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(54) Title: 3,4-DISUBSTITUTED, 3,5-DISUBSTITUTED AND 3,4,5-SUBSTITUTED PIPERIDINES AND PIPERAZINES

(57) Abstract: The invention relates to substituted piperidine piperazine, morpholine and thiomorpholine compounds useful in the treatment of Alzheimer's disease and more specifically to compounds that are capable of inhibiting beta-secretase, an enzyme that cleaves amyloid precursor protein to produce amyloid beta peptide (A-beta), a major component of the amyloid plaques found in the brains of Alzheimer's sufferers.



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**3,4-DISUBSTITUTED, 3,5-DISUBSTITUTED AND 3,4,5-SUBSTITUTED
PIPERIDINES AND PIPERAZINES**

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Background of the Invention**Field of the Invention**

The invention relates to substituted piperidine and
15 piperazine compounds useful in the treatment of Alzheimer's
disease and more specifically to compounds that are capable of
inhibiting beta-secretase, an enzyme that cleaves amyloid
precursor protein to produce amyloid beta peptide (A-beta), a
major component of the amyloid plaques found in the brains of
20 Alzheimer's sufferers.

Description of Related Art

Alzheimer's disease (AD) is a progressive degenerative
disease of the brain primarily associated with aging. Clinical
25 presentation of AD is characterized by loss of memory,
cognition, reasoning, judgment, and orientation. As the disease
progresses, motor, sensory, and linguistic abilities are also
affected until there is global impairment of multiple cognitive
functions. These cognitive losses occur gradually, but
30 typically lead to severe impairment and eventual death in the
range of four to twelve years.

Alzheimer's disease is characterized by two major pathologic
observations in the brain: neurofibrillary tangles and beta
amyloid (or neuritic) plaques, comprised predominantly of an
35 aggregate of a peptide fragment know as A-beta. Individuals
with AD exhibit characteristic beta-amyloid deposits in the
brain (beta amyloid plaques) and in cerebral blood vessels (beta
amyloid angiopathy) as well as neurofibrillary tangles.
Neurofibrillary tangles occur not only in Alzheimer's disease

5 but also in other dementia-inducing disorders. On autopsy, large numbers of these lesions are generally found in areas of the human brain important for memory and cognition.

Smaller numbers of these lesions in a more restricted anatomical distribution are found in the brains of most aged
10 humans who do not have clinical AD. Amyloidogenic plaques and vascular amyloid angiopathy also characterize the brains of individuals with Trisomy 21 (Down's Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type (HCHWA-D), and other neurodegenerative disorders. Beta-amyloid is a
15 defining feature of AD, now believed to be a causative precursor or factor in the development of disease. Deposition of A-beta in areas of the brain responsible for cognitive activities is a major factor in the development of AD. Beta-amyloid plaques are predominantly composed of amyloid beta peptide (A-beta, also
20 sometimes designated betaA4). A-beta peptide is derived by proteolysis of the amyloid precursor protein (APP) and is comprised of 39-42 amino acids. Several proteases called secretases are involved in the processing of APP.

Cleavage of APP at the N-terminus of the A-beta peptide by
25 beta-secretase and at the C-terminus by the gamma-secretase complex constitutes the beta-amyloidogenic pathway, i.e. the pathway by which A-beta is formed. Cleavage of APP by alpha-secretase produces alpha-sAPP, a secreted form of APP that does not result in beta-amyloid plaque formation. This alternate
30 pathway precludes the formation of A-beta peptide. A description of the proteolytic processing fragments of APP is found, for example, in U.S. Patent Nos. 5,441,870; 5,721,130; and 5,942,400.

An aspartyl protease has been identified as the enzyme
35 responsible for processing of APP at the beta-secretase cleavage site. The beta-secretase enzyme has been disclosed using varied nomenclature, including BACE, Asp, and Memapsin. See, for

5 example, Sindha et al., 1999, *Nature* 402:537-554 (p501) and published PCT application WO00/17369.

Several lines of evidence indicate that progressive cerebral deposition of beta-amyloid peptide (A-beta) plays a seminal role in the pathogenesis of AD and can precede cognitive
10 symptoms by years or decades. See, for example, Selkoe, 1991, *Neuron* 6:487. Release of A-beta from neuronal cells grown in culture and the presence of A-beta in cerebrospinal fluid (CSF) of both normal individuals and AD patients has been demonstrated. See, for example, Seubert et al., 1992, *Nature*
15 359:325-327.

It has been proposed that A-beta peptide accumulates as a result of APP processing by beta-secretase, thus inhibition of this enzyme's activity is desirable for the treatment of AD. *In vivo* processing of APP at the beta-secretase cleavage site is
20 thought to be a rate-limiting step in A-beta production, and is thus a therapeutic target for the treatment of AD. See for example, Sabbagh, M., et al., 1997, *Alz. Dis. Rev.* 3, 1-19.

BACE1 knockout mice fail to produce A-beta, and present a normal phenotype. When crossed with transgenic mice that over
25 express APP, the progeny show reduced amounts of A-beta in brain extracts as compared with control animals (Luo et al., 2001 *Nature Neuroscience* 4:231-232). This evidence further supports the proposal that inhibition of beta-secretase activity and reduction of A-beta in the brain provides a therapeutic method
30 for the treatment of AD and other beta amyloid disorders.

