, each being independently selected from the group consisting of halo, alkyl, -CN, -NH\(_2\), -NH(alkyl), -N(alkyl)\(_2\), hydroxy and alkoxy groups.

In another embodiment, \( R_1 \) and \( R_2 \) are joined together to form a cyclohexyl ring, which is unsubstituted.

In another embodiment, \( R_1 \) and \( R_2 \) are joined together to form a cyclohexyl ring, which is substituted with 1-3 substituents which can be the same or different, each being independently selected from the group consisting of halo, alkyl, -CN, -NH\(_2\), -NH(alkyl), -N(alkyl)\(_2\), hydroxy and alkoxy groups.

In another embodiment, \( U \) is N, and \( R_1 \) and \( R_2 \) are joined together to form a piperidinyl ring including the N of U as the nitrogen of said piperidinyl ring, which is unsubstituted.
In another embodiment, \( U \) is \( N \), and \( R^1 \) and \( R^2 \) are joined together to form a piperidinyl ring including the \( N \) of \( U \) as the nitrogen of said piperidinyl ring, wherein said piperidinyl ring is substituted with 1-3 substituents which can be the same or different, each being independently selected from the group consisting of halo, alkyl, -CN, -NH\(_2\), -NH(alkyl), -N(alkyl)\(_2\), hydroxy and alkoxy groups.

In another embodiment, \( R^6 \) is \( H \).

In another embodiment, \( R^6 \) is alkyl.

In another embodiment, \( R^6 \) is methyl.
In another embodiment R⁶ is alkyl substituted with 1-5 independently selected R²¹ moieties.

In another embodiment R⁶ is alkyl substituted with one R²¹ moiety.
In another embodiment R⁶ is alkyl substituted with one R²¹ moiety, and said R²¹ moiety is -OR₁⁵.

In another embodiment R⁶ is alkyl substituted with one R²¹ moiety, said R²¹ moiety is -OR₁⁵, and said R¹⁵ is selected from the group consisting of: H and alkyl.

In another embodiment R⁶ is alkyl substituted with one R²¹ moiety, said R²¹ moiety is -OR₁⁵, and said R¹⁵ is H.

In another embodiment R⁶ is alkyl substituted with one R²¹ moiety, said R²¹ moiety is -OR₁⁵, and said R¹⁵ is alkyl (e.g. methyl).

In another embodiment R⁶ is alkyl substituted with one R²¹ moiety, said R²¹ moiety is -OR₁⁵, and said R¹⁵ is selected from the group consisting of: H and alkyl.

In another embodiment R⁶ is alkyl substituted with one R²¹ moiety, said R²¹ moiety is -OR₁⁵, and said R¹⁵ is H.

In another embodiment R⁶ is alkyl substituted with one R²¹ moiety, said R²¹ moiety is -OR₁⁵, and said R¹⁵ is alkyl (e.g. methyl).

In another embodiment R⁷ is selected from the group consisting of: (a) aryl substituted with 1-3 R²¹ moieties (e.g. phenyl substituted 1-3 halos, such as, 1-3 F), (b) aryl (e.g. phenyl) substituted with -OR₁⁵ wherein R¹⁵ is (i) an alkyl substituted with 1-3 halos (e.g. F), or (ii) alkyl, (c) aryl (e.g., phenyl), (d) aryl (e.g. phenyl) substituted with alkyl wherein said alkyl is substituted with 1-3 halos (e.g.,
F), (e) aryl substituted with aryl (e.g. -phenyl-phenyl), (f) alkyl, (g) heteroaryl (e.g. thienyl or pyridyl), (h) arylalkyl-, and (i) cycloalkyl).

In another embodiment, R7 is aryl.

In another embodiment, R7 is an unsubstituted phenyl.

In another embodiment, R7 is a phenyl which is substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH2, -NH(alkyl), -N(alkyl)2, hydroxy, alkoxy, aryl and heteroaryl groups.

In another embodiment, R7 is phenyl substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH2, -NH(alkyl), -N(alkyl)2, hydroxy, alkoxy, aryl and heteroaryl groups.

In another embodiment, R7 is phenyl substituted with 1-3 independently selected halos.

In another embodiment, R7 is phenyl substituted with 1-3 F.

In another embodiment, R7 is phenyl substituted with 1 F.

In another embodiment R7 is p-Cl-phenyl.

In another embodiment, R7 is unsubstituted naphthyl.

In another embodiment, R7 is naphthyl which is substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH2, -NH(alkyl), -N(alkyl)2, hydroxy, alkoxy, aryl and heteroaryl groups.

In another embodiment, R7 is unsubstituted biphenyl.

In another embodiment, R7 is biphenyl which is substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH2, -NH(alkyl), -N(alkyl)2, hydroxy and alkoxy groups.

In another embodiment, R7 is R7 is 3-(1,1'-biphenyl)-yl.

In another embodiment, R7 is R7 is 4-(1,1'-biphenyl)-yl.
In another embodiment, $R_6$ is H and $R_7$ is a biphenyl which can be unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH$_2$, -NH(alkyl), -N(alkyl)$_2$, hydroxy and alkoxy groups.

In another embodiment, $R_6$ is methyl, and $R_7$ is a biphenyl which can be unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH$_2$, -NH(alkyl), -N(alkyl)$_2$, hydroxy and alkoxy groups.

In another embodiment, $R_6$ is H, and $R_7$ is a phenyl which can be unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH$_2$, -NH(alkyl), -N(alkyl)$_2$, hydroxy and alkoxy groups.

In another embodiment, $R_6$ is methyl, and $R_7$ is a biphenyl which can be unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH$_2$, -NH(alkyl), -N(alkyl)$_2$, hydroxy and alkoxy groups.

In another embodiment, $R_6$ and $R_7$ are joined to form a spirocyclic unit shown below:

In another embodiment, $R_6$ and $R_7$ are joined to form a spirocyclic unit shown below:
In another embodiment R<sup>6</sup> is alkyl substituted with 1-5 independently selected R<sup>21</sup> moieties, and R<sup>7</sup> is phenyl substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH<sub>2</sub>, -NH(alkyl), -N(alkyl)<sub>2</sub>, hydroxy, alkoxy, aryl and heteroaryl groups.

In another embodiment R<sup>6</sup> is alkyl substituted with one R<sup>21</sup> moiety, and R<sup>7</sup> is phenyl substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH<sub>2</sub>, -NH(alkyl), -N(alkyl)<sub>2</sub>, hydroxy, alkoxy, aryl and heteroaryl groups.

In another embodiment R<sup>6</sup> is alkyl substituted with one R<sup>21</sup> moiety, and R<sup>7</sup> is phenyl substituted with 1-3 independently selected halos.

In another embodiment R<sup>6</sup> is alkyl substituted with one R<sup>21</sup> moiety, and R<sup>7</sup> is phenyl substituted with 1-3 F.

In another embodiment R<sup>6</sup> is alkyl substituted with one R<sup>21</sup> moiety, and said R<sup>21</sup> moiety is -OR<sup>15</sup>, and R<sup>7</sup> is phenyl substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH<sub>2</sub>, -NH(alkyl), -N(alkyl)<sub>2</sub>, hydroxy, alkoxy, aryl and heteroaryl groups.

In another embodiment R<sup>6</sup> is alkyl substituted with one R<sup>21</sup> moiety, and said R<sup>21</sup> moiety is -OR<sup>15</sup>, and R<sup>7</sup> is phenyl substituted with 1-3 independently selected halos.
In another embodiment R^6 is alkyl substituted with one R^{21} moiety, and said
R^{21} moiety is -OR^{15}, and R^7 is phenyl substituted with 1-3 independently selected
F.

In another embodiment R^6 is alkyl substituted with one R^{21} moiety, and said
R^{21} moiety is -OR^{15}, and R^7 is phenyl substituted with 1-3 independently selected
F.

In another embodiment R^6 is alkyl substituted with one R^{21} moiety, and said
R^{21} moiety is -OR^{15}, and R^7 is phenyl substituted with 1-3 independently selected
halo, alkyl, -CN, -NH_{2}, -NH(alkyl), -N(alkyl)_{2}, hydroxy, alkoxy, aryl and
heteroaryl groups.

In another embodiment R^6 is alkyl substituted with one R^{21} moiety, and said R^{21}
moiety is -OR^{15}, and said R^{15} is selected from the group consisting of: H and
alkyl, and R^7 is phenyl substituted with 1-3 independently selected halos.

In another embodiment R^6 is alkyl substituted with one R^{21} moiety, and said R^{21}
moiety is -OR^{15}, and said R^{15} is selected from the group consisting of: H and
alkyl, and R^7 is phenyl substituted with 1-3 independently selected F.

In another embodiment R^6 is alkyl substituted with one R^{21} moiety, and said R^{21}
moiety is -OR^{15}, and said R^{15} is selected from the group consisting of: H and
alkyl, and R^7 is phenyl substituted with 1-3 independently selected F.

In another embodiment R^6 is alkyl substituted with one R^{21} moiety, and said R^{21}
moiety is -OR^{15}, and said R^{15} is selected from the group consisting of: H and
alkyl, and R^7 is phenyl substituted with 1-3 independently selected halos.

In another embodiment R^6 is alkyl substituted with one R^{21} moiety, and said R^{21}
moiety is -OR^{15}, and said R^{15} is selected from the group consisting of: H and
alkyl, and R^7 is phenyl substituted with 1-3 independently selected halos.
In another embodiment R\textsuperscript{6} is alkyl substituted with one R\textsuperscript{21} moiety, said R\textsuperscript{21} moiety is -OR\textsuperscript{15}, and said R\textsuperscript{15} is H, and said R\textsuperscript{15} is selected from the group consisting of: H and alkyl, and R\textsuperscript{7} is phenyl substituted with 1-3 independently selected F.

In another embodiment R\textsuperscript{6} is alkyl substituted with one R\textsuperscript{21} moiety, said R\textsuperscript{21} moiety is -OR\textsuperscript{15}, and said R\textsuperscript{15} is H, and said R\textsuperscript{15} is selected from the group consisting of: H and alkyl, and R\textsuperscript{7} is phenyl substituted with 1 F.

In another embodiment R\textsuperscript{6} is alkyl substituted with one R\textsuperscript{21} moiety, said R\textsuperscript{21} moiety is -OR\textsuperscript{15}, and said R\textsuperscript{15} is alkyl (e.g. methyl), and R\textsuperscript{7} is phenyl substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH\textsubscript{2}, -NH(alkyl), -N(alkyl)\textsubscript{2}, hydroxy, alkoxy, aryl and heteroaryl groups.

In another embodiment R\textsuperscript{6} is alkyl substituted with one R\textsuperscript{21} moiety, said R\textsuperscript{21} moiety is -OR\textsuperscript{15}, and said R\textsuperscript{15} is alkyl (e.g. methyl), and R\textsuperscript{7} is phenyl substituted with 1-3 independently selected halos.

In another embodiment R\textsuperscript{6} is alkyl substituted with one R\textsuperscript{21} moiety, said R\textsuperscript{21} moiety is -OR\textsuperscript{15}, and said R\textsuperscript{15} is alkyl (e.g. methyl), and R\textsuperscript{7} is phenyl substituted with 1 F.

In another embodiment R\textsuperscript{6} is alkyl substituted with one R\textsuperscript{21} moiety, said R\textsuperscript{21} moiety is -OR\textsuperscript{15}, and said R\textsuperscript{15} is alkyl (e.g. methyl), and R\textsuperscript{7} is phenyl substituted with 1 F.

In another embodiment R\textsuperscript{6} is alkyl substituted with 1-3 independently selected R\textsuperscript{21} moieties, and R\textsuperscript{7} is phenyl substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH\textsubscript{2}, -NH(alkyl), -N(alkyl)\textsubscript{2}, hydroxy, alkoxy, aryl and heteroaryl groups.

In another embodiment R\textsuperscript{6} is alkyl substituted with one R\textsuperscript{21} moiety, and R\textsuperscript{7} is phenyl substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo,
alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy, alkoxy, aryl and heteroaryl groups.

In another embodiment R⁶ is methyl substituted with one R²¹ moiety, and R⁷ is phenyl substituted with 1-3 independently selected halos.

In another embodiment R⁶ is methyl substituted with one R²¹ moiety, and R⁷ is phenyl substituted with 1-3 F.

In another embodiment R⁶ is methyl substituted with one R²¹ moiety, and said R²¹ moiety is -OR, and R⁷ is phenyl substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy, alkoxy, aryl and heteroaryl groups.

In another embodiment R⁶ is methyl substituted with one R²¹ moiety, and said R²¹ moiety is -OR, and R⁷ is phenyl substituted with 1-3 independently selected halos.

In another embodiment R⁶ is methyl substituted with one R²¹ moiety, and said R²¹ moiety is -OR, and R⁷ is phenyl substituted with 1-3 independently selected F.

In another embodiment R⁶ is methyl substituted with one R²¹ moiety, and said R²¹ moiety is -OR, and R⁷ is phenyl one F.

In another embodiment R⁶ is methyl substituted with one R²¹ moiety, said R²¹ moiety is -OR, and said R¹⁵ is selected from the group consisting of: H and alkyl, and R⁷ is phenyl substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy, alkoxy, aryl and heteroaryl groups.

In another embodiment R⁶ is methyl substituted with one R²¹ moiety, said R²¹ moiety is -OR, and said R¹⁵ is selected from the group consisting of: H and alkyl, and R⁷ is phenyl substituted with 1-3 independently selected halos.
In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected F.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with one F.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.

In another embodiment R° is methyl substituted with one R° moiety, said R° moiety is -OR, and said R° is selected from the group consisting of: H and alkyl, and R° is phenyl substituted with 1-3 independently selected halos.
In another embodiment, \( R^6 \) is methyl substituted with one \( R^{21} \) moiety, said \( R^{21} \) moiety is \(-OR^{15}\), and said \( R^{15} \) is alkyl (e.g. methyl), and \( R^7 \) is phenyl substituted with 1-3 independently selected F.

In another embodiment, \( R^6 \) is methyl substituted with one \( R^{21} \) moiety, said \( R^{21} \) moiety is \(-OR^{15}\), and said \( R^{15} \) is alkyl (e.g. methyl), and \( R^7 \) is phenyl substituted with one F.

In another embodiment, \( R^6 \) is selected from the group consisting of: H, methyl, cyclopropyl, \(-C(O)CH_2CH_3\), \(-CHF_2\), \(-CF_3\), \(-C(O)OCH_3\), \(-CH_2OH\), \(-CH_2OCH_3\), \(-CH_2OCH(CH_3)_{2}\), \(-C(O)OH\), \(-C(CH_3)_3\), \(-C(OH)(CH_3)_{2}\), \(-C(O)CH_3\), \(-CH(CH_3)OH\), \(-CH_2C(OH)(CH_3)_{2}\), \(-CH_2CH_2OH\) and

In another embodiment, \( R^7 \) is selected from the group consisting of:

- \( \begin{array}{c}
\text{H} \\
\text{H} \\
\text{H} \\
\text{CH}_3
\end{array} \)
- \( \begin{array}{c}
\text{F} \\
\text{F}
\end{array} \)
- \( \begin{array}{c}
\text{H} \\
\text{CH}_3
\end{array} \)
- \( \begin{array}{c}
\text{OCH}_3
\end{array} \)
- \( \begin{array}{c}
\text{H}_3\text{CO}
\end{array} \)
- \( \begin{array}{c}
\text{OCF}_3
\end{array} \)
- Thienyl (e.g. \( \begin{array}{c}
\text{S}
\end{array} \))
- \( \begin{array}{c}
\text{N}
\end{array} \)
- \( \begin{array}{c}
\text{C}(\text{CH}_3)_3
\end{array} \)
- \( \begin{array}{c}
\text{C}_8\text{H}_8
\end{array} \)
In another embodiment \( R^6 \) and \( R^7 \) taken together with the carbon to which
they are bound form a spiro ring selected from the group consisting of:
In another embodiment $R^6$ is selected from the group consisting of: H, methyl, cyclopropyl, \(-\text{C}(\text{O})\text{CH}_2\text{CH}_3\), \(-\text{CHF}_2\), \(-\text{CF}_3\), \(-\text{C}(\text{O})\text{OCH}_3\), \(-\text{CH}_2\text{OH}\), \(-\text{CH}_2\text{OCH}_3\), \(-\text{CH}_2\text{OCH}(\text{CH}_3)_2\), \(-\text{C}(\text{O})\text{OH}\), \(-\text{C}(\text{CH}_3)_3\), \(-\text{C}(\text{OH})(\text{CH}_3)_2\), \(-\text{C}(\text{O})\text{CH}_3\), \(-\text{CH}(\text{CH}_3)\text{OH}\), \(-\text{CH}_2\text{C}(\text{OH})(\text{CH}_3)_2\), \(-\text{CH}_2\text{CH}_2\text{OH}\) and

\[
\begin{align*}
\text{and} & \quad \text{and} \\
& \quad \text{R}^7 \text{ is selected from the group consisting of:}
\end{align*}
\]
In another embodiment, $R^8$ is H.
In another embodiment, $R^8$ is alkyl.
In another embodiment, $R^8$ is methyl.
In another embodiment, $R^{10}$ is aryl.
In another embodiment, $R^{10}$ is phenyl.
In another embodiment \( R_{10} \) is aryl substituted with 1 to 3 independently selected \( R_{21} \) moieties.

In another embodiment \( R_{10} \) is aryl substituted with 1 to 3 \( R_{21} \) moieties, wherein each \( R_{21} \) moiety is the same or different -OR \( 15 \) group.

In another embodiment \( R_{10} \) is aryl substituted with 1 \( R_{21} \) moiety.

In another embodiment \( R_{10} \) is aryl substituted with one \( R_{21} \) moiety, and said \( R_{21} \) moiety is -OR \( 15 \).

In another embodiment \( R_{10} \) is aryl substituted with one \( R_{21} \) moiety, said \( R_{21} \) moiety is -OR \( 15 \), and said \( R_{15} \) is alkyl.

In another embodiment \( R_{10} \) is aryl substituted with one \( R_{21} \) moiety, said \( R_{21} \) moiety is -OR \( 15 \), said \( R_{15} \) is alkyl, and said alkyl is methyl (i.e., said \( R_{21} \) moiety is -OCH \(_3\)).

In another embodiment \( R_{10} \) is phenyl substituted with 1 to 3 independently selected \( R_{21} \) moieties.

In another embodiment \( R_{10} \) is phenyl substituted with 1 to 3 \( R_{21} \) moieties, wherein each \( R_{21} \) moiety is the same or different -OR \( 15 \) group.

In another embodiment \( R_{10} \) is phenyl substituted with 1 \( R_{21} \) moiety.

In another embodiment \( R_{10} \) is phenyl substituted with one \( R_{21} \) moiety, and said \( R_{21} \) moiety is -OR \( 15 \).

In another embodiment \( R_{10} \) is phenyl substituted with one \( R_{21} \) moiety, said \( R_{21} \) moiety is -OR \( 15 \), and said \( R_{15} \) is alkyl.

In another embodiment \( R_{10} \) is phenyl substituted with one \( R_{21} \) moiety, said \( R_{21} \) moiety is -OR \( 15 \), said \( R_{15} \) is alkyl, and said alkyl is methyl (i.e., said \( R_{21} \) moiety is -OCH \(_3\)).

In another embodiment \( R_{10} \) is:

\[ \text{Diagram} \]

In another embodiment \( R_{10} \) is:
In another embodiment $R^{10}$ is ary1 substituted with 1 to 3 $R^{21}$ moieties, wherein each $R^{21}$ moiety is the same or different halo.

In another embodiment $R^{10}$ is ary1 substituted with 1 to 3 $R^{21}$ moieties, wherein each $R^{21}$ moiety is F.

In another embodiment $R^{10}$ is ary1 substituted with one $R^{21}$ moiety, and said $R^{21}$ moiety is halo.

In another embodiment $R^{10}$ is ary1 substituted with one $R^{21}$ moiety, said $R^{21}$ moiety is -halo, and said halo is F.

In another embodiment $R^{10}$ is phenyl substituted with 1 to 3 $R^{21}$ moieties, wherein each $R^{21}$ moiety is the same or different halo.

In another embodiment $R^{10}$ is phenyl substituted with 1 to 3 $R^{21}$ moieties, wherein each $R^{21}$ moiety is F.

In another embodiment $R^{10}$ is phenyl substituted with one $R^{21}$ moiety, and said $R^{21}$ moiety is halo.

In another embodiment $R^{10}$ is phenyl substituted with one $R^{21}$ moiety, said $R^{21}$ moiety is -halo, and said halo is F.
In another embodiment $R^{10}$ is:

wherein the $-R^{10}-R^9$ moiety is:

In another embodiment, $R^{10}$ is unsubstituted heteroaryl.

In another embodiment $R^{10}$ is unsubstituted heteroaryl wherein said heteroaryl is pyridyl.

In another embodiment $R^{10}$ is:

wherein the $-R^{10}-R^9$ moiety is:
In another embodiment, $R^{10}$ is selected from the group consisting of:

\[
\begin{align*}
&\text{O} \\
&\text{F} \\
&\text{N} \\
&\text{and} \\
&\text{C}
\end{align*}
\]

In another embodiment, $R^9$ is unsubstituted heteroaryl.

In another embodiment of this invention, $R^9$ is selected from the group consisting of heteroaryl and heteroaryl substituted with 1-3 $R^{21}$ groups, and wherein each $R^{21}$ is independently selected.

In another embodiment, $R^9$ is heteroaryl which is substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, CN, NH$_2$, NH(alkyl), N(alkyl)$_2$, hydroxy and alkoxy groups.

In another embodiment of this invention, $R^9$ is selected from the group consisting of imidazolyl and imidazolyl substituted with 1-3 $R^{21}$ groups, and wherein each $R^{21}$ is independently selected.

In another embodiment of this invention, $R^9$ is imidazolyl substituted with 1-3 $R^{21}$ groups, and wherein each $R^{21}$ is independently selected.

In another embodiment, $R^9$ is imidazolyl substituted with 1-3 substituents independently selected from the group consisting of halo, alkyl, CN, NH$_2$, NH(alkyl), N(alkyl)$_2$, hydroxy and alkoxy groups.

In another embodiment, $R^9$ is imidazol-1-yl.

In another embodiment, $R^9$ is 4-methyl-imidazol-1-yl.

In another embodiment, $R^9$ is 5-chloro-4-methyl-imidazol-1-yl.
In another embodiment R_{10} is selected from the group consisting of aryl and aryl substituted with one or more R_{21} groups, and R_{9} is selected from the group consisting of heteroaryl and heteroaryl substituted with one or more R_{21} groups, and wherein each R_{21} is independently selected.

In another embodiment R_{10} is selected from the group consisting of phenyl and phenyl substituted with 1-3 independently selected R_{21} groups, and R_{9} is selected from the group consisting of imidazolyl and imidazolyl substituted with 1-3 independently selected R_{21} groups.

In another embodiment R_{10} is selected from the group consisting of heteroaryl and heteroaryl substituted with 1-3 R_{21} groups, and the R_{9} group is selected from the group consisting of heteroaryl and heteroaryl substituted with 1-3 R_{21} groups, and wherein each R_{21} is independently selected.