At present there are no effective treatments for halting, preventing, or reversing the progression of Alzheimer's disease. Therefore, there is an urgent need for pharmaceutical agents capable of slowing the progression of Alzheimer's disease and/or
35 preventing it in the first place.

Compounds that are effective inhibitors of beta-secretase, that inhibit beta-secretase-mediated cleavage of APP, that are

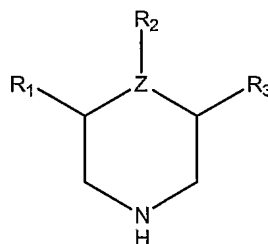
- 5 effective inhibitors of A-beta production, and/or are effective to reduce amyloid beta deposits or plaques, are needed for the treatment and prevention of disease characterized by amyloid beta deposits or plaques, such as AD.

5

Summary of the Invention

The invention encompasses the substituted piperidine and piperazine compounds of the formulas shown below, pharmaceutical compositions containing the compounds and methods employing such compounds or compositions in the treatment of Alzheimer's disease and more specifically compounds that are capable of inhibiting beta-secretase, an enzyme that cleaves amyloid precursor protein to produce A-beta peptide, a major component of the amyloid plaques found in the brains of Alzheimer's sufferers.

In one aspect, the invention provides compounds of the formula I:



(I)

or a pharmaceutically acceptable salt or ester thereof, wherein Z is CH or N;

wherein R₁ and R₃ are independently:

(I) C₁-C₁₀ alkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -O-phenyl, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are independently -H or C₁-C₆ alkyl, -OC(=O)NR_{1-a}R_{1-b}, -S(=O)₀₋₂R_{1-a}, -NR_{1-a}C(=O)NR_{1-a}R_{1-b}, -C(=O)NR_{1-a}R_{1-b}, and -S(=O)₂NR_{1-a}R_{1-b}, -(CH₂)₀₋₃-(C₃-C₈) cycloalkyl where cycloalkyl can be optionally substituted with one, two or three substituents selected from the group

5 consisting of C_1 - C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -
CF₃, C_1 - C_6 alkoxy, -O-phenyl, -CO-OH, -CO-O-(C_1 - C_4 alkyl), -NR_{1-a}R_{1-b}; C_1 - C_3 alkoxy-(R_{1-aryl}), C_1 - C_3 alkoxy-(R_{1-heteroaryl}),

(II) -(CH₂)_{n1}-(R_{1-aryl}) where n₁ is zero or one and where
R_{1-aryl} is phenyl, 1-naphthyl, 2-naphthyl and indanyl, indenyl,
10 dihydronaphthyl, tetralinyl optionally substituted with one,
two, three or four of the following independently selected
substituents on the aryl ring:

(1) C_1 - C_6 alkyl optionally substituted with one,
two or three substituents independently selected from the group
15 consisting of C_1 - C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -S(C_{1-6}
alkyl), -S(aryl- C_{1-6} alkyl), -S(heteroaryl- C_{1-6} alkyl), -S=O(C_{1-6}
alkyl), -S=O(aryl- C_{1-6} alkyl), -S=O(heteroaryl- C_{1-6} alkyl), -
SO₂(C_{1-6} alkyl), -SO₂(aryl- C_{1-6} alkyl), -SO₂(heteroaryl- C_{1-6} alkyl),
-NR_{1-a}R_{1-b}, -C $\equiv$ N, -CF₃, C_1 - C_3 alkoxy, C_1 - C_3 alkoxy-(R_{1-aryl}), C_1 - C_3
20 alkoxy-(R_{1-heteroaryl}),

(2) C_2 - C_6 alkenyl with one or two double bonds,
optionally substituted with one, two or three substituents
independently selected from the group consisting of -F, -Cl,
-Br, -I, -OH, -SH, -S(C_{1-6} alkyl), -S(aryl- C_{1-6} alkyl), -
25 S(heteroaryl- C_{1-6} alkyl), -S=O(C_{1-6} alkyl), -S=O(aryl- C_{1-6} alkyl),
-S=O(heteroaryl- C_{1-6} alkyl), -SO₂(C_{1-6} alkyl), -SO₂(aryl- C_{1-6}
alkyl), -SO₂(heteroaryl- C_{1-6} alkyl), -C $\equiv$ N, -CF₃, C_1 - C_3 alkoxy, -
NR_{1-a}R_{1-b}, C_1 - C_3 alkoxy-(R_{1-aryl}), C_1 - C_3 alkoxy-(R_{1-heteroaryl}),

(3) C_2 - C_6 alkynyl with one or two triple bonds,
30 optionally substituted with one, two or three substituents
independently selected from the group consisting of -F, -Cl,
-Br, -I, -OH, -SH, -S(C_{1-6} alkyl), -S(aryl- C_{1-6} alkyl), -
S(heteroaryl- C_{1-6} alkyl), -S=O(C_{1-6} alkyl), -S=O(aryl- C_{1-6} alkyl),
-S=O(heteroaryl- C_{1-6} alkyl), -SO₂(C_{1-6} alkyl), -SO₂(aryl- C_{1-6}
35 alkyl), -SO₂(heteroaryl- C_{1-6} alkyl), -C $\equiv$ N, -CF₃, C_1 - C_3 alkoxy, -
NR_{1-a}R_{1-b}, C_1 - C_3 alkoxy-(R_{1-aryl}), C_1 - C_3 alkoxy-(R_{1-heteroaryl}),