In another embodiment R_{10} is selected from the group consisting of pyridyl and pyridyl substituted with 1-3 R_{21} groups, and the R_{9} group is selected from the group consisting of imidazolyl and imidazolyl substituted with 1-3 R_{21} groups, and wherein each R_{21} is independently selected.

In another embodiment R_{10} is pyridyl, and the R_{9} group is imidazolyl substituted with 1-3 R_{21} groups, and wherein each R_{21} is independently selected.

In another embodiment the R_{9}-R_{10} moiety is:

![Chemical structure](image)

In another embodiment the R_{9}-R_{10} moiety is:
In another embodiment the R\textsuperscript{9} - R\textsuperscript{10} - moiety is:

\[ \text{alkyl} \]

In another embodiment the R\textsuperscript{9} - R\textsuperscript{10} - moiety is:

\[ \text{H}_3\text{CO} \]

In another embodiment the R\textsuperscript{9} - R\textsuperscript{10} - moiety is:

\[ \text{F}_3\text{CO} \]

In another embodiment the R\textsuperscript{9} - R\textsuperscript{10} - moiety is:

\[ \text{H}_3\text{C} \]
In another embodiment, the present application discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in Formula:

wherein the various moieties are defined above.

In another embodiment, the present application discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in Formula:
wherein the various moieties are defined above.

In another embodiment, the present application discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in Formula:

![Chemical Structure 1]

wherein the various moieties are defined above.

In another embodiment, the present application discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in Formula:

![Chemical Structure 2]

wherein the various moieties are defined above.

In another embodiment, the present application discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in Formula:

![Chemical Structure 3]

wherein the various moieties are defined above.
In another embodiment, this invention discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

\[
\begin{array}{c}
\text{U} \\
R^1 \\
R^2 \\
R^3 \\
R^4 \\
R^5 \\
R^6 \\
R^7 \\
R^8 \\
R^9 \\
R^{10}
\end{array}
\]

wherein U is N;
R^1 is H;
R^2 is alkyl;
R^3 is H;
R^4 is 3-(1,1'-biphenyl)-yl;
R^8 is H;
R^{10} is phenyl; and
R^9 is imidazol-1-yl.

In another embodiment, this invention discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

\[
\begin{array}{c}
\text{U} \\
R^1 \\
R^2 \\
R^3 \\
R^4 \\
R^5 \\
R^6 \\
R^7 \\
R^8 \\
R^9 \\
R^{10}
\end{array}
\]

wherein U is N;
R^1 is H;
R^2 is alkyl;
R^3 is H;
R^4 is phenyl;
R^9 is H;
R\textsuperscript{10} is alkoxy-substituted phenyl; and
R\textsuperscript{9} is 4-methyl-imidazol-1-yl.

In another embodiment, this invention discloses a compound, or pharmacetically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

\[
\begin{array}{c}
\text{U} \\
\text{N} \\
\text{O}
\end{array}
\]

wherein U is N;
R\textsuperscript{1} is H;
R\textsuperscript{2} is alkyl;
R\textsuperscript{6} is H;
R\textsuperscript{7} is 4-fluoro-phen-1-yl;
R\textsuperscript{8} is H;
R\textsuperscript{10} is phenyl; and
R\textsuperscript{9} is imidazol-1-yl.

In another embodiment, this invention discloses a compound, or pharmacetically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

\[
\begin{array}{c}
\text{U} \\
\text{N} \\
\text{O}
\end{array}
\]

wherein U is N;
R\textsuperscript{1} is H;
R\textsuperscript{2} is methyl;
R\textsuperscript{6} is H;
In another embodiment, this invention discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

wherein U is N;
R¹ and R² are connected to form a 5-membered ring;
R⁶ is H;
R⁷ is 3-(1,1'-biphenyl)-yl;
R⁸ is H;
R¹⁰ is phenyl; and
R⁹ is imidazol-1-yl.

In another embodiment, this invention discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

wherein U is N;
R¹ is H;
R² is alkyl;
R\textsuperscript{6} and R\textsuperscript{7} are connected to form a 5-membered spirocyclic ring wherein said spirocyclic ring is fused with a benzo ring;

- R\textsuperscript{8} is H;
- R\textsuperscript{10} is phenyl; and
- R\textsuperscript{9} is imidazol-1-yl.

In another embodiment, this invention discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

![Chemical Structure](image)

wherein U is N;

- R\textsuperscript{1} is H;
- R\textsuperscript{2} is alkoxyalkyl;
- R\textsuperscript{6} is alkyl;
- R\textsuperscript{7} is phenyl;
- R\textsuperscript{8} is H;
- R\textsuperscript{10} is phenyl; and
- R\textsuperscript{9} is imidazol-1-yl.

In another embodiment, this invention discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

![Chemical Structure](image)

wherein U is N;
R\textsuperscript{1} is H;  
R\textsuperscript{2} is arylalkyl;  
R\textsuperscript{6} and R\textsuperscript{7} are connected to form a 5-membered spirocyclic ring wherein said spirocyclic ring is fused with a benzo ring;  
R\textsuperscript{8} is H;  
R\textsuperscript{10} is alkoxy-substituted phenyl; and  
R\textsuperscript{9} is imidazol-1-yl.

In another embodiment, this invention discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

![Chemical Structure Diagram]

wherein U is N;  
R\textsuperscript{1} is H;  
R\textsuperscript{2} is (alkoxy)aryl-alkyl--;  
R\textsuperscript{6} and R\textsuperscript{7} are connected to form a 5-membered spirocyclic ring wherein said spirocyclic ring is fused with a benzo ring;  
R\textsuperscript{8} is H;  
R\textsuperscript{10} is (alkoxy-substituted)aryl; and  
R\textsuperscript{9} is imidazol-1-yl.

In another embodiment, this invention discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:
wherein \( U = \text{N}; \)
\( R^1 \) is H;
\( R^2 \) is alkoxy-alkyl-
\( R^6 \) is alkyl;
\( R^7 \) is phenyl substituted with halo;
\( R^8 \) is H;
\( R^{10} \) is (alkoxy-substituted)aryl; and
\( R^9 \) is imidazol-1-yl.

In another embodiment, this invention discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

wherein \( U = \text{N}; \)
\( R^1 \) is H;
\( R^2 \) is alkoxy-alkyl-
\( R^6 \) is alkyl;
\( R^7 \) is phenyl substituted with halo;
\( R^8 \) is H;
\( R^{10} \) is (alkoxy-substituted)aryl; and
\( R^9 \) is 4-alkyl-imidazol-1-yl.
In another embodiment, this invention discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

![Chemical Structure](image)

wherein $U$ is N;
- $R^1$ is H;
- $R^2$ is alkoxy-alkyl-;
- $R^6$ and $R^7$ are connected to form a 5-membered spirocyclic ring;
- $R^8$ is H;
- $R^{10}$ is (alkoxy-substituted)aryl; and
- $R^9$ is 4-alkyl-imidazol-1-yl.

In another embodiment, this invention discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

![Chemical Structure](image)

wherein $U$ is N;
- $R^1$ is H;
- $R^2$ is alkoxy-alkyl-;
- $R^6$ and $R^7$ are connected to form a 5-membered spirocyclic ring wherein said spirocyclic ring is fused with a benzo ring;
- $R^8$ is H;
- $R^{10}$ is (alkoxy-substituted)aryl; and
R^9 is 4-alkyl-imidazol-yl.

In another embodiment, this invention discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

wherein U is N;
R^1 is H;
R^2 is alkoxy-alkyl-;
R^6 and R^7 are connected to form a 5-membered spirocyclic ring wherein said spirocyclic ring is fused with a benzo ring;
R^8 is H;
R^{10} is (alkoxy-substituted)aryl; and
R^9 is 5-halo-4-alkyl-imidazol-1-yl.

In another embodiment, this invention discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

wherein U is N;
R^1 is H;
R^2 is alkoxy-alkyl-;
R^6 and R^7 are connected to form a 5-membered spirocyclic ring;
R^8 is H;
R^{10} is (alkoxy-substituted)aryl; and
R^9 is 4-alkyl-imidazol-1-yl.

In another embodiment, this invention discloses a compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

wherein U is N;
R^1 is H;
R^2 is alkoxy-alkyl-;
R^6 is alkyl;
R^7 is phenyl substituted with halo;
R^8 is H;
R^{10} is (alkoxy-substituted)aryl; and
R^9 is 5-halo-4-alkyl-imidazol-1-yl.

Other embodiments are directed to any one of the above embodiments wherein R^1 and R^8 cis to each other instead of trans, that is the formulas above have the moiety:

Other embodiments are directed to any one of the above embodiments wherein R^6 has the stereochemistry:
Other embodiments are directed to any one of the above embodiments wherein $R^7$ has the stereochemistry:

Thus Other embodiments are directed to any one of the above embodiments wherein $R^6$ and $R^7$ have the stereochemistry

Other embodiments are directed to any one of the above embodiments wherein $R^6$ and $R^7$ have the stereochemistry

An illustrative group of compounds of the invention are shown in Table 1 (Compounds 1 to 9).

**Table 1**
(Compounds 1 to 9)
and

and
Representative compounds of the invention also include compounds 10 to 161 (Tables 3 to 13 below), 162 (Method M below), 163 (Method N below), and 164 (Method O below).

Thus, one embodiment of this invention is directed to a compound selected from the group consisting of:

(8E)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-ALPHA,ALPHA-DIMETHYL-3-(3,4,5-TRIFLUOROPHENYL)-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE-3-METHANOL (ENANTIOMER A);

(-)-(8E)-3-(3-CHLORO-4-FLUOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3-METHYL-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE (ENANTIOMER);
(8Z)-3-(4-FLUOROPHENYL)-5,6-DIHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3,6,6-TRIMETHYL-3H,8H-[1,2,4]OXADIAZOLO[3,4-c][1,4]OXAZINE;

(8E)-3-(3,5-DIFLUOROPHENYL)-5,6,7,8- TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE-3-METHANOL;
(+)-(8E)-5-FLUORO-2,3,5',6',7',8'-HEXAHYDRO-8'[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]SPIRO[1H-INDENE-I,3']-[3H][1,2,4]OXADIAZOLO[4,3-a]PYRIDINE;

(8E)-6,8-DIFLUORO-2,3,5',6',7',8'-HEXAHYDRO-8'[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]SPIRO[4H-I-

BENZOPYRAN-4,3'-[3H][1,2,4]OXADIAZOLO[4,3-a]PYRIDINE] (ENANTIOMER A);
(8Z)-3(R)-(4-FLUOROPHENYL)-5,6-DIHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3,6(R)-DIMETHYL-3H,8H-[1,2,4]OXADIAZOLO[3,4-c][1,4]OXAZINE;

(8E)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3-(3,4,5-TRIFLUOROPHENYL)-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE-3-METHANOL (ENANTIOMER A);
(8E)-3-(3,5-DIFLUOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3-METHYL-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE;

(-)-(8E)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3-METHYL-3-[4-(TRIFLUOROMETHOXY)PHENYL]-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE;
(8E)-3-(4-CHLOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3-METHYL-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE;

(8E)-3-(4-FLUOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3,6(R)-DIMETHYL-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE (SINGLE DIASTEREOMER);

(8E)-3-(4-METHYLPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-1-METHYLSPIRO[3H-INDOLE-3,3'][3H][1,2,4]OXADIAZOLO[4,3-a]PYRIDIN]-2(1H)-ONE (ENANTIOMER);
(8E)-3-(4-FLUOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL][METHYLENE]-3-METHYL-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE;

5-(4-FLUOROPHENYL)-3-[(E)-2-[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]ETHENYL]-ALPHA,ALPHA,5-TRIMETHYL-2,4-OXADIAZOLE-4(5H)-ETHANOL;

(8E)-3-(4-FLUOROPHENYL)-5,6,7,8-TETRAHYDRO-3-(METHOXYMETHYL)-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL][METHYLENE]-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE;
(8E)-3-(4-FLUOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-ALPHA,ALPHA-DIMETHYL-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE-3-METHANOL (ENANTIOMER A);

(-)-(8E)-5-FLUORO-5',6',7',8'-TETRAHYDRO-8'-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]SPIRO[3H-INDOLE-3,3'-[3H][1,2,4]OXADIAZOLO[4,3-a]PYRIDIN]-2(1H)-ONE;

(8E)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3-(4-METHOXYPHENYL)-3-METHYL-3H-[1,2,4]OXADIAZOLO[4,3-A]PYRIDINE (ENANTIOMER B);
(8E)-3-(4-FLUOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE-3-METHANOL (ENANTIOMER A);

(8E)-3-(2,4-DIFLUOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE-3-METHANOL;
(8E)-3-(4-FLUOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-ALPHA-METHYL-3H-[1,2,4]OXADIAZOLO[4,3-A]PYRIDINE-3-METHANOL (DIASTEREOMER 2);

(8E)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3-METHYL-3-(3,4,5-TRIFLUOROPHENYL)-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE (ENANTIOMER A);
(+)-(8E)-7-FLUORO-2,3,5',6',7',8'-HEXAHYDRO-8'-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]SPIRO [4H-I'-BENZOPYRAN-4,3'-[3H][1,2,4]OXADIAZOLO[4,3-a]PYRIDINE];

(8Z)-3(R)-(4-FLUOROPHENYL)-5,6-DIHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3-METHYL-3H,8H-[1,2,4]OXADIAZOLO[3,4-c][1,4]OXAZINE;
(8E)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3-METHYL-3-[(TRIFLUOROMETHYL)PHENYL]-3H-[1,2,4]OXADIAZOLO[4,3-A]PYRIDINE (ENANTIOMER B);

(8E)-3-(4-FLUOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-ALPHA-METHYL-3H-[1,2,4]OXADIAZOLO[4,3-A]PYRIDINE-3-METHANOL (DIASTEREOMER 4);
Another embodiment of this invention is directed to the compound:
(8E)-5,6,7,8- TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1 H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-ALPHA,ALPHA-DIMETHYL-3-(3,4,5-TRIFLUOROPHENYL)-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE-3-METHANOL (ENANTIOMER A).

Another embodiment of this invention is directed to the compound:

(-)-(8E)-3-(3-CHLORO-4-FLUOROPHENYL)-5,6,7,8- TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1 H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3-METHYL-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE (ENANTIOMER).
Another embodiment of this invention is directed to the compound:

\[ (+)-(8'E)-6\text{-FLUORO-2,3,5',6',7',8'-HEXAHYDRO-8}'-[3\text{-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL}METHYLENE]SPIRO[4H-1-BENZOPYRAN-4,3'-[3H][1,2,4]OXADIAZOLO[4,3-a]PYRIDINE \text{ (ENANTIOMER)}.] \]

Another embodiment of this invention is directed to the compound:

\[ (8E)-3-(3,4\text{-DIFLUOROPHENYL})\text{-5,6,7,8-TETRAHYDRO-8}^-{[3\text{-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL}METHYLENE]}\text{-3-METHYL-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE \text{ (ENANTIOMER A)}.} \]

Another embodiment of this invention is directed to the compound:

\[ (8Z)-3(R)-(4\text{-FLUOROPHENYL})\text{-5,6-DIHYDRO-8}^-{[3\text{-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL}METHYLENE]}\text{-3,6(S)-DIMETHYL-3H,8H-[1,2,4]OXADIAZOLO[3,4-c][1,4]OXAZINE.} \]
Another embodiment of this invention is directed to the compound:

\[
(8Z)-3-(4-\text{FLUOROPHENYL})-5,6-\text{DIHYDRO}-8-[[3-\text{METHOXY}-4-(4-\text{METHYL}-1H-IMIDAZOL-1-YL)PHENYL]}\text{METHYLENE}]-3,6,6-\text{TRIMETHYL}-3H,8H-\text{[1,2,4]OXADIAZOLO}[3,4-c][1,4]OXAZINE.
\]

Another embodiment of this invention is directed to the compound:

\[
(8E)-3-(3,5-\text{DIFLUOROPHENYL})-5,6,7,8-\text{TETRAHYDRO}-8-[[3-\text{METHOXY}-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]}\text{METHYLENE}]-3H-\text{[1,2,4]OXADIAZOLO}[4,3-a]\text{PYRIDINE}-3-\text{METHANOL}
\]

Another embodiment of this invention is directed to the compound:
Another embodiment of this invention is directed to the compound:

(+)-(8E)-5-FLUORO-2,3,5',6',7',8'-HEXAHYDRO-8'-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]SPIRO[1 H-INDENE-1,3'-[3H][1,2,4]OXADIAZOLO[4,3-a]PYRIDINE].

Another embodiment of this invention is directed to the compound:


Another embodiment of this invention is directed to the compound:
(8Z)-3(R)-(4-FLUOROPHENYL)-5,6-DIHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3,6(R)-DIMETHYL-3H,8H-[1,2,4]OXADIAZOLO[3,4-c][1,4]OXAZINE.

Another embodiment of this invention is directed to the compound:

(8E)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3-(3,4,5-TRIFLUOROPHENYL)-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE-3 METHANOL (ENANTIOMER A).

Another embodiment of this invention is directed to the compound:

(8E)-3-(3,5-DIFLUOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3-METHYL-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE.
Another embodiment of this invention is directed to the compound:

(-)-(8E)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3-METHYL-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE.

Another embodiment of this invention is directed to the compound:

(8E)-3-(4-CHLOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3-METHYL-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE.
Another embodiment of this invention is directed to the compound:

(8E)-3-(4-FLUOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-S^R-DIMETHYL-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE (SINGLE DIASTEREOMER).

Another embodiment of this invention is directed to the compound:

(8E)-3-(4-FLUOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-S^R-DIMETHYL-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE.

Another embodiment of this invention is directed to the compound:

(8E)-3-(4-FLUOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-S^R-DIMETHYL-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE.
Another embodiment of this invention is directed to the compound:

(8E)-3-(4-FLUOROPHENYL)-5,6,7,8-TETRAHYDRO-3-(METHOXYMETHYL)-3-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE.

Another embodiment of this invention is directed to the compound:
Another embodiment of this invention is directed to the compound:

(8E)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3-(4-METHOXYPHENYL)-3-METHYL-3H-[1,2,4]OXADIAZOLO[4,3-A]PYRIDINE (ENANTIOMER B).
Another embodiment of this invention is directed to the compound:

\[
(8E)-3-(4-FLUOROPHENYL)-5,6,7,8\text{-TETRAHYDRO}-8-\left[\text{[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE}\right]-3H-1,2,4\text{-OXADIAZOLO}[4,3-a]\text{PYRIDINE-3-METHANOL (ENANTIOMER A).}
\]

Another embodiment of this invention is directed to the compound:

\[
(8E)-3-(2,4-DIFLUOROPHENYL)-5,6,7,8\text{-TETRAHYDRO}-8-\left[\text{[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE}\right]-3H-1,2,4\text{-OXADIAZOLO}[4,3-a]\text{PYRIDINE-3-METHANOL.}
\]
Another embodiment of this invention is directed to the compound:

(8E)-3-(4-FLUOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]ALPHA-METHYL-3H-[1,2,4]OXADIAZOLO[4,3-A]PYRIDINE-3-METHANOL (DIASTEREOMER 2).

Another embodiment of this invention is directed to the compound:

(8E)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]-3-METHYL-3-(3,4,5-TRIFLUOROPHENYL)-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE (ENANTIOMER A).

Another embodiment of this invention is directed to the compound:

(+M8 Ε )-7-FLUORO-2,3,5',6\',7,8'-HEXAHYDRO-8'-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]SPIRO [4H-I -BENZOPYRAN-4,3'-[3H][1,2,4]OXADIAZOLO[4,3-a]PYRIDINE].
Another embodiment of this invention is directed to the compound:

\[(8Z)-3(R)-(4\text{-FLUOROPHENYL})-5,6\text{-DIHYDRO}-8\text{-}[3\text{-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL}]METHYLENE\]-3-METHYL-3H,8H-[1,2,4]OXADIAZOLO[3,4-c][1,4]OXAZINE.\n
Another embodiment of this invention is directed to the compound:

\[(8E)-5,6,7,8\text{-TETRAHYDRO-8}-[3\text{-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL}]METHYLENE\]-3-METHYL-3H-[4-(TRIFLUOROMETHYL)PHENYL]-3H-[1,2,4]OXADIAZOLO[4,3-A]PYRIDINE (ENANTIOMER B)\n
Another embodiment of this invention is directed to the compound:
Another embodiment of this invention is directed to the compound:

(8E)-3-(4-FLUOROPHENYL)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]- ALPHA-METHYL-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE-3-METHANOL (DIASTEREOMER 4).

Another embodiment of this invention is directed to the compound:

(8E)-5,6,7,8-TETRAHYDRO-8-[[3-METHOXY-4-(4-METHYL-1H-IMIDAZOL-1-YL)PHENYL]METHYLENE]- ALPHA-METHYL-3-(3,4,5-TRIFLUOROPHENYL)-3H-[1,2,4]OXADIAZOLO[4,3-a]PYRIDINE-3-METHANOL (DIASTEREOMER 2).

Another embodiment of this invention is directed to the compound:

Another embodiment of this invention is directed to Compound 1 (see Table 2).

Another embodiment of this invention is directed to Compound 2 (see Table 2).

Another embodiment of this invention is directed to Compound 3 (see Table 2).

Thus, another embodiment of this invention is directed to Compound 4 (see Table 2).

Another embodiment of this invention is directed to Compound 5 (see Table 2).

Another embodiment of this invention is directed to Compound 6 (see Table 2).

Another embodiment of this invention is directed to Compound 7 (see Table 2).

Another embodiment of this invention is directed to Compound 8 (see Table 2).

Another embodiment of this invention is directed to Compound 9 (see Table 2).

Another embodiment of this invention is directed to Compound 10 (see Table 3).

Another embodiment of this invention is directed to Compound 11 (see Table 3).

Another embodiment of this invention is directed to Compound 12 (see Table 3).

Another embodiment of this invention is directed to Compound 13 (see Table 3).

Another embodiment of this invention is directed to Compound 14 (see Table 3).

Another embodiment of this invention is directed to Compound 15 (see Table 3).
Another embodiment of this invention is directed to Compound 16 (see Table 3).
Another embodiment of this invention is directed to Compound 17 (see Table 3).
Another embodiment of this invention is directed to Compound 18 (see Table 3).
Another embodiment of this invention is directed to Compound 19 (see Table 3).
Another embodiment of this invention is directed to Compound 20 (see Table 3).
Another embodiment of this invention is directed to Compound 21 (see Table 3).
Another embodiment of this invention is directed to Compound 22 (see Table 3).
Another embodiment of this invention is directed to Compound 23 (see Table 3).
Another embodiment of this invention is directed to Compound 24 (see Table 3).
Another embodiment of this invention is directed to Compound 25 (see Table 3).
Another embodiment of this invention is directed to Compound 26 (see Table 3).
Another embodiment of this invention is directed to Compound 27 (see Table 3).
Another embodiment of this invention is directed to Compound 28 (see Table 3).
Another embodiment of this invention is directed to Compound 29 (see Table 3).
Another embodiment of this invention is directed to Compound 30 (see Table 3).
Another embodiment of this invention is directed to Compound 31 (see Table 3).

Another embodiment of this invention is directed to Compound 32 (see Table 3).

Another embodiment of this invention is directed to Compound 33 (see Table 3).

Another embodiment of this invention is directed to Compound 34 (see Table 3).

Another embodiment of this invention is directed to Compound 35 (see Table 3).

Another embodiment of this invention is directed to Compound 36 (see Table 3).

Another embodiment of this invention is directed to Compound 37 (see Table 3).

Another embodiment of this invention is directed to Compound 38 (see Table 3).

Another embodiment of this invention is directed to Compound 39 (see Table 3).

Another embodiment of this invention is directed to Compound 40 (see Table 3).

Another embodiment of this invention is directed to Compound 41 (see Table 3).

Another embodiment of this invention is directed to Compound 420 (see Table 3).

Another embodiment of this invention is directed to Compound 43 (see Table 3).

Another embodiment of this invention is directed to Compound 44 (see Table 3).

Another embodiment of this invention is directed to Compound 45 (see Table 3).
Another embodiment of this invention is directed to Compound 46 (see Table 3).

Another embodiment of this invention is directed to Compound 47 (see Table 3).

Another embodiment of this invention is directed to Compound 48 (see Table 3).

Another embodiment of this invention is directed to Compound 49 (see Table 3).

Another embodiment of this invention is directed to Compound 50 (see Table 4).

Another embodiment of this invention is directed to Compound 51 (see Table 4).

Another embodiment of this invention is directed to Compound 52 (see Table 4).

Another embodiment of this invention is directed to Compound 53 (see Table 4).

Another embodiment of this invention is directed to Compound 54 (see Table 4).

Another embodiment of this invention is directed to Compound 55 (see Table 4).

Another embodiment of this invention is directed to Compound 56 (see Table 4).

Another embodiment of this invention is directed to Compound 57 (see Table 4).

Another embodiment of this invention is directed to Compound 58 (see Table 4).

Another embodiment of this invention is directed to Compound 59 (see Table 4).

Another embodiment of this invention is directed to Compound 60 (see Table 4).
Another embodiment of this invention is directed to Compound 61 (see Table 4).

Another embodiment of this invention is directed to Compound 62 (see Table 4).

Another embodiment of this invention is directed to Compound 63 (see Table 4).

Another embodiment of this invention is directed to Compound 64 (see Table 4).

Another embodiment of this invention is directed to Compound 65 (see Table 4).

Another embodiment of this invention is directed to Compound 66 (see Table 4).

Another embodiment of this invention is directed to Compound 67 (see Table 4).

Another embodiment of this invention is directed to Compound 68 (see Table 4).

Another embodiment of this invention is directed to Compound 69 (see Table 4).

Another embodiment of this invention is directed to Compound 70 (see Table 4).

Another embodiment of this invention is directed to Compound 71 (see Table 4).

Another embodiment of this invention is directed to Compound 72 (see Table 4).

Another embodiment of this invention is directed to Compound 73 (see Table 4).

Another embodiment of this invention is directed to Compound 74 (see Table 4).

Another embodiment of this invention is directed to Compound 75 (see Table 4).
Another embodiment of this invention is directed to Compound 76 (see Table 4).
Another embodiment of this invention is directed to Compound 77 (see Table 4).
Another embodiment of this invention is directed to Compound 78 (see Table 4).
Another embodiment of this invention is directed to Compound 79 (see Table 4).
Another embodiment of this invention is directed to Compound 80 (see Table 4).
Another embodiment of this invention is directed to Compound 81 (see Table 4).
Another embodiment of this invention is directed to Compound 82 (see Table 4).
Another embodiment of this invention is directed to Compound 83 (see Table 4).
Another embodiment of this invention is directed to Compound 84 (see Table 4).
Another embodiment of this invention is directed to Compound 85 (see Table 4).
Another embodiment of this invention is directed to Compound 86 (see Table 5).
Another embodiment of this invention is directed to Compound 87 (see Table 5).
Another embodiment of this invention is directed to Compound 88 (see Table 5).
Another embodiment of this invention is directed to Compound 89 (see Table 5).
Another embodiment of this invention is directed to Compound 90 (see Table 5).
Another embodiment of this invention is directed to Compound 91 (see Table 5).
Another embodiment of this invention is directed to Compound 92 (see Table 5).
Another embodiment of this invention is directed to Compound 93 (see Table 5).
Another embodiment of this invention is directed to Compound 94 (see Table 5).
Another embodiment of this invention is directed to Compound 95 (see Table 5).
Another embodiment of this invention is directed to Compound 96 (see Table 5).
Another embodiment of this invention is directed to Compound 97 (see Table 6).
Another embodiment of this invention is directed to Compound 98 (see Table 6).
Another embodiment of this invention is directed to Compound 99 (see Table 6).
Another embodiment of this invention is directed to Compound 100 (see Table 6).
Another embodiment of this invention is directed to Compound 101 (see Table 7).
Another embodiment of this invention is directed to Compound 102 (see Table 7).
Another embodiment of this invention is directed to Compound 103 (see Table 8).
Another embodiment of this invention is directed to Compound 104 (see Table 8).
Another embodiment of this invention is directed to Compound 105 (see Table 8).
Another embodiment of this invention is directed to Compound 106 (see Table 8).
Another embodiment of this invention is directed to Compound 107 (see Table 9).
Another embodiment of this invention is directed to Compound 108 (see Table 9).
Another embodiment of this invention is directed to Compound 109 (see Table 9).
Another embodiment of this invention is directed to Compound 110 (see Table 10).
Another embodiment of this invention is directed to Compound 111 (see Table 10).
Another embodiment of this invention is directed to Compound 112 (see Table 10).
Another embodiment of this invention is directed to Compound 113 (see Table 10).
Another embodiment of this invention is directed to Compound 114 (see Table 10).
Another embodiment of this invention is directed to Compound 115 (see Table 10).
Another embodiment of this invention is directed to Compound 116 (see Table 10).
Another embodiment of this invention is directed to Compound 117 (see Table 11).
Another embodiment of this invention is directed to Compound 118 (see Table 11).
Another embodiment of this invention is directed to Compound 119 (see Table 11).
Another embodiment of this invention is directed to Compound 120 (see Table 11).
Another embodiment of this invention is directed to Compound 121 (see Table 11).
Another embodiment of this invention is directed to Compound 122 (see Table 4).
Another embodiment of this invention is directed to Compound 123 (see Table 4).
Another embodiment of this invention is directed to Compound 124 (see Table 11).
Another embodiment of this invention is directed to Compound 125 (see Table 11).
Another embodiment of this invention is directed to Compound 126 (see Table 11).
Another embodiment of this invention is directed to Compound 127 (see Table 11).
Another embodiment of this invention is directed to Compound 128 (see Table 11).
Another embodiment of this invention is directed to Compound 129 (see Table 11).
Another embodiment of this invention is directed to Compound 130 (see Table 11).
Another embodiment of this invention is directed to Compound 131 (see Table 11).
Another embodiment of this invention is directed to Compound 132 (see Table 11).
Another embodiment of this invention is directed to Compound 133 (see Table 11).
Another embodiment of this invention is directed to Compound 134 (see Table 11).
Another embodiment of this invention is directed to Compound 135 (see Table 11).
Another embodiment of this invention is directed to Compound 136 (see Table 11).
Another embodiment of this invention is directed to Compound 137 (see Table 11).
Another embodiment of this invention is directed to Compound 138 (see Table 11).
Another embodiment of this invention is directed to Compound 139 (see Table 12).
Another embodiment of this invention is directed to Compound 140 (see Table 12).
Another embodiment of this invention is directed to Compound 141 (see Table 12).
Another embodiment of this invention is directed to Compound 142 (see Table 12).
Another embodiment of this invention is directed to Compound 143 (see Table 12).
Another embodiment of this invention is directed to Compound 144 (see Table 12).
Another embodiment of this invention is directed to Compound 145 (see Table 12).
Another embodiment of this invention is directed to Compound 146 (see Table 12).
Another embodiment of this invention is directed to Compound 147 (see Table 12).
Another embodiment of this invention is directed to Compound 148 (see Table 12).
Another embodiment of this invention is directed to Compound 149 (see Table 12).
Another embodiment of this invention is directed to Compound 150 (see Table 12).
Another embodiment of this invention is directed to Compound 151 (see Table 12).
Another embodiment of this invention is directed to Compound 152 (see Table 12).
Another embodiment of this invention is directed to Compound 153 (see Table 12).
Another embodiment of this invention is directed to Compound 154 (see Table 12).
Another embodiment of this invention is directed to Compound 155 (see Table 12).
Another embodiment of this invention is directed to Compound 156 (see Table 12).
Another embodiment of this invention is directed to Compound 157 (see Table 12).
Another embodiment of this invention is directed to Compound 158 (see Table 13).
Another embodiment of this invention is directed to Compound 159 (see Table 13).
Another embodiment of this invention is directed to Compound 160 (see Table 13).
Another embodiment of this invention is directed to Compound 161 (see Table 13).
Another embodiment of this invention is directed to Compound 162 (see Method M).
Another embodiment of this invention is directed to Compound 163 (see Method N).
Another embodiment of this invention is directed to Compound 164 (see Method O).
Other embodiments of this invention are directed to pharmaceutically acceptable salts of any one of the embodiments above directed to any one of compounds 1 to 164.

Other embodiments of this invention are directed to pharmaceutically acceptable esters of any one of the embodiments above directed to any one of compounds 1 to 164.

Other embodiments of this invention are directed to solvates of any one of the embodiments above directed to any one of compounds 1 to 164.

One embodiment of this invention is directed to a compound of formula I.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of a compound of formula I.

Another embodiment of this invention is directed to a pharmaceutically acceptable ester of a compound of formula I.

Another embodiment of this invention is directed to a solvate of a compound of formula I.

Another embodiment of this invention is directed to a compound of formula I in isolated form.

Another embodiment of this invention is directed to a compound of formula I in pure form.

Another embodiment of this invention is directed to a compound of formula I in pure and isolated form.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of formula I and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a pharmaceutically acceptable salt of one or more (e.g., one) compounds of formula I and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a pharmaceutically acceptable
ester of one or more (e.g., one) compounds of formula I and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a solvate of one or more (e.g., one) compounds of formula I and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of formula I, and an effective amount of one or more (e.g., one) other pharmaceutically active ingredients (e.g.,) drugs, and a pharmaceutically acceptable carrier. Examples of the other pharmaceutically active ingredients include, but are not limited to drugs selected form the group consisting of: (a) drugs useful for the treatment of Alzheimer's disease, (b) drugs useful for inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), (c) drugs useful for treating neurodegenerative diseases, and (d) drugs useful for inhibiting gamma-secretase.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of formula I, and effective amount of one or more BACE inhibitors, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of formula I, and effective amount of one or more cholinesterase inhibitors (e.g., acetyl- and/or butyrylcholinesterase inhibitors), and a pharmaceutically acceptable carrier.

The compounds of formula I can be useful as gamma secretase modulators and can be useful in the treatment and prevention of diseases such as, for example, central nervous system disorders such as Alzheimers disease and Downs Syndrome.

Thus, another embodiment of this invention is directed to a method for modulating (including inhibiting, antagonizing and the like) gamma-secretase
comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of such treatment.

Another embodiment of this invention is directed to a method for modulating (including inhibiting, antagonizing and the like) gamma-secretase, comprising administering an effective amount of a compound of formula I to a patient in need of treatment.

Another embodiment of this invention is directed to a method of treating one or more neurodegenerative diseases, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

Another embodiment of this invention is directed to a method of inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

Another embodiment of this invention is directed to a method of inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), comprising administering an effective amount of a compound of formula I to a patient in need of treatment.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of a compound of formula I to a patient in need of treatment.

This invention also provides combination therapies for (1) modulating gamma-secretase, or (2) treating one or more neurodegenerative diseases, or (3)
inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), or (4) treating Alzheimer's disease. The combination therapies are directed to methods comprising the administration of an effective amount of one or more (e.g. one) compounds of formula I and the administration of an effective amount of one or more (e.g., one) other pharmaceutical active ingredients (e.g., drugs). The compounds of formula I and the other drugs can be administered separately (i.e., each is in its own separate dosage form), or the compounds of formula I can be combined with the other drugs in the same dosage form.

Thus, other embodiments of this invention are directed to any one of the methods of treatment, or methods of inhibiting, described herein, wherein an effective amount of the compound of formula I is used in combination with an effective amount of one or more other pharmaceutically active ingredients selected from the group consisting of: BACE inhibitors (beta secretase inhibitors), muscarinic antagonists (e.g., mi agonists or m2 antagonists), cholinesterase inhibitors (e.g., acetyl- and/or butyrylcholinesterase inhibitors); gamma secretase inhibitors; gamma secretase modulators; HMG-CoA reductase inhibitors; non- steroidal anti-inflammatory agents; N-methyl-D-aspartate receptor antagonists; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; an antibiotic; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; GABAA inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity; PDE-10 inhibitors and cholesterol absorption inhibitors (e.g., ezetimibe).

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more (e.g., one) compounds of formula I, in combination with an effective (i.e., therapeutically effective) amount of one or more cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl][methyl]-1 H -inden-1-one hydrochloride, i.e., donepezil hydrochloride,
available as the Aricept® brand of donepezil hydrochloride), to a patient in need of treatment.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of a compound of formula I, in combination with an effective amount of one or more (e.g., one) cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 H-inden-1-one hydrochloride, i.e., donepezil hydrochloride, available as the Aricept® brand of donepezil hydrochloride), to a patient in need of treatment.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more (e.g., one) compounds of formula I, in combination with an effective amount of one or more compounds selected from the group consisting of Aβ antibody inhibitors, gamma secretase inhibitors and beta secretase inhibitors.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more (e.g., one) compounds of formula I, in combination with an effective amount of one or more BACE inhibitors.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of formula I, in combination with an effective amount of Exelon (rivastigmine).

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of formula I, in combination with an effective amount of Cognex (tacrine).

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of formula I, in combination with an effective amount of a Tau kinase inhibitor.
Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of formula I, in combination with an effective amount of one or more Tau kinase inhibitor (e.g., GSK3beta inhibitor, cdk5 inhibitor, ERK inhibitor).

This invention also provides a method of treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of formula I, in combination with an effective amount of one anti-Abeta vaccination (active immunization).

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of formula I, in combination with an effective amount of one or more APP ligands.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more agents that upregulate insulin degrading enzyme and/or nephrilysin.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more cholesterol lowering agents (for example, statins such as Atorvastatin, Fluvastatin, Lovastatin, Mevastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin, and cholesterol absorption inhibitor such as Ezetimibe).

This invention also provides a method of treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of formula I, in combination with an effective amount of one or more fibrates (for example, clofibrate, Clofibrade, Etofibrate, Aluminium Clofibrate).

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of formula I, in combination with an effective amount of one or more LXR agonists.
Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of formula I, in combination with an effective amount of one or more LRP mimics.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of formula I, in combination with an effective amount of one or more 5-HT6 receptor antagonists.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more nicotinic receptor agonists.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more H3 receptor antagonists.

This invention also provides a method of treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of formula I, in combination with an effective amount of one or more histone deacetylase inhibitors.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of formula I, in combination with an effective amount of one or more hsp90 inhibitors.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of formula I, in combination with an effective amount of one or more muscarinic receptor agonists.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective amount of one or more
compounds of formula I, in combination with an effective amount of one or more
5-HT6 receptor antagonists mGluRI or mGluR5 positive allosteric modulators or agonists.

Another embodiment of this invention is directed to a method of treating
Alzheimer's disease, comprising administering an effective amount of one or more
compounds of formula I, in combination with an effective amount of one or more
mGluR2/3 antagonists.

Another embodiment of this invention is directed to a method of treating
Alzheimer's disease, comprising administering an effective amount of one or more
anti-inflammatory agents that can reduce neuroinflammation.

Another embodiment of this invention is directed to a method of treating
Alzheimer's disease, comprising administering an effective amount of one or more
Prostaglandin EP2 receptor antagonists.

This invention also provides a method of treating Alzheimer's disease,
comprising administering an effective amount of one or more compounds of
formula I, in combination with an effective amount of one or more PAI-1 inhibitors.

This invention also provides a method of treating Alzheimer's disease,
comprising administering an effective amount of one or more compounds of
formula I, in combination with an effective amount of one or more agents that can
induce Abeta efflux such as gelsolin.

This invention also provides a method of treating Downs syndrome,
comprising administering an effective amount of one or more (e.g., one)
compounds of formula I to a patient in need of treatment.

This invention also provides a method of treating Downs syndrome,
comprising administering an effective amount of a compound of formula I to a
patient in need of treatment.

This invention also provides a method of treating Downs syndrome,
comprising administering an effective amount of one or more (e.g., one)
compounds of formula I, in combination with an effective amount of one or more cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 H-inden-1-one hydrochloride, i.e., donepezil hydrochloride, available as the Aricept\textsuperscript{®} brand of donepezil hydrochloride), to a patient in need of treatment.

This invention also provides a method of treating Downs syndrome, comprising administering an effective amount of a compound of formula I, in combination with an effective amount of one or more (e.g., one) cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 H-inden-1-one hydrochloride, i.e., donepezil hydrochloride, available as the Aricept\textsuperscript{®} brand of donepezil hydrochloride), to a patient in need of treatment.

This invention also provides a method of treating mild cognitive impairment, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

This invention also provides a method of treating glaucoma, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

This invention also provides a method of treating cerebral amyloid angiopathy, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

This invention also provides a method of treating stroke, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

This invention also provides a method of treating dementia, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

This invention also provides a method of treating microgliosis, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.
This invention also provides a method of treating brain inflammation, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

This invention also provides a method of treating olfactory function loss, comprising administering an effective amount of one or more (e.g., one) compounds of formula I to a patient in need of treatment.

This invention also provides combinations (i.e., pharmaceutical compositions) comprising an effective amount of one or more (e.g., one) compounds of formula I, in combination with an effective amount of one or more compounds selected from the group consisting of cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 H-inden-1-one hydrochloride, i.e., donepezil hydrochloride, available as the Aricept® brand of donepezil hydrochloride), Aβ antibody inhibitors, gamma secretase inhibitors and beta secretase inhibitors. The pharmaceutical compositions also comprise a pharmaceutically acceptable carrier.

This invention also provides a kit comprising, in separate containers, in a single package, pharmaceutical compositions for use in combination, wherein one container comprises an effective amount of a compound of formula I in a pharmaceutically acceptable carrier, and another container (i.e., a second container) comprises an effective amount of another pharmaceutically active ingredient (as described above), the combined quantities of the compound of formula I and the other pharmaceutically active ingredient being effective to: (a) treat Alzheimer's disease, or (b) inhibit the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), or (c) treat neurodegenerative diseases, or (d) modulate the activity of gamma-secretase.

Another embodiment of this invention is directed to a pharmaceutically acceptable salt of a compound of formula (I), said compound of formula (I) being selected from the group consisting of: II to X.
Another embodiment of this invention is directed to a pharmaceutically acceptable ester of a compound of formula (I), said compound of formula (I) being selected from the group consisting of: \( \Pi \) to \( X \).

Another embodiment of this invention is directed to a solvate of a compound of formula (I), said compound of formula (I) being selected from the group consisting of: \( \Pi \) to \( X \).

Another embodiment of this invention is directed to a compound of formula (I) in isolated form, said compound of formula (I) being selected from the group consisting of: said compound of formula (I) being selected from the group consisting of: \( \Pi \) to \( X \).

Another embodiment of this invention is directed to a compound of formula (I) in pure form, said compound of formula (I) being selected from the group consisting of: said compound of formula (I) being selected from the group consisting of: \( \Pi \) to \( X \).

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of formula (I) and a pharmaceutically acceptable carrier, said compound of formula (I) being selected from the group consisting of: said compound of formula (I) being selected from the group consisting of: \( \Pi \) to \( X \).

Another embodiment is directed to a pharmaceutical composition comprising an effective amount of a pharmaceutically acceptable salt of one or more (e.g., one) compounds of formula (I) and a pharmaceutically acceptable carrier, said compound of formula (I) being selected from the group consisting of: said compound of formula (I) being selected from the group consisting of: \( \Pi \) to \( X \).

Another embodiment is directed to a pharmaceutical composition comprising an effective amount of a pharmaceutically acceptable ester of one or more (e.g., one) compounds of formula (I) and a pharmaceutically acceptable carrier, said compound of formula (I) being selected from the group consisting of: said compound of formula (I) being selected from the group consisting of: \( \Pi \) to \( X \).
carrier, said compound of formula (I) being selected from the group consisting of: said compound of formula (I) being selected from the group consisting of: II to X.

Another embodiment is directed to a pharmaceutical composition comprising an effective amount of a solvate of one or more (e.g., one) compounds of formula (I) and a pharmaceutically acceptable carrier, said compound of formula (I) being selected from the group consisting of: said compound of formula (I) being selected from the group consisting of: II to X.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of formula (I), and an effective amount of one or more (e.g., one) other pharmaceutically active ingredients (e.g., drugs), and a pharmaceutically acceptable carrier. Examples of the other pharmaceutically active ingredients include, but are not limited to drugs selected form the group consisting of: (a) drugs useful for the treatment of Alzheimer's disease, (b) drugs useful for inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), (c) drugs useful for treating neurodegenerative diseases, and (d) drugs useful for inhibiting gamma-secretase, said compound of formula (I) being selected from the group consisting of: said compound of formula (I) being selected from the group consisting of: II to X.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of formula (I), and effective amount of one or more BACE inhibitors, and a pharmaceutically acceptable carrier, said compound of formula (I) being selected from the group consisting of: said compound of formula (I) being selected from the group consisting of: II to X.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: II to X, and an effective amount of one or more cholinesterase inhibitors (e.g., acetyl- and/or butyrylcholinesterase inhibitors), and a pharmaceutically acceptable carrier.
Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: II to X, and effective amount of one or more muscarinic antagonists (e.g., mi agonists or m2 antagonists), and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: II to X, and effective amount of Exelon (rivastigmine), and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: II to X, and effective amount of Cognex (tacrine), and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: II to X, and effective amount of a Tau kinase inhibitor, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: II to X, and effective amount of one or more Tau kinase inhibitor (e.g., GSK3beta inhibitor, cdk5 inhibitor, ERK inhibitor), and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: II to X, and effective amount of one anti-Abeta vaccine (active immunization), and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one)
compounds selected from the group consisting of: I to X, and effective amount of one or more APP ligands, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: I to X, and effective amount of one or more agents that upregulate insulin degrading enzyme and/or nephrilysin, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: I to X, and effective amount of one or more cholesterol lowering agents (for example, statins such as Atorvastatin, Fluvastatin, Lovastatin, Mevastatin, Pravastatin, Pravastatin, Rosuvastatin, Simvastatin, and cholesterol absorption inhibitor such as Ezetimibe), and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: I to X, and effective amount of one or more fibrates (for example, clofibrate, Clofibrate, Etofibrate, Aluminium Clofibrate), and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: I to X, and effective amount of one or more LXR agonists, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: I to X, and effective amount of one or more LRP mimics, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one)
compounds selected from the group consisting of: I to X, and effective amount of one or more 5-HT6 receptor antagonists, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: I to X, and effective amount of one or more nicotinic receptor agonists, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: I to X, and effective amount of one or more H3 receptor antagonists, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: I to X, and effective amount of one or more histone deacetylase inhibitors, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: I to X, and effective amount of one or more hsp90 inhibitors, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: I to X, and effective amount of one or more m1 muscarinic receptor agonists, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: I to X, and effective amount of...
one or more 5-HT6 receptor antagonists mGluRI or mGluR5 positive allosteric modulators or agonists, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: II to X, and effective amount of one or more one mGluR2/3 antagonists, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: II to X, and effective amount of one or more anti-inflammatory agents that can reduce neuroinflammation, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: II to X, and effective amount of one or more Prostaglandin EP2 receptor antagonists, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: II to X, and effective amount of one or more PAI-1 inhibitors, and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds selected from the group consisting of: II to X, and effective amount of one or more agents that can induce Abeta efflux such as gelsolin, and a pharmaceutically acceptable carrier.