- 5 (4) -F, Cl, -Br and -I,
 (5) -C₁-C₆ alkoxy optionally substituted with
 one, two or three -F,
 (6) -NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} are as defined
 below,
 10 (7) -OH,
 (8) -C≡N,
 (9) C₃-C₇ cycloalkyl, optionally substituted with
 one, two or three substituents selected from the group
 consisting of -F, -Cl, -Br, -I, -OH, -SH, -S(C₁₋₆ alkyl), -
 15 S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -
 S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆
 alkyl), -SO₂(aryl-C₁₋₆ alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N,
 -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-
 (R_{1-heteroaryl}),
 20 (10) -CO-(C₁-C₄ alkyl),
 (11) -SO₂-NR_{1-a}R_{1-b},
 (12) -CO-NR_{1-a}R_{1-b},
 (13) -SO₂-(C₁-C₄ alkyl),

(III) -(CH₂)_{n1}-(R_{1-heteroaryl}) where n₁ is as defined above

25 and where R_{1-heteroaryl} is selected from the group consisting of:

pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl,
 indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl,
 quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl,
 isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl,
 30 indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl,
 furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl,
 triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl,
 isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-
 carbolinyl, isochromanyl, chromanyl,
 35 tetrahydroisoquinolinyl, isoindolinyl,
 isobenzotetrahydrofuranlyl, isobenzotetrahydrothienyl,
 isobenzothienyl, benzoxazolyl, pyridopyridinyl,

5 benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl,
 benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl,
 pteridinyl, benzothiazolyl, imidazopyridinyl,
 imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl,
 benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl,
 10 benzothiopyranyl, coumarinyl, isocoumarinyl, chromonyl,
 chromanonyl, pyridinyl-N-oxide, tetrahydroquinolinyl,
 dihydroquinolinyl, dihydroquinolinonyl,
 dihydroisoquinolinonyl, dihydrocoumarinyl,
 dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl,
 15 benzoxazolinonyl, pyrrolyl N-oxide, pyrimidinyl N-oxide,
 pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide,
 indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide,
 quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-
 oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-
 20 oxide, thiazolyl N-oxide, indolizinyl N-oxide, indazolyl N-
 oxide, benzothiazolyl N-oxide, benzimidazolyl N-oxide,
 pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-
 oxide, triazolyl N-oxide, tetrazolyl N-oxide,
 benzothiopyranyl S-oxide, benzothiopyranyl S,S-dioxide,

25 where the $R_{1\text{-heteroaryl}}$ group is bonded to $-(CH_2)_{n1}-$
 by any ring atom of the parent $R_{1\text{-heteroaryl}}$ group substituted by
 hydrogen such that the new bond to the $R_{1\text{-heteroaryl}}$ group replaces
 the hydrogen atom and its bond, where heteroaryl is optionally
 substituted with one, two, three or four of:

30 (1) C_1-C_6 alkyl optionally substituted with one,
 two or three substituents independently selected from the group
 consisting of C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -S(C_{1-6}
 alkyl), -S(aryl- C_{1-6} alkyl), -S(heteroaryl- C_{1-6} alkyl), -S=O(C_{1-6}
 alkyl), -S=O(aryl- C_{1-6} alkyl), -S=O(heteroaryl- C_{1-6} alkyl), -
 35 SO₂(C_{1-6} alkyl), -SO₂(aryl- C_{1-6} alkyl), -SO₂(heteroaryl- C_{1-6} alkyl),
 -NR_{1-a}R_{1-b}, -C≡N, -CF₃, C_1-C_3 alkoxy, C_1-C_3 alkoxy-($R_{1\text{-aryl}}$), C_1-C_3
 alkoxy-($R_{1\text{-heteroaryl}}$),

5 (2) C₂-C₆ alkenyl with one or two double bonds, optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl),
10 -S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆ alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(3) C₂-C₆ alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents
15 independently selected from the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆ alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N, -CF₃, C₁-C₃ alkoxy, -
20 NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(4) -F, -Cl, -Br and -I,

(5) -C₁-C₆ alkoxy optionally substituted with one, two, or three -F,

(6) -NR_{N-2}R_{N-3},

25 (7) -OH,

(8) -C≡N,

(9) C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆ alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),
30 (R_{1-heteroaryl}),

35 (10) -CO-(C₁-C₄ alkyl),

(11) -SO₂-NR_{1-a}R_{1-b},

5 (12) $-\text{CO}-\text{NR}_{1-a}\text{R}_{1-b}$,

(13) $-\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ alkyl})$, with the proviso that when n_1 is zero, $\text{R}_{1-\text{heteroaryl}}$ is not bonded to the carbon chain by nitrogen,

(IV) $-(\text{CH}_2)_{n_1}-(\text{R}_{1-\text{heterocycle}})$ where n_1 is as defined above
10 and $\text{R}_{1-\text{heterocycle}}$ is selected from the group consisting of:

morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide,
thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl,
pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl,
tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl,
15 homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl
S,S-dioxide, oxazolidinonyl, dihydropyrazolyl,
dihydropyrrolyl dihydropyrazinyl dihydropyridinyl
dihydropyrimidinyl, dihydrofuryl, dihydropyranyl,
tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide,
20 homothiomorpholinyl S-oxide,

where the $\text{R}_{1-\text{heterocycle}}$ group is bonded by any atom of the parent $\text{R}_{1-\text{heterocycle}}$ group substituted by hydrogen such that the new bond to the $\text{R}_{1-\text{heterocycle}}$ group replaces the hydrogen atom and its bond, where heterocycle is optionally substituted with
25 one, two, three or four:

(1) C_1-C_6 alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of C_1-C_3 alkyl, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OH}$, $-\text{SH}$, $-\text{S}(\text{C}_{1-6} \text{ alkyl})$, $-\text{S}(\text{aryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{S}(\text{heteroaryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{S}=\text{O}(\text{C}_{1-6} \text{ alkyl})$, $-\text{S}=\text{O}(\text{aryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{S}=\text{O}(\text{heteroaryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{SO}_2(\text{C}_{1-6} \text{ alkyl})$, $-\text{SO}_2(\text{aryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{SO}_2(\text{heteroaryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{NR}_{1-a}\text{R}_{1-b}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_3 alkoxy, C_1-C_3 alkoxy- $(\text{R}_{1-\text{aryl}})$, C_1-C_3 alkoxy- $(\text{R}_{1-\text{heteroaryl}})$,
30

(2) C_2-C_6 alkenyl with one or two double
35 bonds, optionally substituted with one, two or three substituents independently selected from the group consisting of $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OH}$, $-\text{SH}$, $-\text{S}(\text{C}_{1-6} \text{ alkyl})$, $-\text{S}(\text{aryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{S}(\text{heteroaryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{S}=\text{O}(\text{C}_{1-6} \text{ alkyl})$, $-\text{S}=\text{O}(\text{aryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{S}=\text{O}(\text{heteroaryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{SO}_2(\text{C}_{1-6} \text{ alkyl})$, $-\text{SO}_2(\text{aryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{SO}_2(\text{heteroaryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{NR}_{1-a}\text{R}_{1-b}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_3 alkoxy, C_1-C_3 alkoxy- $(\text{R}_{1-\text{aryl}})$, C_1-C_3 alkoxy- $(\text{R}_{1-\text{heteroaryl}})$,

5 S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl),
-S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆
alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N, -CF₃, C₁-C₃ alkoxy, -
NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(3) C₂-C₆ alkynyl with one or two triple
10 bonds, optionally substituted with one, two or three
substituents independently selected from the group consisting of
-F, -Cl, -Br, -I, -OH-SH, -S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -
S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl),
-S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆
15 alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N, -CF₃, C₁-C₃ alkoxy, -
NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(4) -F, -Cl, -Br and -I,

(5) -C₁-C₆ alkoxy optionally substituted
with one, two, or three -F,

20 (6) -NR_{N-2}R_{N-3},

(7) -OH,

(8) -C≡N,

(9) C₃-C₇ cycloalkyl, optionally
substituted with one, two or three substituents selected from
25 the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -S(C₁₋₆
alkyl), -S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆
alkyl), -S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-C₁₋₆ alkyl), -
SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆ alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl),
-C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃
30 alkoxy-(R_{1-heteroaryl}),

(10) -CO-(C₁-C₄ alkyl),

(11) -SO₂-NR_{1-a}R_{1-b},

(12) -CO-NR_{1-a}R_{1-b},

(13) -SO₂-(C₁-C₄ alkyl),

35 (14) =O, with the proviso that when n₁ is
zero R_{1-heterocycle} is not bonded to the carbon chain by nitrogen;

5 (V) -H;

(VI) $R_{N-1}-X_N-$ where X_N is selected from the group consisting of:

(A) -CO-,

(B) -SO₂-

10 where R_{N-1} is selected from the group consisting of:

(A) R_{N-aryl} where R_{N-aryl} is phenyl, 1-naphthyl, 2-naphthyl, tetralinyl, indanyl, dihydronaphthyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl, optionally substituted with one, two or three of the following substituents which can be the
15 same or different and are:

(1) C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl),
20 -S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆ alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(2) -OH,

25 (3) -NO₂,

(4) -F, -Cl, -Br, -I,

(5) -CO-OH,

(6) -C≡N,

(7) -(CH₂)₀₋₄-CO-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3}
30 are the same or different and are selected from the group consisting of:

(a) -H,

(b) -C₁-C₆ alkyl optionally substituted with one substituent selected from the group
35 consisting of:

(i) -OH,

(ii) -NH₂,

- 5 (c) $-C_1-C_6$ alkyl optionally substituted with one to three groups independently selected from -F, -Cl, -Br, and -I,
- (d) $-C_3-C_7$ cycloalkyl,
- (e) $-(C_1-C_2 \text{ alkyl})-(C_3-C_7 \text{ cycloalkyl})$,
- 10 (f) $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_3 \text{ alkyl})$,
- (g) $-C_2-C_6$ alkenyl with one or two double bonds,
- (h) $-C_2-C_6$ alkynyl with one or two triple bonds,
- 15 (i) $-C_1-C_6$ hydrocarbyl chain with one double bond and one triple bond,
- (j) $-R_1\text{-aryl}$,
- (k) $-R_1\text{-heteroaryl}$,
- (8) $-(CH_2)_{0-4}-CO-(C_1-C_{12} \text{ alkyl})$,
- 20 (9) $-(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkenyl with one, two or three double bonds})$,
- (10) $-(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkynyl with one, two or three triple bonds})$,
- (11) $-(CH_2)_{0-4}-CO-(C_3-C_7 \text{ cycloalkyl})$,
- 25 (12) $-(CH_2)_{0-4}-CO-R_1\text{-aryl}$,
- (13) $-(CH_2)_{0-4}-CO-R_1\text{-heteroaryl}$,
- (14) $-(CH_2)_{0-4}-CO-R_1\text{-heterocycle}$,
- (15) $-(CH_2)_{0-4}-CO-R_{N-4}$ where R_{N-4} is selected from the group consisting of morpholinyl, thiomorpholinyl,
- 30 piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl where each group is optionally substituted with one, two, three, or four of C_1-C_6 alkyl,
- (16) $-(CH_2)_{0-4}-CO-O-R_{N-5}$ where R_{N-5} is selected from the group consisting of:
- 35 (a) C_1-C_6 alkyl,
- (b) $-(CH_2)_{0-2}-(R_1\text{-aryl})$,

- 5 (c) C₂-C₆ alkenyl containing one or two
double bonds,
- (d) C₂-C₆ alkynyl containing one or two
triple bonds,
- (e) C₃-C₇ cycloalkyl,
- 10 (f) - (CH₂)₀₋₂ - (R₁-heteroaryl),
- (17) - (CH₂)₀₋₄ - SO₂ - NR_{N-2}R_{N-3},
- (18) - (CH₂)₀₋₄ - SO - (C₁-C₈ alkyl),
- (19) - (CH₂)₀₋₄ - SO₂ - (C₁-C₁₂ alkyl),
- (20) - (CH₂)₀₋₄ - SO₂ - (C₃-C₇ cycloalkyl),
- 15 (21) - (CH₂)₀₋₄ - N(H or R_{N-5}) - CO - O - R_{N-5} where R_{N-5}
can be the same or different,
- (22) - (CH₂)₀₋₄ - N(H or R_{N-5}) - CO - N(R_{N-5})₂, where
each R_{N-5} is independently defined herein,
- (23) - (CH₂)₀₋₄ - N - CS - N(R_{N-5})₂, where each R_{N-5} is
20 independently defined herein,
- (24) - (CH₂)₀₋₄ - N(-H or R_{N-5}) - CO - R_{N-2},
- (25) - (CH₂)₀₋₄ - NR_{N-2}R_{N-3},
- (26) - (CH₂)₀₋₄ - R_{N-4},
- (27) - (CH₂)₀₋₄ - O - CO - (C₁-C₆ alkyl),
- 25 (28) - (CH₂)₀₋₄ - O - P(O) - (OR_{N-1})₂ where R_{N-1} is -H
or C₁-C₄ alkyl,
- (29) - (CH₂)₀₋₄ - O - CO - N(R_{N-5})₂,
- (30) - (CH₂)₀₋₄ - O - CS - N(R_{N-5})₂,
- (31) - (CH₂)₀₋₄ - O - (R_{N-5})₂,
- 30 (32) - (CH₂)₀₋₄ - O - (R_{N-5})₂ - COOH,
- (33) - (CH₂)₀₋₄ - S - (R_{N-5})₂,
- (34) - (CH₂)₀₋₄ - O - (C₁-C₆ alkyl optionally
substituted with one, two, three, four, or five of -F),
- (35) C₃-C₇ cycloalkyl,
- 35 (36) C₂-C₆ alkenyl having one or two double
bonds and which is optionally substituted with C₁-C₃ alkyl, -F,
-Cl, -Br, -I, -OH, -SH, -S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -

5 S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl),
-S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆
alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N, -CF₃, C₁-C₃ alkoxy, -
NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(37) C₂-C₆ alkynyl with one or two triple
10 bonds optionally substituted with C₁-C₃ alkyl, -F, -Cl, -Br, -I,
-OH, -SH, -S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆
alkyl), -S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-
C₁₋₆ alkyl), -SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆ alkyl), -
SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b},
15 C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(38) -(CH₂)₀₋₄-N(-H or R_{N-5})-SO₂-R_{N-2}, or

(39) -(CH₂)₀₋₄-C₃-C₇ cycloalkyl,

(B) -R_{N-heteroaryl} where R_{N-heteroaryl} carries the same
definition as R_{1-heteroaryl}, where the R_{N-heteroaryl} group is bonded by
20 any atom of the parent R_{N-heteroaryl} group substituted by hydrogen
such that the new bond to the R_{N-heteroaryl} group replaces the
hydrogen atom and its bond, where heteroaryl is optionally
substituted with one, two, three, or four groups independently
selected from:

25 (1) C₁-C₆ alkyl, optionally substituted with
one, two or three substituents selected from the group
consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -S(C₁₋₆
alkyl), -S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆
alkyl), -S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-C₁₋₆ alkyl), -
30 SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆ alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl),
-C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-
C₃ alkoxy-(R_{1-heteroaryl}),