The compounds of formulas (I) selected from the group consisting of: II to X can be useful as gamma secretase modulators and can be useful in the treatment and prevention of diseases such as, for example, central nervous system disorders (such as Alzheimers disease and Downs Syndrome), and treating mild cognitive
impairment, glaucoma, cerebral amyloid angiopathy, stroke, dementia, microgliosis, brain inflammation, and olfactory function loss.

Thus, another embodiment of this invention is directed to a method for modulating (including inhibiting, antagonizing and the like) gamma-secretase comprising administering an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds of formula (I) to a patient in need of such treatment, said compound of formula (I) being selected from the group consisting of: \text{II} to \text{X}.

Another embodiment of this invention is directed to a method for modulating (including inhibiting, antagonizing and the like) gamma-secretase, comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I) to a patient in need of treatment, said compound of formula (I) being selected from the group consisting of: \text{II} to \text{X}.

Another embodiment of this invention is directed to a method of treating one or more neurodegenerative diseases, comprising administering an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds of formula (I) to a patient in need of treatment, said compound of formula (I) being selected from the group consisting of: \text{II} to \text{X}.

Another embodiment of this invention is directed to a method of treating one or more neurodegenerative diseases, comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I) to a patient in need of treatment, said compound of formula (I) being selected from the group consisting of: \text{II} to \text{X}.

Another embodiment of this invention is directed to a method of inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), comprising administering an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds of formula (I) to a patient in need of treatment, said compound of formula (I) being selected from the group consisting of: \text{II} to \text{X}.
Another embodiment of this invention is directed to a method of inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I) to a patient in need of treatment, said compound of formula (I) being selected from the group consisting of: \( \Pi \) to \( X \).

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds of formula (I) to a patient in need of treatment, said compound of formula (I) being selected from the group consisting of: \( \Pi \) to \( X \).

Another embodiment of this invention is directed to a method of treating mild cognitive impairment, glaucoma, cerebral amyloid angiopathy, stroke, dementia, microgliosis, brain inflammation, or olfactory function loss, comprising administering an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds of formula (I) to a patient in need of treatment, said compound of formula (I) being selected from the group consisting of: \( \Pi \) to \( X \).

Another embodiment of this invention is directed to a method of treating mild cognitive impairment, glaucoma, cerebral amyloid angiopathy, stroke, dementia, microgliosis, brain inflammation, or olfactory function loss, comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I) to a patient in need of treatment, said compound of formula (I) being selected from the group consisting of: \( \Pi \) to \( X \).

This invention also provides combination therapies for (1) modulating gamma-secretase, or (2) treating one or more neurodegenerative diseases, or (3) inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or
around neurological tissue (e.g., the brain), or (4) treating Alzheimer's disease. The combination therapies are directed to methods comprising the administration of one or more (e.g., one) compounds of formula (I), and the administration of one or more (e.g., one) other pharmaceutical active ingredients (e.g., drugs). The compounds of formula (I), and the other drugs can be administered separately (i.e., each is in its own separate dosage form), or the compounds of formula (I) can be combined with the other drugs in the same dosage form.

Thus, other embodiments of this invention are directed to any one of the methods of treatment, or methods of inhibiting, described herein, wherein the compounds of formula (I) are used in combination with an effective amount of one or more other pharmaceutically active ingredients selected from the group consisting of: BACE inhibitors (beta secretase inhibitors); muscarinic antagonists (e.g., m1 agonists or m2 antagonists); cholinesterase inhibitors (e.g., acetyl- and/or butyrylcholinesterase inhibitors); gamma secretase inhibitors; gamma secretase modulators; HMG-CoA reductase inhibitors; non-steroidal anti-inflammatory agents; N-methyl-D-aspartate receptor antagonists; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; an antibiotic; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; GABA_A inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity; PDE-10 inhibitors; Exelon (rivastigmine); Cognex (tacrine); Tau kinase inhibitors (e.g., GSK3beta inhibitors, cdk5 inhibitors, or ERK inhibitors); anti-Abeta vaccine; APP ligands; agents that upregulate insulin cholesterol lowering agents (for example, statins such as Atorvastatin, Fluvastatin, Lovastatin, Mevastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin); cholesterol absorption inhibitors (such as Ezetimibe); fibrates (such as, for example, for example, clofibrate, Clofibrate, Etofibrate, and Aluminium Clofibrate); LXR agonists; LRP mimics; nicotinic receptor agonists; H3 receptor antagonists; histone deacetylase inhibitors; hsp90 inhibitors; m1 muscarinic receptor agonists; 5-HT6 receptor antagonists; mGluRI ; mGluR5;
positive allosteric modulators or agonists; mGluR2/3 antagonists; anti-inflammatory agents that can reduce neuroinflammation; Prostaglandin EP2 receptor antagonists; PAI-1 inhibitors; and agents that can induce Abeta efflux such as gelsolin.

This invention also provides combination therapies for (1) modulating gamma-secretase, or (2) treating one or more neurodegenerative diseases, or (3) inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), or (4) treating Alzheimer's disease.

The combination therapies are directed to methods comprising the administration of one or more (e.g. one) compounds of formula (I) selected from the group consisting of: \( \text{II to X} \), and the administration of one or more (e.g., one) other pharmaceutical active ingredients (e.g., drugs). The compounds of formula \( \text{II to X} \), and the other drugs can be administered separately (i.e., each is in its own separate dosage form), or the compounds of formula \( \text{II to X} \) can be combined with the other drugs in the same dosage form.

Thus, other embodiments of this invention are directed to any one of the methods of treatment, or methods of inhibiting, described herein, wherein the compounds of formula (I), selected from the group consisting of: \( \text{II to X} \) are used in combination with an effective amount of one or more other pharmaceutically active ingredients selected from the group consisting of: BACE inhibitors (beta secretase inhibitors), muscarinic antagonists (e.g., m1 agonists or m2 antagonists), cholinesterase inhibitors (e.g., acetyl- and/or butyrylcholinesterase inhibitors); gamma secretase inhibitors; gamma secretase modulators; HMG-CoA reductase inhibitors; non-steroidal anti-inflammatory agents; N-methyl-D-aspartate receptor antagonists; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; an antibiotic; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; \( \text{GABA}_A \) inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity; PDE-10 inhibitors; Exelon (rivastigmine); Cognex (tacrine); Tau...
kinase inhibitors (e.g., GSK3beta inhibitors, cdk5 inhibitors, or ERK inhibitors); anti-Abeta vaccine; APP ligands; agents that upregulate insulin cholesterol lowering agents (for example, statins such as Atorvastatin, Fluvastatin, Lovastatin, Mevastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin); cholesterol absorption inhibitors (such as Ezetimibe); fibrates (such as, for example, clofibrate, Clofibrate, Etofibrate, and Aluminium Clofibrate); LXR agonists; LRP mimics; nicotinic receptor agonists; H3 receptor antagonists; histone deacetylase inhibitors; hsp90 inhibitors; m1 muscarinic receptor agonists; 5-HT6 receptor antagonists; mGluRI ; mGluR5; positive allosteric modulators or agonists; mGluR2/3 antagonists; anti-inflammatory agents that can reduce neuroinflammation; Prostaglandin EP2 receptor antagonists; PAI-1 inhibitors; and agents that can induce Abeta efflux such as gelsolin.

Other embodiments of this invention are directed to any one of the methods of treatment, or methods of inhibiting, described herein, wherein the compounds of formula (I), selected from the group consisting of: II to X are used in combination with an effective amount of one or more other pharmaceutically active ingredients selected from the group consisting of: BACE inhibitors (beta secretase inhibitors), muscarinic antagonists (e.g., m1 agonists or m2 antagonists), cholinesterase inhibitors (e.g., acetyl- and/or butyrylcholinesterase inhibitors); gamma secretase inhibitors; gamma secretase modulators; HMG-CoA reductase inhibitors; non-steroidal anti-inflammatory agents; N-methyl-D-aspartate receptor antagonists; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; an antibiotic; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; GABA_A inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity; PDE-10 inhibitors; and cholesterol absorption inhibitors (e.g., ezetimibe).

Other embodiments of this invention are directed to any one of the methods of treatment, or methods of inhibiting, described herein, wherein the compounds
of formula (I), selected from the group consisting of: II to X are used in combination with an effective amount of one or more other pharmaceutically active ingredients selected from the group consisting of: Exelon (rivastigmine); Cognex (tacrine); Tau kinase inhibitors (e.g., GSK3beta inhibitors, cdk5 inhibitors, or ERK inhibitors); anti-Abeta vaccine; APP ligands; agents that upregulate insulin cholesterol lowering agents (for example, statins such as Atorvastatin, Fluvastatin, Lovastatin, Mevastatin, Pravastatin, Pravastatin, Rosuvastatin, Simvastatin); cholesterol absorption inhibitors (such as Ezetimibe); fibrates (such as, for example, clofibrate, Clofibride, Etofibrate, and Aluminium Clofibrate); LXR agonists; LRP mimics; nicotinic receptor agonists; H3 receptor antagonists; histone deacetylase inhibitors; hsp90 inhibitors; mI muscarinic receptor agonists; 5-HT6 receptor antagonists; mGlur1; mGlur5; positive allosteric modulators or agonists; mGlur2/3 antagonists; anti-inflammatory agents that can reduce neuroinflammation; Prostaglandin EP2 receptor antagonists; PAI-1 inhibitors; and agents that can induce Abeta efflux such as gelsolin.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds of formula (I) selected from the group consisting of: II to X, in combination with an effective (i.e., therapeutically effective) amount of one or more cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[1-(phenylmethyl)-4-piperidinyl][methyl]-1 H-inden-1-one hydrochloride, i.e., donepezil hydrochloride, available as the Aricept® brand of donepezil hydrochloride), to a patient in need of treatment.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I) selected from the group consisting of: II to X, in combination with an effective (i.e., therapeutically effective) amount of one or more (e.g., one) cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[1-(phenylmethyl)-4-piperidinyl][methyl]-1 H-inden-1-one hydrochloride, i.e., donepezil hydrochloride, available as the Aricept® brand of donepezil hydrochloride), to a patient in need of treatment.
hydrochloride, i.e., donepezil hydrochloride, available as the Aricept® brand of donepezil hydrochloride), to a patient in need of treatment.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds of formula (I) selected from the group consisting of: in combination with an effective (i.e., therapeutically effective) amount of one or more compounds selected from the group consisting of Aβ antibody inhibitors, gamma secretase inhibitors and beta secretase inhibitors.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds of formula (I) selected from the group consisting of: II to X, in combination with an effective (i.e., therapeutically effective) amount of one or more BACE inhibitors.

Another embodiment of this invention is directed to a method of treating Alzheimer's disease, comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I) selected from the group consisting of: II to X, and the Compound of Example 1, in combination with an effective (i.e., therapeutically effective) amount of one or more BACE inhibitors.

Another embodiment of this invention is directed to a method of treating Downs syndrome, comprising administering an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds of formula (I) selected from the group consisting of: II to X to a patient in need of treatment.

Another embodiment of this invention is directed to a method of treating Downs syndrome, comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I) selected from the group consisting of: II to X, to a patient in need of treatment.

Another embodiment of this invention is directed to a method of treating Downs syndrome, comprising administering an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds of formula (I) selected
from the group consisting of: I to X, in combination with an effective (i.e., therapeutically effective) amount of one or more cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 H-inden-1-one hydrochloride, i.e., donepezil hydrochloride, available as the Aricept® brand of donepezil hydrochloride), to a patient in need of treatment.

Another embodiment of this invention is directed to a method of treating Downs syndrome, comprising administering an effective (i.e., therapeutically effective) amount of a compound of formula (I) selected from the group consisting of: I to X, in combination with an effective (i.e., therapeutically effective) amount of one or more (e.g., one) cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 H-inden-1-one hydrochloride, i.e., donepezil hydrochloride, available as the Aricept® brand of donepezil hydrochloride), to a patient in need of treatment.

Another embodiment of this invention is directed to combinations (i.e., pharmaceutical compositions) comprising an effective (i.e., therapeutically effective) amount of one or more (e.g., one) compounds of formula (I) selected from the group consisting of: I to X in combination with an effective (i.e., therapeutically effective) amount of one or more compounds selected from the group consisting of cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 H-inden-1-one hydrochloride, i.e., donepezil hydrochloride, available as the Aricept® brand of donepezil hydrochloride), Aβ antibody inhibitors, gamma secretase inhibitors and beta secretase inhibitors. The pharmaceutical compositions also comprise a pharmaceutically acceptable carrier.

This invention also provides a kit comprising, in separate containers, in a single package, pharmaceutical compositions for use in combination, wherein one container comprises an effective amount of one or more (e.g., one) compounds of formula (I) (e.g., compounds selected from the group consisting of: I to X in a pharmaceutically acceptable carrier, and another container (i.e., a second
container) comprises an effective amount of another pharmaceutically active ingredient (as described above), the combined quantities of the compounds of formula (I) and the other pharmaceutically active ingredient being effective to: (a) treat Alzheimer's disease, or (b) inhibit the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), or (c) treat neurodegenerative diseases, or (d) modulate the activity of gamma-secretase.

This invention also provides a kit comprising, in separate containers, in a single package, pharmaceutical compositions for use in combination, wherein one container comprises an effective amount of a compound selected from the group consisting of the compounds of formulas (I) (e.g. the compounds selected from the group consisting of: Il to X) in a pharmaceutically acceptable carrier, and another container (i.e., a second container) comprises an effective amount of another pharmaceutically active ingredient (as described above), the combined quantities of the compound of formulas (I) and the other pharmaceutically active ingredient being effective to: (a) treat Alzheimer's disease, or (b) inhibit the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), or (c) treat neurodegenerative diseases, or (d) modulate the activity of gamma-secretase.

Other embodiments of this invention are directed to any one of the above methods of treatment, pharmaceutical compositions, or kits wherein the compound of formula I is any one of the compounds 1 to 164.

Other embodiments of this invention are directed to any one of the above methods of treatment, pharmaceutical compositions, or kits wherein the compound of formula I is any one of the compounds in Table 14.

Examples of cholinesterase inhibitors are tacrine, donepezil, rivastigmine, galantamine, pyridostigmine and neostigmine, with tacrine, donepezil, rivastigmine and galantamine being preferred.

Examples of m1 agonists are known in the art. Examples of m2 antagonists are also known in the art; in particular, rti2 antagonists are disclosed in US patents

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"TBAF" means tetrabutyl ammonium fluoride

"At least one" means one or more than one, for example, 1, 2 or 3, or in another example, 1 or 2, or in another example 1.
"One or more" with reference to the use of the compounds of this invention means that one or more than one compound is used, for example, 1, 2 or 3, or in another example, 1 or 2, or in another example 1.

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals. It is noted that the carbons of formula I and other formulas herein may be replaced with 1 to 3 silicon atoms so long as all valency requirements are satisfied.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. "Alkyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, oxime (e.g., =N-OH), -NH(alkyl), -NH(cycloalkyl), -N(alkyl)₂, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, carboxy and -C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. "Alkenyl" may be unsubstituted or optionally
substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, alkoxy and −S(alkyl). Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkylene" means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. Non-limiting examples of alkylene include methylene, ethylene and propylene.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain.

"Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. "Alkynyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally
substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. "Heteroaryl" may also include a heteroaryl as defined above fused to an aryl as defined above. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxaliny, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Alkaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkarylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Carbocyclic" means a non-aromatic saturated or unsaturated mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Carbocyclic rings include cycloalkyl rings and cycloalkenyl rings as defined below. Thus, examples of carbocyclic rings include bicyclic rings, such as, for example, norbomyl, adamantly, norbornenyl, and
The carbocyclic rings are optionally substituted with one or more independently selected "ring system substituents" as defined below.

"Cycloalkyl" means a non-aromatic mono- or multicic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like.

"Cycloalkylalkyl" means a cycloalkyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkylalkyls include cyclohexylmethyl, adamantylmethyl and the like.

"Cycloalkenyl" (or "carbocyclenyl") means a non-aromatic mono or multicic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

"Cycloalkenylalkyl" means a cycloalkenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkenylalkyls include cyclopentenylmethyl, cyclohexenylmethyl and the like.
"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine. "Halo" refers to fluoro, chloro, bromo or iodo.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxy carbonyl, aryloxy carbonyl, aralkoxy carbonyl, alkylsulfonfyl, aryl sulfonfyl, heteroaryl sulfonfyl, alkyithio, arlythio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(=N-CN)-NH\(_2\), -C(=NH)-NH\(_2\), -C(=NH)-NH(alkyl), oxime (e.g., =N-OH), YiY\(_2\)N-, YiY\(_2\)N-alkyl-, YiY\(_2\)NC(O)-, YiY\(_2\)NSO\(_2\)- and -SO\(_2\)NY\(_1\)Y\(_2\), wherein Yi and Y\(_2\) can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, -C(CH\(_3\))\(_2\)- and the like which form moieties such as, for example:

![Image](image_url)

"Heteroarylalkyl" means a heteroaryl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heteroaryls include 2-pyridinylmethyl, quinolinylmethyl and the like.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination with other elements.
combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclols contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any -NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like. "Heterocyclyl" may also mean a single moiety (e.g., carbonyl) which simultaneously replaces two available hydrogens on the same carbon atom on a ring system. Example of such moiety is pyrrolidone:

"Heterocyclylalkyl" means a heterocyclyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heterocyclylalkyls include pipedinylmethyl, piperazinylmethyl and the like.

"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms
present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable heterocyclenyl groups include 1,2,3,4-tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyran-2-yl, dihydrofuranyl, fluorodihydrofuran-2-yl, 7-oxabicyclo[2.2.1]hepten-2-yl, dihydrothiophenyl, dihydrothiopyran-2-yl, and the like. "Heterocyclenyl" may also mean a single moiety (e.g., carbonyl) which simultaneously replaces two available hydrogens on the same carbon atom on a ring system. Example of such moiety is pyrrolidinone:

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\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{C} \\
\end{array}
\]
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"Heterocyclenylalkyl" means a heterocyclenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:
there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms such as, for example, the moieties:

are considered equivalent in certain embodiments of this invention.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy,
ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable arylxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Aryltthio" means an arylthio group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkylthio group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylihio. The bond to the parent moiety is through the sulfur.

"Alkoxy carbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxy carbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryloxycarbonyl group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxy carbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkoxycarbonyl group. Non-limiting example of a suitable aralkoxycarbonyl group is benzylloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(O$_2$) group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.
"Arylsulfonyl" means an aryl-S(O$_2$)$_2$- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization and the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by
reference to standard textbooks such as, for example, T. W. Greene et al.,

When any variable (e.g., aryl, heterocycle, R², etc.) occurs more than one
time in any constituent or in Formula 1, its definition on each occurrence is
independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product
comprising the specified ingredients in the specified amounts, as well as any
product which results, directly or indirectly, from combination of the specified
ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also
contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V.
Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche,
ed., American Pharmaceutical Association and Pergamon Press. The term
"prodrug" means a compound (e.g., a drug precursor) that is transformed *in vivo* to
yield a compound of Formula I or a pharmaceutically acceptable salt, hydrate or
solvate of the compound. The transformation may occur by various mechanisms
(e.g., by metabolic or chemical processes), such as, for example, through
hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi
and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S.
Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B.

For example, if a compound of Formula I or a pharmaceutically acceptable
salt, hydrate or solvate of the compound contains a carboxylic acid functional
group, a prodrug can comprise an ester formed by the replacement of the
hydrogen atom of the acid group with a group such as, for example, (C₁₋₈)alkyl,
(C₂₋₁₂)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms,
1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms,
alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-
(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-
(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-
(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-
(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-
crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁₋C₂)alkylamino(C₂₋C₃)alkyl
(such as beta-dimethylaminoethyl), carbamoyl-(C₁₋C₂)alkyl, N,N-di (C₁₋C₂-
C₃)alkylcarbamoyl-(C₁₋C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂₋C₃)alkyl, and the like.

Similarly, if a compound of Formula I contains an alcohol functional group, a
prodrug can be formed by the replacement of the hydrogen atom of the alcohol
group with a group such as, for example, (CrC₆)alkanoyloxymethyl, 1-((C₁₋C₆-
C₂)alkanoyloxy)ethyl, 1-methyl-1-((C₁₋C₆)alkanoyloxy)ethyl, (C₁₋C₂-
C₆)alkoxycarbonyloxymethyl, N-(C₁₋C₆)alkoxycarbonylaminomethyl, succinoyl,
(C₁₋C₁₀)alkanoyl, alpha-amino(C₁₋C₄)alkanyl, arylacyl and alpha-aminoacyl, or alpha-aminoacyl-
alpha-aminoacyl, where each alpha-aminoacyl group is independently selected from the
naturally occurring L-amino acids, P(O)(OH)₂, -P(O)(O(CrC₆)alkyl)₂ or glycosyl
(the radical resulting from the removal of a hydroxyl group of the hemiacetal form
of a carbohydrate), and the like.

If a compound of Formula I incorporates an amine functional group, a
prodrug can be formed by the replacement of a hydrogen atom in the amine group
with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl
where R and R' are each independently (C₁₋C₅)alkyl, (C₃₋C₇) cycloalkyl, benzyl,
or R-carbonyl is a natural alpha-aminoacyl or natural alpha-aminoacyl, —C(OH)C(O)OY
wherein Y is H, (C₁₋C₆)alkyl or benzyl, —C(OY)² where C is (C₁₋C₄) alkyl
and Y is (CrC₆)alkyl, carboxy (C₁₋C₆)alkyl, amino(C₁₋C₄)alkyl or mono-N—or di-
N,N-(C₁₋C₆)alkylaminoalkyl, —C(Y⁴)² where C is H or methyl and Y is mono-
N—or di-N,N-(CrC₆)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and
the like.

One or more compounds of the invention may exist in unsolvated as well
as solvated forms with pharmaceutically acceptable solvents such as water,
ethanol, and the like, and it is intended that the invention embrace both solvated
and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H₂O.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira et al, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder et al, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham et al, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

"Effective amount" with reference to the amount of a compound of formula I, or another drug, used in a pharmaceutical composition, method of treatment or kit, means a therapeutically effective amount.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the above-noted diseases and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.
The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula I may be formed, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl et al, Camille G. (eds.) Handbook of Pharmaceutical Salts. Properties, Selection and Use. (2002) Zurich: Wiley-VCH; S. Berge et al, Journal of Pharmaceutical Sciences (1977) 66(1) 1-19; P. Gould, International J. of Pharmaceutics (1986) 33 201-217; Anderson et al, The Practice of Medicinal Chemistry (1996), Academic Press, New York; and in The Orange Book (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.
Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quartemized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxyethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, dialkyl, or C_1-4 alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_1-20 alcohol or reactive derivative thereof, or by a 2,3-di (C_6-24)acyl glycerol.

Compounds of Formula I, and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide, enol, keto or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.
The compounds of Formula I may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of Formula I as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of Formula I incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula I may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the compounds of Formula I may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers.
(such as, for example, 4-pyridyl and 3-pyridyl). (For example, if a compound of Formula I incorporates a double bond or a fused ring, both the cis- and trans- forms, as well as mixtures, are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.) Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as $^2$H, $^3$H, $^{13}$C, $^{14}$C, $^{15}$N, $^{18}$O, $^{17}$O, $^{31}$P, $^{32}$P, $^{35}$S, $^{18}$F, and $^{36}$Cl, respectively.

Certain isotopically-labelled compounds of Formula I (e.g., those labeled with $^3$H and $^{14}$C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., $^3$H) and carbon-14 (i.e., $^{14}$C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., $^2$H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of Formula I can generally be prepared by following procedures analogous to those disclosed in the Schemes
and/or in the Examples hereinbelow, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

Polymorphic forms of the compounds of Formula I, and of the salts, solvates, esters and prodrugs of the compounds of Formula I, are intended to be included in the present invention.

The compounds according to the invention can have pharmacological properties; in particular, the compounds of Formula I can be modulators of gamma secretase (including inhibitors, antagonists and the like).

More specifically, the compounds of Formula I can be useful in the treatment of a variety of disorders of the central nervous system including, for example, including, but not limited to, Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration and the like.

Another aspect of this invention is a method of treating a mammal (e.g., human) having a disease or condition of the central nervous system by administering a therapeutically effective amount of at least one compound of Formula I, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound to the mammal.

A preferred dosage is about 0.001 to 500 mg/kg of body weight/day of the compound of Formula I. An especially preferred dosage is about 0.01 to 25 mg/kg of body weight/day of a compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound.

The compounds of this invention may also be useful in combination (administered together or sequentially) with one or more additional agents listed above.

The compounds of this invention may also be useful in combination (administered together or sequentially) with one or more compounds selected from the group consisting of Aβ antibody inhibitors, gamma secretase inhibitors and beta secretase inhibitors.
If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent or treatment within its dosage range.

Accordingly, in an aspect, this invention includes combinations comprising an amount of at least one compound of Formula I, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and an amount of one or more additional agents listed above wherein the amounts of the compounds/ treatments result in desired therapeutic effect.

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. Certain assays are exemplified later in this document.

This invention is also directed to pharmaceutical compositions which comprise at least one compound of Formula I, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and at least one pharmaceutically acceptable carrier.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), *Remington's Pharmaceutical Sciences*, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions,
suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally.

The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

The compounds of this invention may also be delivered subcutaneously.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated.

Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as
age, condition and size of the patient as well as severity of the symptoms being
treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 500 mg/day, preferably 1 mg/day to 200 mg/day, in two to four divided doses.

Another aspect of this invention is a kit comprising a therapeutically effective amount of at least one compound of Formula I, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

Yet another aspect of this invention is a kit comprising an amount of at least one compound of Formula I, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and an amount of at least one additional agent listed above, wherein the amounts of the two or more ingredients result in desired therapeutic effect.

The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art. Reagents and reaction conditions can be changed according to the knowledge of those skilled in the art.

Where NMR data are presented, $^1$H spectra were obtained on either a Varian VXR-200 (200 MHz, $^1$H), Varian Gemini-300 (300 MHz) or XL-400 (400 MHz) and are reported as ppm down field from Me4Si with number of protons, multiplicities, and coupling constants in Hertz indicated parenthetically. Where LC/MS data are presented, analyses was performed using an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Altech platinum C18, 3 micron, 33mm x 7mm ID; gradient flow: 0 min - 10% CH$_3$CN, 5 min - 95% CH$_3$CN, 7 min - 95% CH$_3$CN, 7.5 min - 10% CH$_3$CN, 9 min - stop. The observed parent ion is given.

The following solvents and reagents may be referred to by their abbreviations in parenthesis:

Thin layer chromatography: TLC
dichloromethane: CH$_2$Cl$_2$
ethyl acetate: AcOEt or EtOAc
methanol: MeOH
trifluoroacetate: TFA
triethylamine: Et$_3$N or TEA
butoxycarbonyl: n-Boc or Boc
nuclear magnetic resonance spectroscopy: NMR
liquid chromatography mass spectrometry: LCMS
high resolution mass spectrometry: HRMS

milliliters: ml
millimoles: mmol
microliters: µl
grams: g
milligrams: mg

room temperature or rt (ambient): about 25°C.

N-bromosuccinimide: NBS
N-chlorosuccinimide: NCS

EXAMPLES

Method A
Method A, Step 1

The following method was adapted for the oxadiazoline synthesis (Tsuge, Otohiko; Kanemasa, Shuji; Suga, Hiroyuki; Nakagawa, Norihiko. Bulletin of the Chemical Society of Japan (1987), 60(7), 2463-73).

Compound A1 (R8 = H, R10 = 3-MeO-Phenyl, R9 = 4-(4-Methylimidazol-1-yl), 3g) and A2 (4.2 g) in 135 ml of anhydrous THF was heated at 100°C in a sealed tube under nitrogen overnight. Solvent was evaporated and residue chromatographed using a silica gel column eluted with EtOAc / Hexane to give 2.7 g of A3 (R1 = H, R8 = H, R10 = 3-OMePhenyl, R9 = 4-(4-Methyl-imidazol-1-yl)).

Method A, Step 2

A3 (R1 = H, R8 = H, R10 = 3-MeO-Phenyl, R9 = 4-(4-Methyl-imidazol-1-yl), 2.7 g) and potassium acetate (1.4 g) in 120 ml MeOH was cooled to 0°C before hydroxylamine hydrochloride (1 g) was added. The reaction mixture was stirred for 90 min before the solvent was evaporated. The residue was partitioned in EtOAc and brine. The organic layer was dried over anhydrous Na2SO4. The crude was purified on C18 reverse phase column to give 1g of A4 (R1 = H, R8 = H, R10 = 3-MeO-Phenyl, R9 = 4-(4-Methyl-imidazol-1-yl)).

MS (M+1): 258.

Method A, Step 3

A mixture of A5 (R2 = 3-MeO-propyl, 3 ml) and A6 (R6 = Me, R7 = p-F-phenyl, 1.2 ml) in a sealed tube was heated at 50°C with 2g of 4A molecular sieves under nitrogen for 3h and r.t. for 72 h. The volatile was removed to give A7 (R2 = 3-MeO-Propyl, R6 = Me, R7 = p-F-Phenyl) as an oil which was used for next step without further purification.

Method A, Step 4

A mixture of A4 (R1 = H, R8 = H, R10 = 3-MeO-Phenyl, R9 = 4-(4-Methyl-imidazol-1-yl), 100 mg), N-Chlorosuccinimide (51.9 mg) and pyridine (8 uL) in 1.2
ml of DCM was stirred at r.t. for 10 min followed by addition of A7 (R² = 3-OMePropyl, R⁶ = Me, R⁷ = p-F-Phenyl) and TEA (0.8 mL). The reaction mixture was stirred at r.t. overnight before it was diluted with DCM, washed with brine, dried over anhydrous sodium sulfate. The solvent was removed and residue purified via a reverse phase column eluted with MeCN / Water with 0.1 % formic acid to give product A8 (R¹ = H, R² = 3-OMePropyl, R⁶ = Me, R⁷ = p-F-Phenyl, R⁸ = H, R¹⁰ = 3-MeO-Phenyl, R⁹ = 4-(4-Methyl-imidazol-1-yl)).

¹H NMR (CDCl₃, ppm): 7.96 (br, 1H), 7.59-7.55 (m, 2H), 7.48-7.44 (d, 1H), 7.27-7.5 (m, 1H), 7.18-7.16 (m, 1H), 7.12 (m, 2H), 7.09-7.05 (t, 1H), 6.96 (br, 1H), 6.57-6.53 (d, 1H), 3.89 (s, 3H), 3.27 (s, 3H), 3.29-3.14 (m, 4H), 2.32 (s, 3H), 1.89 (s, 3H), 1.55 (br, 2H). MS (ES-LCMS, M+1) 465.

The compounds in Table 2 were synthesized using methods similar to that of Method A.

Table 2

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The compounds in Table 3 were synthesized using methods similar to that of Method A. In Table 3 "#" means compound number.

**Table 3**

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Method B

\[
\begin{align*}
B1 & \xrightarrow{\text{NH}_2\text{HBr}} B2 & \xrightarrow{TMS} \text{B2} & \xrightarrow{\text{B6}} \text{B3} \\
& \xrightarrow{\text{R}^6\text{R}^7} \text{B3} & \xrightarrow{\text{Et-O-P(O)}\text{Cl-OH}} \text{B4} & \xrightarrow{\text{B5}} \text{B5}
\end{align*}
\]
Method B, step 1:

Triethylamine (10.5 ml) was added slowly to a stirred suspension of B1 (5 g) in 66 ml of anhydrous DCM at 0°C under nitrogen atmosphere. A solution of chlorotrimethylsilane (6.4 ml) in 12 mL in anhydrous DCM was added slowly to the above suspension. The reaction mixture was stirred at r.t. overnight before filtration to remove precipitate. The filtrate was evaporated and the residue oil was redissolved in 150 mL diethyl ether, stirred for 15min, filtered and concentrated to give 5.7 g of B2.

Method B, Step 2

A catalytic amount of trimethylsilyl trifluoromethanesulfonate was added to a stirred mixture of B2 (4.7 g) and A6 (3.3g, R6 = p-F-Phenyl and R7 = carboethoxyl) in 33 mL of anhydrous DCM at r.t. under nitrogen atmosphere. The reaction mixture was refluxed for 48 h before cooled to r.t. and sequentially washed with cold NaHCO3: water (1:1) and cold half-saturated brine. The organic phase was dried over anhydrous sodium sulfate, filtered and solvent removed to give 5 g of B3 (R6 = p-F-Phenyl and R7 = carboethoxyl).
Method B, Step 3

A solution of B3 (R^6 = p-F-Phenyl and R^7 = carboethoxyl) (500 mg, 1 equiv.) in 2.3 ml of anhydrous DMF was slowly added to a solution of B4 (1.3 equiv. obtained following a reference procedure: Tsuge, Otohiko; Kanemasa, Shuji; Suga, Hiroyuki; Nakagawa, Norihiko Bulletin of the Chemical Society of Japan (1987), 60(7), 2463-73) in 0.5 mL of anhydrous DMF at 0°C under nitrogen atmosphere. A solution of TEA (0.33 mL, 1.5equiv.) in 0.4 mL of anhydrous DMF was slowly added to the above reaction mixture. The reaction mixture was stirred at r.t. overnight before dilution with 20 mL of diethyl ether and 20 mL half-saturated brine. The aqueous phase was extracted with EtOAC: hexane (7:3). The organic phase was washed with half-saturated brine then, dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified via a flash silica gel column eluted with DCM/ EtOAc with 1% isopropanol to give B5 (198 mg, R^6 = p-F-Phenyl and R^7 = carboethoxyl).

^1H NMR (CDCl_3, ppm): 67.45-7.42 (m, 2H), 7.07-7.03 (t, 2H), 4.27-4.24 (m, 2H), 4.17-4.10 (m, 4H), 3.52-3.40 (m, 1H), 3.36-3.29 (m, 2H), 3.17-3.14 (m, 1H), 2.95-2.89 (dd, 2H), 1.76-1.40 (m, 2H), 1.31-1.24 (m, 9H).

Method B, Step 4

A mixture of B5 (6.2g, R^6 = p-F-Phenyl and R^7 = carboethoxyl) and sodium iodide in 90 mL acetone was stirred overnight at reflux. The reaction mixture was diluted with 1 L diethyl ether and vigorously stirred for 30 min. The precipitate was filtered and the filtrate was washed with sodium thiosulfate (10.6 g) in brine and partitioned between diethyl ether and brine. The organic phase was dried over anhydrous magnesium sulfate, filtered and solvent evaporated. The residue was purified by a flash silica gel column and eluted with DCM/ EtOAc to give 3 g of B6 (3g, R^6 = p-F-Phenyl and R^7 = carboethoxyl)
Method B, Step 5

A solution of t-BuOK (1.6 g) in 54 ml of anhydrous THF was added dropwise to a stirred solution of B6 (5.4 g, R^6 = p-F-Phenyl and R^7 = carboethoxyl) in 40 mL of anhydrous THF at -65°C under nitrogen atmosphere. The reaction mixture was stirred between -65°C and -40°C until SM was consumed. The reaction mixture was quenched with iced brine, and extracted with EtOAc. The organic phase was washed with NH_4Cl and brine, dried over anhydrous magnesium sulfate, filtered and solvent evaporated. The residue was purified by a flash silica gel column and eluted with DCM/ EtOAc to give 2.2 g of B7 (R^6 = p-F-Phenyl and R^7 = carboethoxyl).

^1H NMR (CDCl_3, ppm): 67.47-7.41 (m, 2H), 7.24-7.06 (m, 2H), 4.34-4.09 (m, 6H), 3.42-3.30 (m, 1H), 3.14-3.08 (m, 1H), 2.78-2.59 (m, 1H), 2.16-1.60 (m, 4H), 1.36-1.22 (m, 9H).

Method B, Step 6

A solution of t-BuOK (733 mg) in 20.5 mL of anhydrous THF was added dropwise to a stirred mixture of B7 (R^6 = p-F-Phenyl and R^7 = carboethoxyl, 2.2 g) and A1 (1 g, R^10 = 3-MeO-Phenyl, R^3 = 4-(4-Methyl-imidazol-1-yl) and R^8 = H) in 29.5 mL of anhydrous THF at -70°C under nitrogen atmosphere. The reaction mixture was stirred between -70°C and -30°C until starting material were consumed. The reaction was quenched with iced brine, and extracted with EtOAc. The organic phase was washed with aqueous NH_4Cl and brine, dried over anhydrous magnesium sulfate, filtered and solvent evaporated to give B8 (R^6 = p-F-Phenyl, R^7 = carboethoxyl, R^10 = 3-MeO-Phenyl, R^9 = 4-(4-Methyl-imidazol-1-yl)) after purification. Compound B8 (R^6 = p-F-Phenyl and R^7 = carboethoxyl, R^10 = 3-MeO-Phenyl, R^9 = 4-(4-Methyl-imidazol-1-yl)) was resolved by chiral AS column and eluted with Hexanes/ Isopropanol with 0.1% DEA to give 930 mg of enantiomer A of B9 (R^6 = p-F-Phenyl, R^7 = carboethoxyl and R^10 = 3-MeO-Phenyl, R^9 = 4-(4-Methyl-imidazol-1-yl)) and 849 mg of enantiomer B of B10(R^6 = p-F-
Phenyl and $R^7 = \text{carboethoxyl}, \ R^{10} = \text{3-MeO-Phenyl}, \ R^9 = \text{4-(4-Methyl-imidazol-1-yl)}$).

$^1$H NMR (CDCl$_3$, ppm) of the enantiomer A of B9 ($R^6 = \text{p-F-Phenyl}$ and $R^7 = \text{carboethoxyl}, \ R^{10} = \text{3-MeO-Phenyl}, \ R^9 = \text{4-(4-Methyl-imidazol-1-yl)}$): $\delta$ 7.68 (s, 1H), 7.51-7.46 (m, 3H), 7.22-7.20 (d, 1H), 7.11-7.07 (t, 2H), 6.98-6.90 (m, 3H), 4.36-4.28 (m, 2H), 3.81 (s, 3H), 3.58-3.52 (m, 1H), 2.88-2.82 (m, 1H), 2.74-2.65 (m, 2H), 2.26 (s, 3H), 1.97-1.95 (m, 1H), 1.75-1.68 (m, 1H), 1.33-1.29 (t, 3H). MS (ES-LCMS, M+1) 491.

Alternatively, B3 can be made by the following procedure:

$$ \begin{align*}
A6 & \quad B1 & \quad B3 \\
O^R^6 & \quad + & \quad \text{Br} & \quad \text{NH}_2\text{HBr} & \quad \text{TiCl}_4 / \text{Et}_3\text{N} & \quad \text{Br} & \quad \text{N} & \quad ^R^6 \\
& & & & & & & R^7
\end{align*} $$

Triethylamine (40 mL, 8eq) was added slowly to a solution of A6 ($R^6 = \text{Me}$ and $R^7 = \text{p-F-phenyl}$; 5g, 1eq) and B1 (10.3g, 1.3eq) in 35 mL anh. DMF and 10 mL DCM while vigorously stirring under nitrogen. A solution of TiCl$_4$ (3.6mL, 0.9eq) in 29 mL DCM was added dropwise at 0°C. The reaction suspension was vigorously stirred at rt. overnight. The reaction mixture was mixed with ether, filtered and the filtrate was washed with ice cold brine 4 times and dried over anhydrous Na$_2$SO$_4$ to give 6.8g of B3 ($R^6 = \text{Me}$ and $R^7 = \text{p-F-phenyl}$).

The compounds in Table 4 were prepared using procedures similar to those of Method B. In Table 4 "#" means compound number. Also, in Table 4, "E" means enantiomer.
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**Method C**

Solid sodium borohydride (57.3 mg) was added to a stirred solution of B9 (400 mg; $R^6 = \text{p-F-Phenyl}$ and $R^7 = \text{carboethoxyl}$, $R^{10} = 3\text{-MeO-Phenyl}$, $R^9 = 4\text{-}(4\text{-Methyl-imidazol-1-yl})$) in 9 mL of MeOH: EtOH (1:2) at 0°C under nitrogen atmosphere. The reaction mixture was stirred at 0°C for 1 hr and then at r.t. for 1 hr, quenched with iced brine, and extracted with EtOAc. The organic phase was dried over anhydrous sodium sulfate and evaporated. Residue was purified via a reverse-phase column with MeCN/ Water with 0.1 % formic acid to give C1 ($R^6 = \text{p-F-Phenyl}$, $R^{10} = 3\text{-MeO-Phenyl}$, $R^9 = 4\text{-}(4\text{-Methyl-imidazol-1-yl})$).

$^1$H NMR (CDCl$_3$, ppm) of the enantiomer A of C1 ($R^6 = \text{p-F-Phenyl}$, $R^{10} = 3\text{-MeO-Phenyl}$, $R^9 = 4\text{-}(4\text{-Methyl-imidazol-1-yl})$): $\delta$ 7.22 (s, 1H), 7.50-7.44 (m, 3H), 7.24-7.22 (d, 1H), 7.1 1-7.07 (t, 2H), 6.98-6.91 (m, 3H), 4.21-4.18 (dd, 2H), 3.85 (s, 3H), 3.36-3.30 (m, 1H), 3.00-2.93 (m, 1H), 2.71-2.70 (m, 2H), 2.28 (s, 3H), 1.99-1.82 (m, 2H). MS (ES-LCMS, M+1) 449.

The compounds in Table 5 were synthesized using methods similar to those in Method C. In Table 5 "#" means compound number. Also, in Table 5, "E" means enantiomer.
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Method D

Sodium hydride (2 mg, 60% in mineral oil) and R\textsubscript{16}-l (16.6 mg, R\textsubscript{16} = Me) was added to a stirred solution of the racemate of C\textsubscript{1} (7.5 mg, R\textsubscript{6} = p-F-Phenyl, R\textsubscript{10} = 3-MeO-Phenyl, R\textsubscript{9} = 4-(4-Methyl-imidazol-1-yl)) in 0.2 ml of anhydrous DMF at r.t. under nitrogen atmosphere. The reaction mixture was stirred at r.t. for 15 min, quenched with iced brine, and extracted with EtOAc. The organic phase was dried over anhydrous sodium sulfate and evaporated. Residue was purified via a reverse-phase column with MeCN/ Water with 0.1 % formic acid to give the racemate of D\textsubscript{1} (R\textsubscript{6} = p-F-Phenyl, R\textsubscript{10} = 3-MeO-Phenyl, R\textsubscript{9} = 4-(4-Methyl-imidazol-1-yl) and R\textsubscript{16} = Me).

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, ppm) of the racemate of D\textsubscript{1} (R\textsubscript{6} = p-F-Phenyl, R\textsubscript{10} = 3-MeO-Phenyl, R\textsubscript{9} = 4-(4-Methyl-imidazol-1-yl), R\textsubscript{16} = Me): \( \delta \) 7.97 (s, 1H), 7.55-7.50 (m, 2H), 7.47 (s, 1H), 7.24-7.19 (d, 1H), 7.10-7.01 (t, 2H), 6.99-6.92 (m, 3H), 4.08-3.88 (dd, 2H), 3.84 (s, 3H), 3.50 (s, 3H), 3.31-3.25 (m, 1H), 2.98-2.93 (m, 1H), 2.80-2.50 (m, 2H), 2.32 (s, 3H), 1.93-1.78 (m, 2H). MS (ES-LCMS, M+1) 463.