(2) -OH,

(3) -NO₂,

35 (4) -F, -Cl, -Br, -I,

(5) -CO-OH,

- 5 (6) $-\text{C}\equiv\text{N}$,
- (7) $-(\text{CH}_2)_{0-4}-\text{CO}-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$,
- (C) $\text{R}_{\text{N-aryl}}-\text{W}-\text{R}_{\text{N-aryl}}$,
- (D) $\text{R}_{\text{N-aryl}}-\text{W}-\text{R}_{\text{N-heteroaryl}}$,
- (E) $\text{R}_{\text{N-aryl}}-\text{W}-\text{R}_{\text{N-heterocycle}}$, where $\text{R}_{\text{N-heterocycle}}$ is the
- 10 same as $\text{R}_{\text{1-heterocycle}}$
- (F) $\text{R}_{\text{N-heteroaryl}}-\text{W}-\text{R}_{\text{N-aryl}}$,
- (G) $\text{R}_{\text{N-heteroaryl}}-\text{W}-\text{R}_{\text{N-heteroaryl}}$,
- (H) $\text{R}_{\text{N-heteroaryl}}-\text{W}-\text{R}_{\text{N-heterocycle}}$,
- (I) $\text{R}_{\text{N-heterocycle}}-\text{W}-\text{R}_{\text{N-aryl}}$,
- 15 (J) $\text{R}_{\text{N-heterocycle}}-\text{W}-\text{R}_{\text{N-heteroaryl}}$,
- (K) $\text{R}_{\text{N-heterocycle}}-\text{W}-\text{R}_{\text{N-heterocycle}}$, and
- where W is
- (1) $-(\text{CH}_2)_{0-4}-$,
- (2) $-\text{O}-$,
- 20 (3) $-\text{S}(\text{O})_{0-2}-$,
- (4) $-\text{N}(\text{R}_{\text{N-5}})-$, or
- (5) $-\text{CO}-$;
- (VII) $-(\text{CR}_{\text{C-x}}\text{R}_{\text{C-y}})_{0-4}-\text{R}_{\text{C-aryl}}$ where $\text{R}_{\text{C-x}}$ and $\text{R}_{\text{C-y}}$ are
- H,
- 25 C_1-C_4 alkyl optionally substituted with one or
- two -OH,
- C_1-C_4 alkoxy optionally substituted with one,
- two, or three of
- F,
- 30 $-(\text{CH}_2)_{0-4}-\text{C}_3-\text{C}_7$ cycloalkyl,
- C_2-C_6 alkenyl containing one or two double bonds,
- C_2-C_6 alkynyl containing one or two triple bonds,
- phenyl,
- and where $\text{R}_{\text{C-x}}$ and $\text{R}_{\text{C-y}}$ are taken together with the carbon to
- 35 which they are attached to form a carbocycle of three, four,
- five, six and seven carbon atoms, optionally where one carbon
- atom is replaced by a heteroatom selected from the group

5 consisting of -O-, -S-, -SO₂-, -NR_{N-2}- and R_{C-aryl} is the same as R_{N-aryl};

(VIII) - (CR_{C-x}R_{C-y})₀₋₄-R_{C-aryl}-R_{C-aryl},

(IX) - (CR_{C-x}R_{C-y})₀₋₄-R_{C-aryl}-R_{C-heteroaryl},

(X) - (CR_{C-x}R_{C-y})₀₋₄-R_{C-heteroaryl}-R_{C-aryl}

10 (XI) - (CR_{C-x}R_{C-y})₀₋₄-R_{C-heteroaryl}-R_{C-heteroaryl},

(XII) - (CR_{C-x}R_{C-y})₀₋₄-R_{C-aryl}-R_{C-heterocycle} and R_{C-heterocycle} is the same as R_{N-heterocycle},

(XIII) - (CR_{C-x}R_{C-y})₀₋₄-R_{C-heteroaryl}-R_{C-heterocycle},

(XIV) - (CR_{C-x}R_{C-y})₀₋₄-R_{C-heterocycle}-R_{C-aryl},

15 (XV) - (CR_{C-x}R_{C-y})₀₋₄-R_{C-heterocycle}-R_{C-heteroaryl},

(XVI) - (CR_{C-x}R_{C-y})₀₋₄-R_{C-heterocycle}-R_{C-heterocycle},

(XVII) - [C(R_{C-1})(R_{C-2})]₁₋₃-CO-N-(R_{C-3})₂ where R_{C-1} and R_{C-2} are the same or different and are selected from the group consisting of:

20 (A) -H,

(B) -C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-C₁₋₆ alkyl), -S₂(C₁₋₆ alkyl), -S₂(aryl-C₁₋₆ alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(C) C₂-C₆ alkenyl with one or two double bonds, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆ alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

5 (D) $-(\text{CH}_2)_{0-4}-\text{C}_3-\text{C}_7$ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OH}$, $-\text{SH}$, $-\text{S}(\text{C}_{1-6} \text{ alkyl})$, $-\text{S}(\text{aryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{S}(\text{heteroaryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{S}=\text{O}(\text{C}_{1-6} \text{ alkyl})$, $-\text{S}=\text{O}(\text{aryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{S}=\text{O}(\text{heteroaryl}-\text{C}_{1-6}$
10 $\text{alkyl})$, $-\text{SO}_2(\text{C}_{1-6} \text{ alkyl})$, $-\text{SO}_2(\text{aryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{SO}_2(\text{heteroaryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_6 alkoxy, $-\text{O}$ -phenyl, $-\text{NR}_{1-a}\text{R}_{1-b}$, C_1-C_3 alkoxy- $(\text{R}_{1-\text{aryl}})$, C_1-C_3 alkoxy- $(\text{R}_{1-\text{heteroaryl}})$,

(E) $-(\text{C}_1-\text{C}_4 \text{ alkyl})-\text{R}_{\text{C}'-\text{aryl}}$ where $\text{R}_{\text{C}'-\text{aryl}}$ is as defined for $\text{R}_{1-\text{aryl}}$,

15 (F) $-(\text{C}_1-\text{C}_4 \text{ alkyl})-\text{R}_{\text{C}-\text{heteroaryl}}$,

(G) $-(\text{C}_1-\text{C}_4 \text{ alkyl})-\text{R}_{\text{C}-\text{heterocycle}}$,

(H) $-\text{R}_{\text{C}-\text{heteroaryl}}$,

(I) $-\text{R}_{\text{C}-\text{heterocycle}}$, and

(J) $-\text{R}_{\text{C}'-\text{aryl}}$,

20 and where $\text{R}_{\text{C}-3}$ is the same or different and is:

(A) $-\text{H}$,

(B) $-\text{C}_1-\text{C}_6$ alkyl optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OH}$, $-\text{SH}$, $-\text{S}(\text{C}_{1-6} \text{ alkyl})$, $-\text{S}(\text{aryl}-$
25 $\text{C}_{1-6} \text{ alkyl})$, $-\text{S}(\text{heteroaryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{S}=\text{O}(\text{C}_{1-6} \text{ alkyl})$, $-\text{S}=\text{O}(\text{aryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{S}=\text{O}(\text{heteroaryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{SO}_2(\text{C}_{1-6} \text{ alkyl})$, $-\text{SO}_2(\text{aryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{SO}_2(\text{heteroaryl}-\text{C}_{1-6} \text{ alkyl})$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_6 alkoxy, $-\text{O}$ -phenyl, and $-\text{NR}_{1-a}\text{R}_{1-b}$, C_1-C_3 alkoxy- $(\text{R}_{1-\text{aryl}})$, C_1-C_3 alkoxy- $(\text{R}_{1-\text{heteroaryl}})$,

30 (C) $-(\text{CH}_2)_{0-4}-\text{C}_3-\text{C}_7$ cycloalkyl,

(D) $-(\text{C}_1-\text{C}_4 \text{ alkyl})-\text{R}_{\text{C}'-\text{aryl}}$,

(E) $-(\text{C}_1-\text{C}_4 \text{ alkyl})-\text{R}_{\text{C}-\text{heteroaryl}}$, or

(F) $-(\text{C}_1-\text{C}_4 \text{ alkyl})-\text{R}_{\text{C}-\text{heterocycle}}$;

(XVIII) $-(\text{CH}_2)_o-\text{Q}-(\text{CH}_2)_p-\text{B}$, where o and p are
35 independently integers of 1-4, Q is O , S , SO , SO_2 , NR_1 , and B is C_{1-6} alkyl, aryl, heteroaryl, or heterocycle;

(XIX) $-\text{O}-\text{R}_9$, $-\text{S}-\text{R}_9$, $-\text{NH}-\text{R}_9$, or $\text{N}(\text{R}_9)_2$;

- 5 (XX) $-\text{OC}(=\text{O})-\text{R}_9$
 (XXI) $-\text{C}(=\text{O})\text{O}-\text{R}_9$
 (XXII) $-\text{N}(\text{R}_8)\text{C}(=\text{O})-\text{R}_9$
 (XXIII) $-\text{C}(=\text{O})\text{N}(\text{R}_8)-\text{R}_9$
 (XXIV) $-\text{SO}_2\text{N}(\text{R}_8)\text{C}(=\text{O})-\text{R}_9$
 10 (XXV) $-\text{C}(=\text{O})\text{N}(\text{R}_8)\text{SO}_2-\text{R}_9$
 (XXVI) $-\text{SO}_2-\text{R}_9$;

wherein R_8 is defined as H or C_1 - C_6 alkyl optionally substituted with one to three groups independently selected from $-\text{OH}$, $-\text{NH}_2$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, and $-\text{I}$;

- 15 wherein R_9 is defined as (I)-(XVIII) above
 and wherein R_2 is C_1 to C_6 alkyl, cyclohexyl, cyclopentyl, pyridinyl, phenyl, isoxazole, pyrazole, furan, thiophene, and other five and six membered heterocycles containing carbon, nitrogen, oxygen and sulfur, said C_1 to C_6 alkyl, cyclohexyl,
 20 cyclopentyl, pyridinyl, phenyl, furan, thiophene may be optionally substituted with one, two or three radicals selected from CF_3 , OCF_3 , hydroxyl, halo, C_{1-2} -alkyl, C_{1-2} -haloalkyl, cyano, carboxyl, C_{1-2} -alkoxycarbonyl, C_{1-2} -hydroxyalkyl, thioalkyl, aminosulfonyl, C_{1-2} -alkylaminosulfonyl, methyl C_{1-2} -haloalkoxy,
 25 amino, C_{1-2} -alkylamino, phenylamino, nitro, C_{1-2} -alkoxy- C_{1-2} -alkyl, C_{1-2} -alkylsulfinyl, C_{1-2} -alkoxy and C_{1-3} -alkylthio.