The compounds in Table 6 were prepared using methods similar to those in Method D. In Table 6 "#" means compound number. Also, in Table 6, "E" means enantiomer.
Table 6

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A solution of lithium hydroxide monohydride (2.8 mg) in 0.05 ml of water was added to a stirred solution the racemate of B8 \((R^6 = p\text{-F-Phenyl, } R^{10} = 3\text{-MeO-Phenyl, } R^9 = 4\text{-}(4\text{-Methyl-imidazol-1-yl})\text{, } 16.5 \text{ mg})\) in 0.05 ml of MeOH. The reaction mixture was stirred at r.t. for 45 min, quenched with iced brine, and extracted with EtOAc. The organic phase was dried over anhydrous magnesium sulfate and evaporated. Residue was purified via a reverse-phase column with MeCN/ Water with 0.1% TFA to give the racemate of E1 \((R^6 = p\text{-F-Phenyl, } R^{10} = 3\text{-MeO-Phenyl, } R^9 = 4\text{-}(4\text{-Methyl-imidazol-1-yl})\text{).}

\(^1\text{H NMR (CD}_3\text{OD, ppm) of E1 (R}^6 = p\text{-F-Phenyl, } R^{10} = 3\text{-MeO-Phenyl, } R^9 = 4\text{-}(4\text{-Methyl-imidazol-1-yl}): }\delta 9.15 \text{ (s, 1H), 7.58-7.53 (m, 4H), 7.45 (s, 1H), 7.28 (s, 1H),} 7.24-7.17 \text{ (m, 3H), 3.93 (s, 3H), 3.59-3.53 (m, 1H), 2.92-2.87 (m, 1H), 2.78-2.72 (m, 2H), 2.41 (s, 3H), 1.97-1.92 (br, 1H), 1.80-1.73 (m, 1H). MS (ES-LCMS, M+1) 463.}

The compounds in Table 7 were prepared using methods similar to those of Method E. In Table 7 "#" means compound number.
A solution of methyl magnesium bromide (0.14 ml, 3 M in ether) was added dropwise to a stirred solution the enantiomer A of B8 (R^6 = p-F-Phenyl, R^{10} = 3-MeO-Phenyl, R^9 = 4-(4-Methyl-imidazol-1-yl), 50 mg) in 1 mL of THF at -50°C under nitrogen atmosphere. The reaction mixture was stirred between -50°C and 10°C until the SM was consumed. The reaction was quenched with iced aqueous NH_4Cl, stirred for 30 min, and then extracted with EtOAc. The organic phase was
dried over anhydrous magnesium sulfate, filtered and solvent evaporated. The residue was purified via a reverse-phase column with MeCN/ Water with 0.1% formic acid to give the enantiomer A of F1(R^6 = p-F-Phenyl, R^{10} = 3-MeO-Phenyl, R^9 = 4-(4-Methyl-imidazol-1-yl) and R^{21} = R^{21} = Me).

\[ \delta 7.86-7.82 \ (m, 2H), \ 7.72 \ (br, 1H), \ 7.42 \ (s, 1H), \ 7.23-7.20 \ (d, 1H), \ 7.10-7.04 \ (t, 2H), \ 6.98-6.93 \ (m, 3H), \ 3.81 \ (s, 3H), \ 3.75-3.70 \ (m, 1H), \ 3.08-3.02 \ (m, 1H), \ 2.85-2.81 \ (m, 1H), \ 2.42-2.33 \ (m, 1H), \ 2.28 \ (s, 3H), \ 1.88-1.80 \ (m, 2H), \ 1.48 \ (s, 3H), \ 1.18 \ (s, 3H). \]

MS (ES-LCMS, M+1 ) 477.

The compounds in Table 8 were prepared using methods similar to those of Method F. In Table 8 "#" means compound number. Also, in Table 8, "E" means enantiomer.
Table 8

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Method G

A solution of methyl magnesium bromide (0.3 ml, 3 M in ether) and TEA (0.4 ml) in 0.7 ml of THF was added dropwise to a stirred solution of the enantiomer A of B9 (250 mg, R⁶ = p-F-Phenyl, R¹⁰ = 3-MeO-Phenyl, R⁹ = 4-(4-Methyl-imidazol-1-yl)) in 1.5 ml of THF at -50°C under nitrogen atmosphere. The reaction mixture was stirred between -50°C and 15°C until SM was consumed, quenched with iced aqueous NH₄Cl, stirred for 30 min, and then extracted with EtOAc. The organic phase was dried over anhydrous magnesium sulfate and evaporated. Residue was purified via a reversed-phase column with MeCN/Water with 0.1% formic acid to give 80 mg of G1 (R⁶ = p-F-Phenyl, R¹⁰ = 3-MeO-Phenyl, R⁹ = 4-(4-Methyl-imidazol-1-yl) and R²¹ = Me).

¹H NMR (CDCl₃, ppm) of the enantiomer A of G1 (R⁶ = p-F-Phenyl, R¹⁰ = 3-MeO-Phenyl, R⁹ = 4-(4-Methyl-imidazol-1-yl) and R²¹ = Me): δ 7.07 (s, 1H), 7.47-7.34 (m, 3H), 7.21-7.19 (d, 1H), 7.14-7.08 (t, 2H), 6.96-6.88 (m, 3H), 3.80 (s, 3H), 3.58-3.53 (m, 1H), 2.81-2.77 (m, 1H), 2.71-2.58 (m, 2H), 2.25 (m, 6H), 1.92-1.85 (m, 1H), 1.72-1.65 (m, 1H). MS (ES-LCMS, M+1) 461.

The compounds in Table 9 were prepared using methods similar to those of Method G. In Table 9 "#" means compound number. Also, in Table 9, "E" means enantiomer.
# Table 9

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Method H

![Chemical structures](image4)
A suspension of sodium borohydride (6.6 mg) in 0.5mL of EtOH was added slowly to a stirred solution of G1 (R6 = p-F-Phenyl, R10 = 3-MeO-Phenyl, R9 = 4-(4-Methyl-imidazol-1-yl) and R21 = Me; 80 mg) in 4.8 mL of MeOH: EtOH (1:2) at 0°C. The reaction mixture was stirred at 0°C for 1 h before quenched with iced brine and extracted with EtOAc. The organic phase was dried over anhydrous magnesium sulfate, filtered and solvent evaporated. Residue was purified via a reverse-phase column with MeCN/ Water with 0.1% formic acid to give 32 mg of diasteromer 1 of product H1 (R6 = p-F-Phenyl, R10 = 3-MeO-Phenyl, R9 = 4-(4-Methyl-imidazol-1-yl) and R21 = Me) and 24.6 mg of diestriomer 2 of product H1 (R6 = p-F-Phenyl, R10 = 3-MeO-Phenyl, R9 = 4-(4-Methyl-imidazol-1-yl) and R21 = Me).

1H NMR (CDCl3, ppm) of diasteromer 1 of product H1 (R6 = p-F-Phenyl, R10 = 3-MeO-Phenyl, R9 = 4-(4-Methyl-imidazol-1-yl) and R21 = Me): δ 8.03 (s, 1H), 7.63-7.59 (m, 2H), 7.44 (s, 1H), 7.24-7.22 (d, 1H), 7.10-7.06 (t, 2H), 6.98-6.92 (m, 3H), 4.58-4.53 (m, 1H), 3.83 (s, 3H), 3.27-3.22 (m, 1H), 2.88-2.83 (m, 1H), 2.75-2.71 (m, 1H), 2.54-2.48 (m, 1H), 2.31 (s, 3H), 1.8-1.80 (m, 2H), 1.37-1.36 (d, 3H). MS (ES-LCMS, M+1) 463.

1H NMR (CDCl3, ppm) of diestriomer 2 of product H1 (R6 = p-F-Phenyl, R10 = 3-MeO-Phenyl, R9 = 4-(4-Methyl-imidazol-1-yl), and R21 = Me): δ 7.94 (s, 1H), 7.50-7.42 (m, 2H), 7.41 (s, 1H), 7.23-7.21 (d, 1H), 7.1 1-7.07 (t, 2H), 6.98-6.91 (m, 3H), 4.53-4.48 (m, 1H), 3.82 (s, 3H), 3.42-3.37 (m, 1H), 2.99-2.94 (m, 1H), 2.77-2.71 (m, 1H), 2.53-2.48 (m, 1H), 2.30 (s, 3H), 1.99-1.80 (m, 2H), 1.15-1.13 (d, 3H). MS (ES-LCMS, M+1) 463.

The compounds in Table 10 were prepared using methods similar to those of Method H. In Table 10 "#" means compound number. Also, in Table 10, "S" means stereoisomer.
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Method I

11 \rightarrow 12

TBAF
Method I, Step 1

Compound 11 (prepared using method similar to B1 to B5, 0.90g, 1.7mmole) was dissolved in 50ml THF and tetrabutylammonium fluoride (1 M in THF, 3.4ml) was added. The reaction was stirred at room temperature for 1h before 100ml EtOAc and 100ml brine were added. The organic layer was washed with brine (2x100ml), dried with Na2SO4, filtered and solvent evaporated. The residue was purified by column (EtOAc/MeOH from 100/0 to 90/10 in 45 minutes, 80g silica) to give I2. Yield, 0.49g, 69%. 1H NMR (CDCl3, ppm): δ 7.23 (dd, 1H), 6.96 (m, 1H),
6.80 (dd, 1H), 4.14-4.40 (m, 6H), 3.60 (m, 1H), 3.48 (m, 1H), 3.38 (m, 2H), 2.94-3.15 (m, 4H), 2.40 (m, 1H), 2.21 (m, 1H), 1.40 (m, 6H).

**Method I, Step 2**

Compound \( \text{I2} \) (0.49g, 1.18mmole) was dissolved in 50ml DCM followed by addition of Mesyl chloride (0.2g) and triethylamine (0.18g). The reaction was stirred at room temperature for 10 minutes before 50ml DCM was added and the organic layer was washed with brine (2x100ml), dried with \( \text{Na}_2\text{SO}_4 \), filtered and solvent evaporated. The residue was dissolved in 50ml AcCN followed by addition of \( \text{LiI} \) (0.31g) and \( \text{CaCO}_3 \) (0.24g). The reaction was stirred at 80°C for 1 hour before 70ml EtOAc was added and the organic layer was washed with brine (2x100ml), dried with \( \text{Na}_2\text{SO}_4 \), filtered and solvent evaporated. The residue was purified by column (EtOAc/hexane from 50/50 to 100/0 in 35 minutes, 12+4Og silica) to give compound \( \text{I3} \). Yield: 0.4g, 64%. \(^1\)H NMR (CDCl\(_3\), ppm): \( \delta \) 7.23 (dd, 1H), 6.96 (m, 1H), 6.80 (dd, 1H), 4.18-4.38 (m, 6H), 3.38 (m, 1H), 3.19 (m, 1H), 2.90-3.10 (m, 4H), 2.34 (m, 1H), 2.22 (m, 1H), 1.87 (m, 2H), 1.39 (m, 6H).

**Method I, Step 3**

Compound \( \text{I3} \) (0.4g, 0.78mmole) was dissolved in 50ml THF and the reaction was cooled to -78°C before Sodium hydride (60% in oil, 62mg) was added and the reaction was slowly warmed up to -20°C was then stirred at -20°C for 2 hours followed by addition of 100ml water and 100ml EtOAc. The organic layer was washed with brine (2x100ml), dried with \( \text{Na}_2\text{SO}_4 \) and concentrated. The residue was purified by column (EtOAc/MeOH from 100/0 to 90/10 in 25 minutes) to give \( \text{I3} \) as a mixture of two stereoisomers. Total yield: 0.2g, 64%. \(^1\)H NMR (CDCl\(_3\), ppm) of \( \text{I4} \): 7.32 (dd, 0.7H), 7.10 (dd, 0.3H), 6.96 (m, 1H), 6.80 (m, 1H), 4.15-4.40 (m, 6H), 3.07-3.25 (m, 1H), 2.80-3.00 (m, 2H), 1.79-2.50 (m, 6H), 1.38 (m, 6H).
Method I, Step 4

Compound 14 (193 mg, 0.51 mmole) was dissolved in THF and the reaction was cooled to -78°C. Butyllithium (2.5 ml in hexane, 0.22 ml) was added and the reaction was stirred at -78°C for 30 minutes before compound I5 (R₁⁰ = 3-MeO-Phenyl, R₉ = 4-(4-Methylimidazol-1-yl)) (110 mg, 0.51 mmole) in 10 ml THF (pre-cooled to -78°C) was added. The reaction was stirred at -78°C for 1 hour, then at room temperature for one hour before solvent was removed and the residue partitioned between 100 ml EtOAc and 100 ml water. The organic layer was washed with water (2×100 ml), dried with Na₂SO₄ and concentrated. The residue was dissolved in 30 ml THF was treated with 50 mg NaBH₄ to reduce excess aldehyde to alcohol. The product was purified by column (DCI/WMeOH from 100/0 to 90/10 in 25 minutes) to give compound I6 (R₁⁰ = 3-MeO-Phenyl, R₉ = 4-(4-Methylimidazol-1-yl)) as an 86:14/E:Z mixture. Yield: 102 mg, 44%. The pure E isomer was obtained using chiral AS column separation. ¹H NMR (CDCl₃, ppm):

δ 7.76 (s, 1H), 7.55 (s, 1H), 7.27 (d, 1H), 7.22 (dd, 1H), 6.93-7.06 (m, 4H), 6.84 (dd, 1H), 4.37 (m, 2H), 3.87 (s, 3H), 2.90-3.10 (m, 3H), 2.58 (m, 1H), 2.26-2.32 (m, 5H), 1.98 (m, 1H), 1.86 (m, 1H).

Two enantiomers of this compound can be separated using Chiral OD column using IPA/hexane (75/25) as the solvent.

The compounds in Table 11 were synthesized using methods similar to those of Method I. In Table 11 "#" means compound number. Also, in Table 11, "E" means enantiomer.
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Method J

Step 1

NBS (421 mg, 2.4 mmol) was added to a solution of J1 (R6 = Me, R7 = p-F-Phenyl, R21 = Me, obtained using method similar to that led to I2, 889 mg, 2.2 mmol) in CCl4 (12 ml), and the reaction solution was stirred at room temperature for one hour. A catalytic amount of benzoyl peroxide (52 mg, 0.22 mmol) was added and the reaction solution was stirred at 60°C for 12 hours. The reaction solution was clarified by filtration and the filtrate was concentrated under reduced pressure. The residue was diluted with ethyl acetate, and washed with saturated solution of sodium thiosulfate, and brine. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain 1.0 g of product J2 (R6 = Me, R7 = p-F-Phenyl, R21 = Me) as a 1:1 mixture, which was used as is in the next reaction.

Step 2

To a solution of J2 (R6 = Me, R7 = p-F-Phenyl, R21 = Me, 1.0 g, 2.1 mmol) and A1 (R10 = 3-MeO-Phenyl, R9 = 4-(4-Methylimidazol-1-yl) and R8 = H, 427 mg, 1.98 mmol) [US 2007/0219181, page 62] in THF (40 ml) at room temperature
was added sodium hydride (238 mg, 5.94 mmol) all at once, and the reaction solution was stirred at room temperature for 12 hours. The reaction solution was quenched with water, and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was dissolved in DMF (10 mL) and treated with sodium hydride (476 mg, 11.9 mmol). The reaction solution was stirred at room temperature for one hour before it was quenched with water. The layers were separated and the organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography using Silica Gel (hexane:triethylamine = 99:1) to obtain products J3 (R\(^6\) = Me, R\(^7\) = p-F-Phenyl, R\(^{21}\) = R\(^{21}\) = Me, R\(^{10}\) = 3-MeO-Phenyl, R\(^9\) = 4-(4-Methylimidazol-1-yl)), J4 (R\(^6\) = Me, R\(^7\) = p-F-Phenyl, R\(^{21}\) = R\(^{21}\) = Me, R\(^{10}\) = 3-MeO-Phenyl, R\(^9\) = 4-(4-Methylimidazol-1-yl)) and J5 (R\(^6\) = Me, R\(^7\) = p-F-Phenyl, R\(^{21}\) = R\(^{21}\) = Me, R\(^{10}\) = 3-MeO-Phenyl, R\(^9\) = 4-(4-Methylimidazol-1-yl)) in a ratio of 2:1:1, respectively.

\(^{1}\)H NMR (CDCl\(_3\), ppm) of J3: \(\delta\) 7.70 (s, 1H), 7.56 (m, 2H), 7.49 (s, 1H), 7.26 (m, 1H), 7.18 (d, 1H, J = 8.0 Hz), 7.09 (m, 2H), 6.92 (s, 1H), 6.55 (s, 1H), 3.84 (s, 3H), 3.13 (d, 1H, J = 11.2 Hz), 2.78 (d, 1H, J = 11.2 Hz), 2.88 (s, 3H), 1.88 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H). MS (ES-LCMS, M+1) 463.3.

\(^{1}\)H NMR (CDCl\(_3\), ppm) of J4: \(\delta\) 7.89 (s, 1H), 7.70 (s, 1H), 7.54 (m, 2H), 7.18 (m, 2H), 7.08 (m, 2H), 6.92 (s, 1H), 6.49 (s, 1H), 3.90 (s, 3H), 3.06 (d, 1H, J = 10.8 Hz), 2.72 (d, 1H, J = 10.4 Hz), 3.90 (s, 3H), 1.86 (s, 3H), 1.40 (s, 3H), 1.30 (s, 3H). MS (ES-LCMS, M+1) 463.3.

\(^{1}\)H NMR (CDCl\(_3\), ppm) J5: \(\delta\) 7.70 (s, 1H), 7.59 - 7.62 (m, 2H), 7.50 (d, 1H, J = 16.8 Hz), 7.22 (d, 1H, J = 8.4 Hz), 7.14 (d, 1H, J = 8.0 Hz), 6.06 - 7.10 (m, 3H), 6.92 (s, 1H), 6.70 (d, 1H, J = 16.0 Hz), 3.86 (s, 3H), 3.01 (s, 2H), 2.29 (s, 3H), 1.93 (s, 3H), 1.62 (br, 1H), 1.17 (s, 3H), 0.96 (s, 3H). MS (ES-LCMS, M+1) 465.3.
The compounds in Table 12 were synthesized using methods similar to those of Method J. In Table 12 "#" means compound number.

**Table 12**

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Method K

K1

K2

K3

K4

K5
Method K, Step 1

A mixture 7-fluoro-1-methylisatin (K1, 3.54 g, 19.8 mmol) and 3-(tert-butyldiphenylsilyloxy)propan-1-amine (6.90 g, 22.0 mmol) in EtOH (50 ml) was heated at 60°C for 2 h then concentrated to provide 9.55 g (100%) of product K2.

Method K, Step 2

To a solution of 3-diethyl 2-(hydroxyimino)ethylphosphonate (3.90 g, 20.0 mmol) in DMF (40 ml) at 0°C was added N-bromosuccinimide (3.55 g, 20.0 mmol in DMF (10 ml)). The reaction was stirred at 0°C for 1 h 30 then a solution of product from Step 1 (9.55 g, 19.8 mmol) and triethylamine (2.80 mL, 20.0 mmol) in DCM (15 mL) was added. The reaction was stirred 1 h 30 at 0°C then worked-up with 1:1 Et2O/AcEt and brine. The residue was purified by chromatography over silica gel (eluted with Hexanes/EtOAc 99:1 to EtOAc) to provide 5.55 g (42%) of product K3.

Method K, Step 3

To a mixture of product K3 (5.55 g, 8.31 mmol) in THF (50 mL) was added TBAF 1N in THF (10.0 mL, 10.0 mmol) and the reaction was stirred at RT overnight. After concentration, the residue was taken up in EtOAc and 0.2 N glacial HCl and brine, extracted with EtOAc, dried and concentrated. The residue
was purified by chromatography over silica gel (eluted with DCM/MeOH 100:0 to 80:20) to give 2.57 g (72%) of product K4.

**Method K, Step 4**

To a solution of product K4 (2.57 g, 6.00 mmol) in DCM (40 mL) at 0°C was added methanesulfonyl chloride (605 μL, 7.78 mmol) followed by triethylamine (1.25 mL, 9.00 mmol) and the reaction was stirred 10 min at RT. The final mixture was diluted with sat. NH4Cl, extracted with DCM, dried and concentrated. The residue was purified by chromatography over silica gel (eluted with EtOAc/MeOH 100:0 to 80:20) to give 2.32 g (76%) of intermediate mesylate. This intermediate was treated with LiI (1.60 g, 12 mmol) and CaCO3 (1.20 g, 12.00 mmol) in acetonitrile (40 mL) and heated 1 h at 80°C then diluted with sat. Na2S2O3 and sat. NaHCO3, extracted with EtOAc, dried and concentrated then purified by chromatography over silica gel (eluted with EtOAc/MeOH 100:0 to 80:20) to provide 1.97 g (80%) of product K5.

**Method K, Step 5**

To a solution of product K5 (1.95 g, 3.60 mmol) in THF (25 mL) at 0°C was added tBuOK 1N in THF (3.80 mL, 3.80 mmol) and the reaction was stirred 15 min. 3-Methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (780 mg, 3.60 mmol) was then added followed, 5 min later, by tBuOK 1N in THF (3.80 mL, 3.80 mmol). The reaction was stirred 1 h at 0°C then poured into half-brine, extracted with EtOAc, dried and concentrated. The residue was purified by chromatography over silica gel (eluted with DCM/MeOH 100:0 to 80:20) to give 1.44 g of product as a Z (K6) and E (K7) racemic mixture.

The mixture (700 mg) was purified by HPLC over Chiracel OD column (eluted with Hexanes/isopropanol 15:85) to provide, in order of elution:

- Compound K(6), (Z) isomer, enantiomer 1, 103 mg: [α]D = -69.1 (c = 1, DCM); 1H NMR (CDCl3 400 MHz) for (-)-K6: δ 7.86 (s, 1H), 7.71 (s, 1H), 7.10-7.30
(m, 4H), 7.06 (m, 1H), 6.93 (s, 1H), 6.75 (s, 1H), 3.89 (s, 3H), 3.40 (s, 3H), 2.98 (m, 1H), 2.85 (m, 1H), 2.60-2.70 (m, 2H), 2.29 (s, 3H), 1.90-2.10 (m, 2H); LCMS (MH⁺) = 474.42; retention time = 3.21 min.

Compound K(7), (E) isomer, enantiomer 1, 216 mg: [α]D = -31.5 (c = 1, DCM); ¹H NMR (CDCl₃ 400 MHz) for (-)-K7: δ 7.71 (s, 1H), 7.56 (s, 1H), 7.25-7.35 (m, 2H), 7.00-7.20 (m, 3H), 6.98 (s, 1H), 6.93 (s, 1H), 3.85 (s, 3H), 3.40 (s, 3H), 2.99 (m, 1H), 2.80-2.90 (m, 2H), 2.72 (m, 1H), 2.29 (s, 3H), 1.85-2.00 (m, 2H); LCMS (MH⁺) = 474.42; retention time = 3.12 min.

Compound K(7), (E) isomer, enantiomer 2 for (K7), 149 mg: [α]D = +39.5 (c = 1, DCM); ¹H NMR identical to (E) isomer, enantiomer 1; LCMS (MH⁺) = 474.42; retention time = 3.09 min.

Compound K(6), (Z) isomer, enantiomer 2 (K6), 85 mg: [α]D = +76.1 (c = 1, DCM); ¹H NMR identical to (Z) isomer, enantiomer 1; LCMS (MH⁺) = 474.42; retention time = 3.09 min.

The compounds in Table 13 were synthesized using Method similar to those of Method K. In Table 13 "#" means compound number. Also, in Table 13, "E" means enantiomer.

### Table 13

<table>
<thead>
<tr>
<th>#</th>
<th>Structure</th>
<th>Ret. Time (min)</th>
<th>Obs. Mass</th>
<th>Enantiomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>158</td>
<td><img src="image" alt="Structure" /></td>
<td>2.9</td>
<td>460</td>
<td>E</td>
</tr>
</tbody>
</table>
Method L
Route 1:

\[
\begin{align*}
\text{L1} & : R^9-R^{10} & \rightarrow & R^9-R^{10} \quad (\text{L2}) \\
\text{L2} & : R^9-R^{10} & \rightarrow & R^9-R^{10} \quad (\text{L3}) \\
\text{L4} & : \text{NH}_2 & + & \text{OR}^6 \quad (\text{L5}) \\
\text{L5} & : \quad \rightarrow & \text{R}^2 \quad (\text{L6}) \\
\end{align*}
\]

\text{L7}
If one were to follow a procedure similar to that of Method A, one would prepare compounds L7 and L10.

If one were to follow Route 2, one would convert L10 to L7.

If one were to treat L10 (1 equiv) with Dess-Martin periodinane reagent (1.2 equiv) in DCM at room temperature, one would obtain L11 after aqueous work up and chromatography.

If one were to add n-BuLi to a THF solution of CBr₄ at -78°C, and after 30 minutes add a THF solution of L11 drop wise, and warm up the reaction mixture to room temperature, and follow by aqueous work up, one would obtain L12. If one were to treat L12 with 1 equiv of n-BuLi then one would obtain L13 after aqueous work up and purification.

If one were to treat L13 with bromide L14 in toluene in the presence of triethylamine, Pd(PPPh₃)₄ and CuI, one would obtain L7 after aqueous work up and chromatograph.
Method M

NaH (0.09g) was added slowly to a stirred solution of M1 (obtained using method similar to Method B leading to B5, 1.07 g) and succinimide (1 eq.) in 50 ml of anhydrous THF at -20°C under nitrogen atmosphere. The reaction mixture was stirred between -20°C and 0°C for 1h, then 50°C for 24h. It was then cooled to 0°C before NaH (0.09g) and aldehyde M3 (0.39g in 10mL of anhydrous THF) was added to the mixture. After stirring at 0°C for 0.5h, and r.t. for 24h, the reaction was quenched with iced water, and extracted with EtOAc. The organic phase was washed with NH₄Cl and brine, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by a flash silica gel column and eluted with MeOH/DCM to give 0.14 g of 162.
Method N:

If one were to react Compound N1 (wherein N1 is 5-(4-methyl-1H-imidazol-1-yl)-2,3-dihydro-1H-inden-1-one, i.e., R^9 is 4-(4-methylimidazol-1-yl), and R^{10} and R^8, taken together with the atoms to which they are bound, form an indanone ring, see, for example, CA: 125460-31-3) with compound A2, following procedures similar to Method A step 1 and step 2, one would obtain compounds N2 and N3 (wherein R^1 is H). If one were to react N3 with compound A7 (wherein R^2 is 3-MeO-propyl, R^6 is Me, and R^7 is p-F-phenyl), following a procedure similar to Method A step 4, one would obtain compound N4 (i.e. (E)-5-(4-fluorophenyl)-4-(3-methoxypropyl)-5-methyl-3-((5-(4-methyl-1H-imidazol-1-yl)-2,3-dihydro-1H-inden-1-ylidene)methyl)-4,5-dihydro-1,2,4-oxadiazole, identified as compound 163 below).
If one were to react compound B7 (wherein R6 is p-F-Phenyl and R7 is carboethoxyl) with compound N1 (wherein N1 is 5-(4-methyl-1H-imidazol-1-yl)-2,3-dihydro-1H-inden-1-one, i.e., R9 is 4-(4-Methylimidazol-1-yl), and R10 and R8, together with the atoms to which they are bound, form an indanone ring, see, for example, CA:125460-31-3), following a procedure similar to Method B step 6, one would obtain compound O1 (i.e., (E)-ethyl 3-(4-fluorophenyl)-8-(5-(4-methyl-1H-imidazol-1-yl)-2,3-dihydro-1H-inden-1-ylidene)-5,6,7,8-tetrahydro-3H-[1,2,4]oxadiazolo[4,3-a]pyridine-3-carboxylate, identified as compound 164 below).

Compounds 165, 166, and 167:
were prepared using procedures similar to those of Method A. Thus, another embodiment of this invention is directed to compounds of formula I selected from the group consisting of compounds 165, 166 and 167. Another embodiment of this invention is directed to compounds of formula I selected from the group consisting of compounds 1 to 167. Another embodiment is directed to compound 165. Another embodiment is directed to compound 166. Another embodiment is directed to compound 167.

**Assay:**

Secretase Reaction and Aβ Analysis in Whole Cells: HEK293 cells overexpressing APP with Swedish and London mutations were treated with the specified compounds for 5 hour at 37 °C in 100 ml of DMEM medium containing 10% fetal bovine serum. At the end of the incubation, total Aβ, Aβ40 and Aβ42 were measured using electrochemiluminescence (ECL) based sandwich immunoassays. Total Aβ was determined using a pair of antibodies TAG-W02 and biotin-4G8, Aβ40 was identified with antibody pairs TAG-G2-10 and biotin-4G8,
while A\(\beta\)42 was identified with TAG-G2-11 and biotin-4G8. The ECL signal was measured using Sector Imager 2400 (Meso Scale Discovery).

MS Analysis of A\(\beta\) Profile: A\(\beta\) profile in conditioned media was determined using surface enhanced laser desorption/ionization (SELDI) mass spectrometry. Conditioned media was incubated with antibody W02 coated PS20 ProteinChip array. Mass spectra of A\(\beta\) captured on the array were read on SELDI ProteinChip Reader (Bio-Rad) according to manufacture’s instructions.

CSF A\(\beta\) Analysis: A\(\beta\) in rat CSF was determined using MSD technology as described above. A\(\beta\)40 was measured using antibody pair Tag-G2-10 and biotin-4G8, while A\(\beta\)42 was measured using Tag-anti A\(\beta\)42 (Meso Scale Discovery) and biotin-4G8. The ECL signal was measured using Sector Imager 2400 (Meso Scale Discovery).

MS analysis of A\(\beta\) profile: To isolate A\(\beta\) products from conditioned media, cells expressing APP were grown to 90% confluence and re-fed with fresh media containing \(\gamma\)-secretase modulator. The conditioned media, harvested after 16 h of incubation, were incubated overnight with antibody W02 in RIPA buffer (20 mM Tris-HCl, pH7.4, 150 mM NaCl, 0.2% Twenn 20, 0.2% Triton 100 and 0.2% NP40). Protein A plus G agarose (Calbiochem) was added to the reaction and the mixture was rocked at room temperature for another 2 h. The agarose beads were then collected by centrifugation and washed 3 times with RIPA buffer and twice with 20 mM Tris (pH 7.4). The immunoprecipitated peptides were eluted from the beads with 10 \(\mu\)L of 10% acetonitrile/ 0.1 % trifluoroacetic acid (TFA). Matrix-assisted laser desorption/ionization mass spectrometry (MALDI MS) analysis of A\(\beta\) was performed on a Voyager-DE STR mass spectrometer (ABI, Framingham, MA). The instrument is equipped with a pulsed nitrogen laser (337 nm). Mass spectra were acquired in the linear mode with an acceleration voltage of 20 kV. Each spectrum presented in this work represents an average of 256 laser shots. To prepare the sample-matrix solution, 1 \(\mu\)L of immunoprecipitated A\(\beta\) sample was mixed with 3 \(\mu\)L of saturated \(\alpha\)-cyano-4-hydroxycinnamic acid
solution in 0.1 % TFA/acetonitrile. The sample-matrix solution was then applied to the sample plate and dried at ambient temperature prior to mass spectrometric analysis. All the spectra were externally calibrated with a mixture of bovine insulin and ACTH (18-39 clip).

Compounds 1 to 162 had an Ab42 IC50 from about 10 nM to 21.5 uM.

The compounds in Table 14 had an Ab42 IC50 from about 10 nM to 100 uM and an Abtotal/Ab42 IC50 ratio from about 5 to 1000.

**Table 14**

![Chemical structures](image-url)
While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.
WHAT IS CLAIMED IS:

1. A compound, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:

```
\[
\begin{array}{c}
\text{Formula I}
\end{array}
\]
```

wherein:

- $U$ is $\text{\_CR}^5$ or $N$;
- $G$ is $O$ or $S$;
- $V$ is selected from the group consisting of a bond, $O$, $\text{-C(O)}$, and $N(R^{14})$;
- $R^1$ is selected from the group consisting of $H$, halo, alkyl-, alkenyl-, alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl-, wherein each of said alkyl-, alkenyl- and alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl-can be unsubstituted or optionally independently substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below;
- $R^2$ is selected from the group consisting of $H$, alkyl-, alkenyl-, alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl-, wherein each of said alkyl-, alkenyl- and alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl-can be unsubstituted or optionally independently substituted with 1-5 substituents which can be the same
or different, each substituent being independently selected from the group consisting of the moieties shown below;

or, alternatively, \( R^1 \) and \( R^2 \) may be joined together to form a C5-C8 cycloalkyl or a 5-8 membered heterocyclyl moiety, with each of said cycloalkyl or heterocyclyl moiety being unsubstituted or optionally independently being substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below;

or, alternatively, \( R^1 \) and \( R^8 \) are taken together to form a bond;

\( R^5, R^6 \) and \( R^7 \) can be the same or different, each being independently selected from the group consisting of H, -C(O)R \(^{15} \), -C(O)OR \(^{15} \), -C(O)N(R \(^{15} \))(R \(^{16} \)), -C(=NOR \(^{15} \))R \(^{16} \), alkyl-, alkenyl-, alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroaryalkyl-, heteroarylalkyl- and heterocyclylalkyl-, wherein each of said alkyl-, alkenyl- and alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroaryalkyl-, heteroarylalkyl- and heterocyclylalkyl- can be unsubstituted or optionally independently substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below;

or alternately, \( R^6 \) and \( R^7 \) can be joined together to form a carbocyclic spirocyclic moiety or a heterocyclic spirocyclic moiety wherein each of said carbocyclic spirocyclic moiety and heterocyclic spirocyclic moiety can be: (i) unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below, or (ii) fused with an aryl, heteroaryl, cycloalkyl or heterocycloalkyl ring, wherein each of said carbocyclic spirocyclic moiety, heterocyclic spirocyclic moiety, aryl, heteroaryl, cycloalkyl and heterocycloalkyl ring can be unsubstituted or optionally independently substituted with 1-4 substituents which can be the
same or different, each substituent being independently selected from the group consisting of the moieties shown below;

R\(^8\) is selected from the group consisting of H, halo, -CN, -OR\(^{15}\), -C(O)R\(^{15}\), -C(O)OR\(^{15}\), -C(O)N(R\(^{15}\))(R\(^{16}\)), -SR\(^{15}\), -S(O)N(R\(^{15}\))(R\(^{16}\)), -CH(R\(^{15}\))(R\(^{16}\)),

-alkyl-N(R\(^{15}\))(R\(^{16}\)), -N(R\(^{15}\))C(O)R\(^{16}\), -CH\(_2\)-N(R\(^{15}\))C(O)R\(^{16}\),

-alkyl-N(R\(^{15}\))C(O)N(R\(^{16}\))(R\(^{17}\)), -alkyl-N(R\(^{15}\))C(O)N(R\(^{16}\)), -alkyl-N(R\(^{15}\))C(O)N(R\(^{16}\))(R\(^{17}\)),

alcyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl-, with each of said alkyl-, alkenyl-, alkynyl-, aryl-, alyralkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl- being unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below;

R\(^{10}\) is selected from the group consisting of a bond, alkyl-, aryl-, alyralkyl-, arylalkenyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl-, heterocyclyalkyl- and the moieties:

![Diagrams of chemical structures]
where \( X \) is O, N(R\(^{14}\)) or S;

wherein each of said alkyl-, aryl-, arylalkyl-, arylalkenyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and the above-noted moieties for R\(^{10}\) can be unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each being independently selected from the group consisting of the moieties shown below;

or, alternatively, R\(^{8}\) and R\(^{10}\), together with the carbon atom to which they are bound, can form a C\(_{4}\)-C\(_{7}\) carbocyclic (e.g., cycloalkyl) ring, or a 4-7 membered heterocyclyl ring, or a C\(_{4}\)-C\(_{7}\) carbocyclyl (e.g., cycloalkenyl) ring, or a 4-7 membered heterocyclenyl ring; and wherein said carbocyclic ring, heterocyclyl ring, carbocyclyl ring, or heterocyclenyl ring is optionally substituted with 1-5 independently selected R\(^{21}\) substituents;

R\(^{8}\) is selected from the group consisting of alkyl-, alkenyl-, alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclenyl-, wherein each of said alkyl-, alkenyl- and alkynyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl- and heterocyclenylalkyl-can be unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of the moieties shown below;

R\(^{14}\) is selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocyclyl, heterocyclenylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -CN, -C(O)R\(^{15}\), -C(O)OR\(^{15}\), -C(O)N(R\(^{15}\))(R\(^{16}\)), -S(O)N(R\(^{15}\))(R\(^{16}\)), -S(O)\(_{2}\)N(R\(^{15}\))(R\(^{16}\)), -C(=NOR\(^{15}\))R\(^{16}\), and -P(O)(OR\(^{15}\))(OR\(^{16}\)), and wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocyclyl, heterocyclenylalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups is optionally substituted with 1-5 substituents independently selected from the group consisting of the moieties shown below;
R_{15}, R_{16} and R_{17} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, arylheterocyclyl, R^{18}-alkyl, R^{18}-cycloalkyl, R^{18}-cycloalkylalkyl, R^{18}-heterocyclyl, R^{18}-heterocyclylalkyl, R^{18}-aryl, R^{18}-arylalkyl, R^{18}-heteroaryl and R^{18}-heteroarylalkyl;

R^{18} is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, -NO_{2}, halo, heteroaryl, -CF_{3}, -CN, -C(O)R^{19}, -C(O)OH, -C(O)OR^{19}, -C(O)NHR^{20}, -C(O)NH_{2}, -C(O)NH_{2}-C(O)N(alkyl)_{2}, -C(O)N(alkyl)(aryl), -C(O)N(alkyl)(heteroaryl), -SR^{19}, -S(O)_{2}R^{20}, -S(O)NH_{2}, -S(O)NH(alkyl), -S(O)N(alkyl)(alkyl), -S(O)NH(aryl), -S(O)_{2}NH_{2}, -S(O)_{2}NHR^{19}, -S(O)_{2}N(heterocyclyl), -S(O)_{2}N(alkyl)_{2}, -S(O)_{2}N(alkyl)(aryl), -S(O)_{2}N(aryl), -OCF_{3}, -OH, -OR^{20}, -O-heterocyclyl, -O-cycloalkylalkyl, -O-heterocyclylalkyl, -NH_{2}, -NHR^{20}, -N(alkyl)_{2}, -N(arylalkyl)_{2}, -N(arylalkyl)-(heteroarylalkyl), -NHHC(O)R^{20}, -NHHC(O)NH_{2}, -NHHC(O)NH(alkyl), -NHC(O)N(alkyl)(alkyl), -N(alkyl)C(O)NH(alkyl), -N(alkyl)C(O)N(alkyl)(alkyl), -NHC(S)_{2}R^{20}, -NHS(O)_{2}NH(alkyl), -NHS(O)_{2}N(alkyl)(alkyl), -N(alkyl)S(O)_{2}NH(alkyl) and -N(alkyl)S(O)_{2}N(alkyl)(alkyl);

or, alternately, two R^{18} moieties on adjacent carbons can be linked together to form:

\[
\begin{align*}
\text{or} & \\
\text{or} & \\
\end{align*}
\]

R^{19} is alkyl, cycloalkyl, aryl, arylalkyl or heteroarylalkyl;

R^{20} is alkyl, cycloalkyl, aryl, halo substituted aryl, arylalkyl, heteroaryl or heteroarylalkyl;

wherein each of the carbocyclic spirocyclic, heterocyclic spirocyclic, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^{1}, R^{2}, R^{5}, R^{6}, R^{7}, R^{8}, R^{9}, R^{10} and R^{14} are independently unsubstituted or substituted by 1 to 5 R^{21} groups independently selected from the group consisting of alkyl, alkenyl, alkynyl,
compounds, or pharmaceutically acceptable salts, solvates, esters or prodrugs of said compound, said compound having the general structure shown in the formula:
wherein:

\( U \) is C or N-;

\( R^1 \) is selected from the group consisting of: H, halo, alkyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl-, wherein each of said alkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, -CN, -NH\(_2\), -NH(alkyl), -N(alkyl)\(_2\), hydroxy and alkoxy groups;

\( R^2 \) is selected from the group consisting of: H, alkyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl-, wherein each of said alkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, -CN, -NH\(_2\), -NH(alkyl), -N(alkyl)\(_2\), hydroxy and alkoxy groups;

or, alternatively, \( R^1 \) and \( R^2 \) may be joined together to form a C5-C8 cycloalkyl or a 5-8 membered heterocyclyl moiety, with each of said cycloalkyl or heterocyclyl moiety being unsubstituted or optionally independently being substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, -CN, -NH\(_2\), -NH(alkyl), -N(alkyl)\(_2\), hydroxy and alkoxy groups;

\( R^6 \) and \( R^7 \) can be the same or different, each being independently selected from the group consisting of H, alkyl-, aryl-, arylalkyl-, alkylaryl-, cycloalkyl-, cycloalkylalkyl-, heteroaryl-, heteroarylalkyl-, heterocyclyl- and heterocyclyalkyl-, wherein each of said alkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with 1-5 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, -CN, -NH\(_2\), -NH(alkyl), -N(alkyl)\(_2\), hydroxy, alkoxy, -aryl and -heteroaryl groups;
or alternately, R\(^6\) and R\(^7\) can be joined together to form a cyclic moiety (spirocyclic) which can be optionally substituted or fused with an aryl or heteroaryl ring, with each of said aryl or heteroaryl ring being unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH\(_2\), -NH(alkyl), -N(alkyl)\(_2\), hydroxy, alkoxy, aryl and heteroaryl groups;

R\(^8\) is selected from the group consisting of H, alkyl, cycloalkyl, aryl and heteroaryl, with each of said alkyl, cycloalkyl, aryl and heteroaryl being unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH\(_2\), -NH(alkyl), -N(alkyl)\(_2\), hydroxy and alkoxy groups;

R\(^9\) is heteroaryl which can be unsubstituted or optionally independently substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH\(_2\), -NH(alkyl), -N(alkyl)\(_2\), hydroxy and alkoxy groups.

3. The compound of claim 1, wherein U is C(R\(^5\)).

4. The compound of claim 1, wherein U is N.

5. The compound of claim 1, wherein R\(^2\) is selected from the group consisting of H, alkyl, alkoxyalkyl-, (4-alkoxy)phenylmethyl-, and arylalkyl.
6. The compound of Claim 1 wherein \( R^2 \) is selected from the group consisting of: methyl, 3-methoxypropyl-, phenylmethyl-, and (4-methoxy)phenylmethyl.

7. The compound of Claim 1 wherein \( R^2 \) is selected from the group consisting of: H, -(CH\(_2\))\(_3\)OCH\(_3\), -CH\(_3\), -CH\(_2\)CH\(_3\), -(CH\(_2\))\(_2\)OCH\(_3\), -(CH\(_2\))\(_2\)CH(CH\(_3\))\(_2\), -CH\(_2\)CH(CH\(_3\))CH\(_2\)CH\(_3\), -CH\(_2\)CH\(_2\)CH\(_3\),

8. The compound of claim 1, wherein \( U \) is N and \( R^2 \) is 3-methoxypropyl.

9. The compound of claim 1, wherein:
   (a) \( R^1 \) is selected from the group consisting of: H and alkyl, or
   (b) \( R^1 \) is selected from the group consisting of: H and methyl, or
   (c) \( R^1 \) is methyl.

10. The compound of claim 1, wherein:
    (a) \( R^1 \) and \( R^2 \) are joined together to form a cyclopentyl ring, which is unsubstituted, or
    (b) wherein \( R^1 \) and \( R^2 \) are joined together to form a cyclopentyl ring, which is substituted with 1-3 substituents which can be the same or different, each
being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy and alkoxy groups, or

(c) R¹ and R² are joined together to form a cyclohexyl ring, which is unsubstituted, or

(d) R¹ and R² are joined together to form a cyclohexyl ring, which is substituted with 1-3 substituents which can be the same or different, each being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy and alkoxy groups.

11. The compound of claim 1, wherein:
   (a) U is N, and R¹ and R² are joined together to form a piperidinyl ring including the N of U as the nitrogen of said piperidinyl ring, which is unsubstituted, or
   (b) U is N, and R¹ and R² are joined together to form a piperidinyl ring including the N of U as the nitrogen of said piperidinyl ring, wherein said piperidinyl ring is substituted with 1-3 substituents which can be the same or different, each being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy and alkoxy groups.

12. The compound of claim 1, wherein:
   (a) U is N, and R¹ and R² are joined together to form a pyrrolidinyl ring including the N of U as the nitrogen of said pyrrolidinyl ring, which is unsubstituted, or
   (b) U is N, and R¹ and R² are joined together to form a pyrrolidinyl ring including the N of U as the nitrogen of said pyrrolidinyl ring, wherein said pyrrolidinyl ring is substituted with 1-3 substituents which can be the same or different, each being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy and alkoxy groups.

13. The compound of claim 1, wherein:
(a) U is N, and R¹ and R² are joined together to form a piperazinyl ring including the N of U as a nitrogen of said piperazinyl ring, which is unsubstituted, or

(b) U is N, and R¹ and R² are joined together to form a piperazinyl ring including the N of U as a nitrogen of said piperazinyl ring, wherein said piperazinyl ring is substituted with 1-3 substituents which can be the same or different, each being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy and alkoxy groups.

14. The compound of Claim 1 wherein R⁶ is selected from the group consisting of: H, alkyl, cycloalkyl, -C(O)OR¹⁵, alkyl substituted with 1-3 halos, -C(O)R¹⁵, and alkyl substituted with -OR¹⁵.

15. The compound of claim 1, wherein R⁶ is selected from the group consisting of: H, methyl, methyl substituted with -OH, and methyl substituted with OCH₃.

16. The compound of claim 1 wherein R⁷ is selected from the group consisting of: (a) aryl substituted with 1-3 R²¹ moieties, (b) aryl substituted with -OR¹⁵ wherein R¹⁵ is (i) an alkyl substituted with 1-3 halos, or (ii) alkyl, (c) aryl, (d) aryl substituted with alkyl wherein said alkyl is substituted with 1-3 halos, (e) aryl substituted with aryl, (f) alkyl, (g) heteroaryl, (h) arylalkyl-, and (i) cycloalkyl.

17. The compound of claim 1 wherein:

(a) R⁷ is aryl, or

(b) R⁷ is an unsubstituted phenyl, or

(c) R⁷ is a phenyl which is substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy, alkoxy, aryl and heteroaryl groups, or
(d) R⁷ is unsubstituted naphthyl, or
(e) R⁷ is naphthyl which is substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy, alkoxy, aryl and heteroaryl groups, or
(f) R⁷ is unsubstituted biphenyl, or
(g) R⁷ is biphenyl which is substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy and alkoxy groups.

18. The compound of claim 1, wherein:
(a) R⁶ is H and R⁷ is a biphenyl which can be unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy and alkoxy groups, or
(b) wherein R⁶ is methyl, and R⁷ is a biphenyl which can be unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy and alkoxy groups, or
(c) R⁶ is H, and R⁷ is a phenyl which can be unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy and alkoxy groups, or
(d) R⁶ is methyl, and R⁷ is a biphenyl which can be unsubstituted or optionally independently substituted with 1-4 substituents which can be the same or different, each substituent being independently selected from the group
consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy and alkoxy groups, or

(e) R⁶ is alkyl substituted with 1-5 independently selected R²¹ moieties, and R⁷ is phenyl substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy, alkoxy, aryl and heteroaryl groups, or

(f) R⁶ is alkyl substituted with one R²¹ moiety, and R⁷ is phenyl substituted with 1-3 substituents which can be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, hydroxy, alkoxy, aryl and heteroaryl groups,

(g) R⁶ and R⁷ are joined to form the spirocyclic unit:

(h) R⁶ and R⁷ are joined to form the spirocyclic unit:

19. The compound of claim 1, wherein R⁸ is H.

20. The compound of claim 1, wherein R⁸ is alkyl.

21. The compound of claim 1, wherein R⁸ is methyl.
22. The compound of claim 1, wherein $R_{10}$ is aryl.

23. The compound of claim 1 wherein:
   (a) $R_{10}$ is aryl substituted with 1 to 3 independently selected $R_{21}$ moieties, or
   (b) $R_{10}$ is aryl substituted with 1 to 3 $R_{21}$ moieties, wherein each $R_{21}$ moiety is the same or different -OR$_{15}$ group, or
   (c) $R_{10}$ is aryl substituted with 1 $R_{21}$ moiety, or
   (d) $R_{10}$ is aryl substituted with one $R_{21}$ moiety, and said $R_{21}$ moiety is -OR$_{15}$, or
   (e) $R_{10}$ is aryl substituted with one $R_{21}$ moiety, said $R_{21}$ moiety is -OR$_{15}$, and said $R_{15}$ is alkyl, or
   (f) $R_{10}$ is aryl substituted with one $R_{21}$ moiety, said $R_{21}$ moiety is -OR$_{15}$, said $R_{15}$ is alkyl, and said alkyl is methyl.

24. The compound of claim 1, wherein:
   (a) $R_{10}$ is phenyl, or
   (b) $R_{10}$ is phenyl substituted with 1 to 3 independently selected $R_{21}$ moieties, or
   (c) $R_{10}$ is phenyl substituted with 1 to 3 $R_{21}$ moieties, wherein each $R_{21}$ moiety is the same or different -OR$_{15}$ group, or
   (d) $R_{10}$ is phenyl substituted with 1 $R_{21}$ moiety, or
   (e) $R_{10}$ is phenyl substituted with one $R_{21}$ moiety, and said $R_{21}$ moiety is -OR$_{15}$, or
   (f) $R_{10}$ is phenyl substituted with one $R_{21}$ moiety, said $R_{21}$ moiety is -OR$_{15}$, and said $R_{15}$ is alkyl, or
   (g) $R_{10}$ is phenyl substituted with one $R_{21}$ moiety, said $R_{21}$ moiety is -OR$_{15}$, said $R_{15}$ is alkyl, and said alkyl is methyl.

25. The compound of claim 1, wherein $R_{10}$ is heteroaryl.
26. The compound of claim 1, wherein;
   (a) \( R^9 \) is unsubstituted heteroaryl,
   (b) \( R^9 \) is heteroaryl which is substituted with 1-3 substituents which
can be the same or different, each substituent being independently selected from
the group consisting of halo, alkyl, CN, NH\(_2\), NH(alkyl), N(alkyl)\(_2\), hydroxy and
alkoxy groups, or
   (c) \( R^9 \) is imidazol-1-yl, or
   (d) \( R^9 \) is 4-methyl-imidazol-1-yl, or
   (e) \( R^9 \) is 5-chloro-4-methyl-imidazol-1-yl.

27. The compound of claim 1 wherein \( R^{10} \) is selected from the group
consisting of:

28. The compound of claim 1 wherein:
   (a) the -\( R^{10}\)-\( R^9 \) moiety is:
   (b) the -\( R^{10}\)-\( R^9 \) moiety is:
The compound of claim 1 wherein;

(a) the $R^9$-$R^{10}$ moiety is:

(b) the $R^9$-$R^{10}$ moiety is:

(c) the $R^9$-$R^{10}$ moiety is:

(d) the $R^9$-$R^{10}$ moiety is:
(e) the $R^9$-$R^{10}$-moiety is:

(f) the $R^9$-$R^{10}$-moiety is:

(g) the $R^9$-$R^{10}$-moiety is:

30. The compound of claim 1 having the formula:
31. The compound of claim 1 having the formula:

32. The compound of claim 1 having the formula:

33. The compound of claim 1 having the formula:
34. Another embodiment of this invention is directed to the compound:

\[
\text{Structure Image}
\]

35. The compound of claim 1 having the formula:

\[
\text{Structure Image}
\]

36. The compound of claim 1 having the formula:

\[
\text{Structure Image}
\]

37. The compound of claim 1 having the formula:
38. The compound of claim 1 having the formula:

![Chemical Structure Image]

39. The compound of claim 1 having the formula:

![Chemical Structure Image]

40. The compound of claim 1 having the formula:
41. The compound of claim 1 having the formula:

42. The compound of claim 1 having the formula:

43. The compound of claim 1 having the formula:
44. The compound of claim 1 having the formula:

\[
\begin{array}{c}
\text{CH}_3 \\
\text{N} \quad \text{O} \\
\text{CH}_3 \\
\text{N} \quad \text{O} \\
\text{CH}_3 \\
\text{N} \quad \text{O} \\
\text{CH}_3 \\
\text{N} \quad \text{O} \\
\text{CH}_3 \\
\end{array}
\]

45. The compound of claim 1 having the formula:

\[
\begin{array}{c}
\text{CH}_3 \\
\text{N} \quad \text{O} \\
\text{CH}_3 \\
\text{N} \quad \text{O} \\
\text{CH}_3 \\
\text{N} \quad \text{O} \\
\text{CH}_3 \\
\text{N} \quad \text{O} \\
\text{CH}_3 \\
\end{array}
\]

46. The compound of claim 1 having the formula:

\[
\begin{array}{c}
\text{CH}_3 \\
\text{N} \quad \text{O} \\
\text{CH}_3 \\
\text{N} \quad \text{O} \\
\text{CH}_3 \\
\text{N} \quad \text{O} \\
\text{CH}_3 \\
\text{N} \quad \text{O} \\
\text{CH}_3 \\
\end{array}
\]

47. The compound of claim 1 having the formula:

\[
\begin{array}{c}
\text{CH}_3 \\
\text{N} \quad \text{O} \\
\text{CH}_3 \\
\text{N} \quad \text{O} \\
\text{CH}_3 \\
\text{N} \quad \text{O} \\
\text{CH}_3 \\
\text{N} \quad \text{O} \\
\text{CH}_3 \\
\end{array}
\]

48. The compound of claim 1 having the formula:
49. The compound of claim 1 having the formula:

49. The compound of claim 1 having the formula:

50. The compound of claim 1 having the formula:

51. The compound of claim 1 having the formula:
52. The compound of claim 1 having the formula:

53. The compound of claim 1 having the formula:

54. The compound of claim 1 having the formula:

55. The compound of claim 1 having the formula:
56. The compound of claim 1 having the formula:

57. The compound of claim 1 having the formula:

58. The compound of claim 1 having the formula:

59. The compound of claim 1 having the formula:
60. The compound of claim 1 having the formula:

61. The compound of claim 1 having the formula:

62. A compound selected from the group consisting of: compounds 1 to 167.

63. The compound of claim 62 wherein said compound is a pharmaceutically acceptable salt of the compound of claim 62.

64. The compound of claim 62 wherein said compound is a solvate of the compound of claim 62.
65. The compound of claim 62 wherein said compound is an ester of the compound of claim 62.

66. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1, and a pharmaceutically acceptable carrier.

67. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 62, and a pharmaceutically acceptable carrier.

68. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1, and a pharmaceutically acceptable carrier, and an effective amount of one or more other pharmaceutically active drugs selected form the group consisting of: (a) drugs useful for the treatment of Alzheimer's disease, (b) drugs useful for inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue, (c) drugs useful for treating neurodegenerative diseases, and (d) drugs useful for inhibiting gamma-secretase.

69. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 62, and a pharmaceutically acceptable carrier, and an effective amount of one or more other pharmaceutically active drugs selected form the group consisting of: (a) drugs useful for the treatment of Alzheimer's disease, (b) drugs useful for inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue, (c) drugs useful for treating neurodegenerative diseases, and (d) drugs useful for inhibiting gamma-secretase.

70. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1, and a pharmaceutically acceptable carrier, and an effective amount of one or more BACE inhibitors.
71. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 62, and a pharmaceutically acceptable carrier, and an effective amount of one or more BACE inhibitors.

72. A pharmaceutical composition:

(1) comprising a therapeutically effective amount of at least one compound of claim 1, or a pharmaceutically acceptable salt, solvate, or ester thereof, and at least one pharmaceutically acceptable carrier, or

(2) comprising a therapeutically effective amount of at least one compound of claim 1, or a pharmaceutically acceptable salt, solvate, or ester thereof, and at least one pharmaceutically acceptable carrier, and an effective amount of one or more other pharmaceutically active drugs selected from the group consisting of: (a) drugs useful for the treatment of Alzheimer's disease, (b) drugs useful for inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue, (c) drugs useful for treating neurodegenerative diseases, and (d) drugs useful for inhibiting gamma-secretase, or

(3) comprising a therapeutically effective amount of at least one compound of claim 1, or a pharmaceutically acceptable salt, solvate, or ester thereof, and at least one pharmaceutically acceptable carrier, and an effective amount of one or more BACE inhibitors,

(4) comprising a therapeutically effective amount of at least one compound of claim 1, or a pharmaceutically acceptable salt, solvate, or ester thereof, and at least one pharmaceutically acceptable carrier, and effective amount of one or more cholinesterase inhibitors, or

(5) comprising a therapeutically effective amount of at least one compound of claim 1, and at least one pharmaceutically acceptable carrier, and effective amount of one or more cholinesterase inhibitors, or
(6) comprising a therapeutically effective amount of at least one compound of claim 1, or a pharmaceutically acceptable salt, solvate, or ester thereof, and at least one pharmaceutically acceptable carrier, and effective amount of one or more BACE inhibitors, muscarinic antagonists, cholinesterase inhibitors; gamma secretase inhibitors; gamma secretase modulators; HMG-CoA reductase inhibitors; non-steroidal anti-inflammatory agents; N-methyl-D-aspartate receptor antagonists; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; an antibiotic; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; GABA_A inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity; PDE-10 inhibitors and cholesterol absorption inhibitors, or

(7) comprising a therapeutically effective amount of at least one compound of claim 1, and at least one pharmaceutically acceptable carrier, and effective amount of one or more BACE inhibitors, muscarinic antagonists, cholinesterase inhibitors; gamma secretase inhibitors; gamma secretase modulators; HMG-CoA reductase inhibitors; non-steroidal anti-inflammatory agents; N-methyl-D-aspartate receptor antagonists; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; an antibiotic; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; GABA_A inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity; PDE-10 inhibitors and cholesterol absorption inhibitors, or

(8) comprising a therapeutically effective amount of at least one compound of claim 1, or a pharmaceutically acceptable salt, solvate, or ester thereof, and at least one pharmaceutically acceptable carrier, and an effective amount of donepezil hydrochloride, or
(9) comprising a therapeutically effective amount of at least one compound of claim 1, and at least one pharmaceutically acceptable carrier, and an effective amount of donepezil hydrochloride.

73. A method of modulating gamma-secretase comprising administering an effective amount of one or more compounds of claim 1 to a patient in need of such treatment.

74. A method of treating one or more neurodegenerative diseases, comprising administering an effective amount of one or more compounds of claim 1 to a patient in need of treatment.

75. A method of inhibiting the deposition of amyloid protein in, on or around neurological tissue, comprising administering an effective amount of one or more compounds of claim 1 to a patient in need of treatment.

76. A method of treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1 to a patient in need of treatment.

77. A method of treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 62 to a patient in need of treatment.

78. A method of treating Alzheimer's disease, comprising administering an effective amount of a compound of claim 1 to a patient in need of treatment.

80. A method of (a) modulating gamma-secretase, (b) treating one or more neurodegenerative diseases, (c) inhibiting the deposition of amyloid protein in, on or around neurological tissue, or (d) treating Alzheimer's disease, comprising administering administering:

1. an effective amount of a compound of claim 1, and
2. an effective amount of one or more other pharmaceutically active ingredients selected from the group consisting of: BACE inhibitors, muscarinic antagonists, cholinesterase inhibitors; gamma secretase inhibitors; gamma secretase modulators; HMG-CoA reductase inhibitors; non-steroidal anti-inflammatory agents; N-methyl-D-aspartate receptor antagonists; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; an antibiotic; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; GABA_A inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity; PDE-10 inhibitors and cholesterol absorption inhibitors,

to a patient in need of such treatment.

81. A method of treating Alzheimer's disease, comprising administering an effective amount of a compound of claim 1, and an effective amount of one or more compounds selected from the group consisting of Aβ antibody inhibitors, gamma secretase inhibitors and beta secretase inhibitors, to a patient in need of such treatment.

82. A method of treating Alzheimer's disease, comprising administering an effective amount of a compound of claim 1, and an effective amount of one or more BACE inhibitors, to a patient in need of such treatment.

83. A method of:
(1) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of one or more cholinesterase, to a patient in need of treatment, or

(2) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of donepezil hydrochloride, to a patient in need of treatment, or

(3) treating Alzheimer's disease, comprising administering an effective amount of a compound claim 1, in combination with an effective amount of one or more cholinesterase, to a patient in need of treatment, or

(4) treating Alzheimer's disease, comprising administering an effective amount of a compound of claim 1, in combination with an effective amount of donepezil hydrochloride, to a patient in need of treatment, or

(5) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of (rivastigmine, to a patient in need of such treatment, or

(6) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of tacrine, to a patient in need of such treatment, or

(7) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of a Tau kinase inhibitor, to a patient in need of such treatment, or

(8) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of one or more Tau kinase inhibitors selected from the group consisting of: GSK3beta inhibitors, cdk5 inhibitors, ERK inhibitors, to a patient in need of such treatment, or

(9) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an
effective amount of one anti-Abeta vaccination, to a patient in need of such treatment, or

(10) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of one or more APP ligands, to a patient in need of such treatment, or

(11) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of one or more agents that upregulate insulin degrading enzyme and/or neprilysin, to a patient in need of such treatment, or

(12) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of one or more cholesterol lowering agents, to a patient in need of such treatment, or

(13) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of one or more cholesterol lowering agents selected from the group consisting of: Atorvastatin, Fluvastatin, Lovastatin, Mevastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin, and Ezetimibe, to a patient in need of such treatment, or

(14) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of one or more fibrates, to a patient in need of such treatment, or

(15) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of one or more fibrates selected from the group consisting of, clofibrate, Clofibride, Etofibrate, Aluminium Clofibrate, to a patient in need of such treatment, or

(16) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an
effective amount of one or more LXR agonists, to a patient in need of such
treatment, or

(17) treating Alzheimer's disease, comprising administering an
effective amount of one or more compounds of claim 1, in combination with an
effective amount of one or more LRP mimics, to a patient in need of such
treatment, or

(18) treating Alzheimer's disease, comprising administering an
effective amount of one or more compounds of claim 1, in combination with an
effective amount of one or more 5-HT6 receptor antagonists, to a patient in need
of such treatment, or

(19) treating Alzheimer's disease, comprising administering an
effective amount of one or more compounds of claim 1, in combination with an
effective amount of one or more nicotinic receptor agonists, to a patient in need of
such treatment, or

(20) treating Alzheimer's disease, comprising administering an
effective amount of one or more compounds of claim 1, in combination with an
effective amount of one or more H3 receptor antagonists, to a patient in need of
such treatment, or

(21) treating Alzheimer's disease, comprising administering an
effective amount of one or more compounds of claim 1, in combination with an
effective amount of one or more histone deacetylase inhibitors, to a patient in
need of such treatment, or

(22) treating Alzheimer's disease, comprising administering an
effective amount of one or more compounds of claim 1, in combination with an
effective amount of one or more hsp90 inhibitors, to a patient in need of such
treatment, or

(23) treating Alzheimer's disease, comprising administering an
effective amount of one or more compounds of claim 1, in combination with an
effective amount of one or more m1 muscarinic receptor agonists, to a patient in
need of such treatment, or
(24) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of one or more 5-HT6 receptor antagonists mGluRI or mGluRδ positive allosteric modulators or agonists, to a patient in need of such treatment, or

(25) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of one or more mGluR2/3 antagonists, to a patient in need of such treatment, or

(26) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of formula I, in combination with an effective amount of one or more anti-inflammatory agents that can reduce neuroinflammation, to a patient in need of such treatment, or

(27) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of one or more Prostaglandin EP2 receptor antagonists, to a patient in need of such treatment, or

(28) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of one or more PAI-1 inhibitors, to a patient in need of such treatment, or

(29) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of one or more agents that can induce Abeta efflux, to a patient in need of such treatment, or

(30) treating Alzheimer's disease, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of gelsolin, to a patient in need of such treatment, or

(31) treating Downs syndrome, comprising administering an effective amount of one or more compounds of claim 1 to a patient in need of treatment, or
(32) treating Downs syndrome, comprising administering an effective amount of a compound of claim 1 to a patient in need of treatment, or

(33) treating Downs syndrome, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of one or more cholinesterase inhibitors, to a patient in need of treatment.

(34) treating Downs syndrome, comprising administering an effective amount of one or more compounds of claim 1, in combination with an effective amount of donepezil hydrochloride, to a patient in need of treatment, or

(35) treating Downs syndrome, comprising administering an effective amount of a compound of claim 1, in combination with an effective amount of one or more cholinesterase inhibitors, to a patient in need of treatment.

(37) treating Downs syndrome, comprising administering an effective amount of a compound of claim 1, in combination with an effective amount of donepezil hydrochloride, to a patient in need of treatment, or

(38) treating mild cognitive impairment, comprising administering an effective amount of one or more compounds of claim 1 to a patient in need of treatment, or

(39) treating glaucoma, comprising administering an effective amount of one or more compounds of claim 1 to a patient in need of treatment, or

(40) treating cerebral amyloid angiopathy, comprising administering an effective amount of one or more compounds of claim 1 to a patient in need of treatment, or

(41) treating stroke, comprising administering an effective amount of one or more compounds of claim 1 to a patient in need of treatment, or

(42) This invention also provides a method of treating dementia, comprising administering an effective amount of one or more compounds of claim 1 to a patient in need of treatment, or

(43) treating microgliosis, comprising administering an effective amount of one or more compounds of claim 1 to a patient in need of treatment, or
(44) treating brain inflammation, comprising administering an effective amount of one or more compounds of claim 1 to a patient in need of treatment, or

(45) treating olfactory function loss, comprising administering an effective amount of one or more compounds of claim 1 to a patient in need of treatment.

84. A kit comprising, in separate containers, in a single package, pharmaceutical compositions for use in combination, wherein one container comprises an effective amount of a compound of claim 1 in a pharmaceutically acceptable carrier, and another container comprises an effective amount of another pharmaceutically active ingredient, the combined quantities of the compound of claim 1 and the other pharmaceutically active ingredient being effective to: (a) treat Alzheimer's disease, or (b) inhibit the deposition of amyloid protein in, on or around neurological tissue, or (c) treat neurodegenerative diseases, or (d) modulate the activity of gamma-secretase.
INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/005777

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/10 C07D413/14 C07D498/04 C07D498/10 C07D498/20
A61K31/4245 A61P25/00 A61P25/28

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABSTRACTS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim</th>
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<td>WADE P A ET AL: &quot;A DIHYDROISOXAZOLE-BASED ROUTE TO 2,3,6-TRIDEOXY-3-AMINOHEXOSE DERIVATIVES&quot; TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, vol. 30, no. 44, 1 January 1989 (1989-01-01), pages 5969-5972, XP0092928747 ISSN: 0040-4039 page 5969; compounds 1,2 ------ 1,3-29</td>
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<td>X</td>
<td>US 4 012 377 A (CLAISSE JOHN ANTHONY ET AL) 15 March 1977 (1977-03-15) examples 9,21,22 ------ -/-- 1,3-29</td>
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</table>

Further documents are listed in the continuation of Box C

See patent family annex

Date of the actual completion of the international search
17 July 2008

Date of mailing of the international search report
28/07/2008

Name and mailing address of the ISA/
European Patent Office, P B 5818 Patentlaan 2
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Fax (+31-70) 340-3016

Authorized officer
Sei ner, Irmgard
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>X</td>
<td>DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US;</td>
<td>1,3-29</td>
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<td>.SINGAL, KEWAL KRISHAN: &quot;A convenient one pot synthesis of oxadiazoles&quot; XP002488599 retrieved from STN Database accession no. 1985:62152 CAS RN: 93970-66-2; 93970-67-3; 93970-68-4; 93970-69-5; 93970-70-8; 93970-71-9; 93970-72-0; 94008-63-6; 94475-73-7 abstract &amp; SYNTHETIC COMMUNICATIONS, 14(11), 1047-52 CODEN: SYNAV; ISSN: 0039-7911, 1984, -----</td>
<td></td>
</tr>
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<td>BODE, JEFFREY W. ET AL: ORGANIC LETTERS, 3(10), 1587-1590 CODEN: ORLEF7; ISSN: 1523-7060, 2001, XP002488598 table 2; compounds 3,4 -----</td>
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</tr>
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<td>GB 2 369 617 A (KOREA INST SCIENCE TECHNOLOGY [KR]; KOREA RES INST CHEM TECH [KR]) 5 June 2002 (2002-06-05) page 2 page 8, lines 9,10 claim 3 -----</td>
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**INTERNATIONAL SEARCH REPORT**

**Box No. II** Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **Claims Nos.**
   - Because they relate to subject matter not required to be searched by this Authority, namely:
     - Although claims 73-83 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. **Claims Nos.**
   - Because they relate to part3 of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. **Claims Nos.**
   - Because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a)

**Box No. III** Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. **As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.**

2. **As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.**

3. **As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.**

4. **No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.**

**Remark on Protest**

- The additional search fees were accompanied by the applicants protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicants protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.
### INTERNATIONAL SEARCH REPORT

**Information on patent family members**

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<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>US 4012377</td>
<td>15-03-1977</td>
<td>CH 502364 A</td>
<td>31-01-1971</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 1770092 A</td>
<td>05-01-1972</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 124826 B</td>
<td>27-11-1972</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 8333 M</td>
<td>14-12-1970</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 1579544 A</td>
<td>29-08-1969</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GB 1228142 A</td>
<td>15-04-1971</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NL 6804496 A</td>
<td>01-10-1968</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2002193953 A</td>
<td>10-07-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20020043413 A</td>
<td>10-06-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2002107253 A1</td>
<td>08-08-2002</td>
</tr>
<tr>
<td>US 2006004013</td>
<td>05-01-2006</td>
<td>AU 2005247746 A1</td>
<td>08-12-2005</td>
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<tr>
<td></td>
<td></td>
<td>BR PI0511504 A</td>
<td>22-01-2008</td>
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<tr>
<td></td>
<td></td>
<td>CA 2566094 A1</td>
<td>08-12-2005</td>
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<td>WO 2005115990 A1</td>
<td>08-12-2005</td>
</tr>
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<td></td>
<td>KR 20070026648 A1</td>
<td>08-03-2007</td>
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<td>US 2008070902 A1</td>
<td>20-03-2008</td>
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