In another aspect of the invention, at least one of R_1 , R_2 or R_3 is H; in a further embodiment, at least two of R_1 , R_2 or R_3 is H.

- 30 The invention also includes a method of treating a patient who has, or in preventing a patient from getting, a disease or condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment
 35 (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary

5 Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for
treating cerebral amyloid angiopathy and preventing its
potential consequences, i.e. single and recurrent lobar
hemorrhages, for treating other degenerative dementias,
including dementias of mixed vascular and degenerative origin,
10 dementia associated with Parkinson's disease, dementia
associated with progressive supranuclear palsy, dementia
associated with cortical basal degeneration, or diffuse Lewy
body type of Alzheimer's disease and who is in need of such
treatment which includes administration of a therapeutically
15 effective amount of a compound of formula I.

In an embodiment, this method of treatment can be used
where the disease is Alzheimer's disease.

In an embodiment, this method of treatment can help prevent
or delay the onset of Alzheimer's disease.

20 In an embodiment, this method of treatment can be used
where the disease is mild cognitive impairment.

In an embodiment, this method of treatment can be used
where the disease is Down's syndrome.

In an embodiment, this method of treatment can be used
25 where the disease is Hereditary Cerebral Hemorrhage with
Amyloidosis of the Dutch-Type.

In an embodiment, this method of treatment can be used
where the disease is cerebral amyloid angiopathy.

30 In an embodiment, this method of treatment can be used
where the disease is degenerative dementias.

In an embodiment, this method of treatment can be used
where the disease is diffuse Lewy body type of Alzheimer's
disease.

35 In an embodiment, this method of treatment can treat an
existing disease, such as those listed above.

In an embodiment, this method of treatment can prevent a
disease, such as those listed above, from developing.

5 In an embodiment, this method of treatment can employ
therapeutically effective amounts: for oral administration from
about 0.1 mg/day to about 3,000, preferably about 1,000 mg/day;
for parenteral, sublingual, intranasal, intrathecal
administration from about 0.5 to about 500 mg/day, preferably
10 about 100 mg/day; for depo administration and implants from
about 0.5 mg/day to about 50 mg/day; for topical administration
from about 0.5 mg/day to about 200 mg/day; for rectal
administration from about 0.5 mg to about 500 mg.

 In an embodiment, this method of treatment can employ
15 therapeutically effective amounts: for oral administration from
about 1 mg/day to about 100 mg/day; and for parenteral
administration from about 5 to about 50 mg daily.

 In an embodiment, this method of treatment can employ
therapeutically effective amounts for oral administration from
20 about 5 mg/day to about 50 mg/day.

 The invention also includes a pharmaceutical composition
which includes a compound of formula I or a pharmaceutically
acceptable salt or ester thereof; and an inert diluent or edible
carrier.

25 The invention also includes the use of a compound of
formula I or a pharmaceutically acceptable salt or ester thereof
for the manufacture of a medicament for use in treating a
patient who has, or in preventing a patient from getting, a
disease or condition selected from the group consisting of
30 Alzheimer's disease, for helping prevent or delay the onset of
Alzheimer's disease, for treating patients with mild cognitive
impairment (MCI) and preventing or delaying the onset of
Alzheimer's disease in those who would progress from MCI to AD,
for treating Down's syndrome, for treating humans who have
35 Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-
Type, for treating cerebral amyloid angiopathy and preventing
its potential consequences, i.e. single and recurrent lobar

5 hemorrhages, for treating other degenerative dementias,
including dementias of mixed vascular and degenerative origin,
dementia associated with Parkinson's disease, dementia
associated with progressive supranuclear palsy, dementia
associated with cortical basal degeneration, diffuse Lewy body
10 type of Alzheimer's disease and who is in need of such
treatment.

In an embodiment, this use of a compound of formula (I) can
be employed where the disease is Alzheimer's disease.

15 In an embodiment, this use of a compound of formula (I) can
help prevent or delay the onset of Alzheimer's disease.

In an embodiment, this use of a compound of formula (I) can
be employed where the disease is mild cognitive impairment.

In an embodiment, this use of a compound of formula (I) can
be employed where the disease is Down's syndrome.

20 In an embodiment, this use of a compound of formula (I) can
be employed where the disease is Hereditary Cerebral Hemorrhage
with Amyloidosis of the Dutch-Type.

In an embodiment, this use of a compound of formula (I) can
be employed where the disease is cerebral amyloid angiopathy.

25 In an embodiment, this use of a compound of formula (I) can
be employed where the disease is degenerative dementias.

In an embodiment, this use of a compound of formula (I) can
be employed where the disease is diffuse Lewy body type of
Alzheimer's disease.

30 In an embodiment, this use of a compound of formula (I)
employs a pharmaceutically acceptable salt selected from the
group consisting of salts of the following acids hydrochloric,
hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, citric,
methanesulfonic, $\text{CH}_3-(\text{CH}_2)_n-\text{COOH}$ where n is 0 thru 4, $\text{HOOC}-$
35 $(\text{CH}_2)_n-\text{COOH}$ where n is as defined above, $\text{HOOC}-\text{CH}=\text{CH}-\text{COOH}$, and
phenyl-COOH.

5 The invention also includes methods for inhibiting beta-secretase activity, for inhibiting cleavage of amyloid precursor protein (APP), in a reaction mixture, at a site between Met596 and Asp597, numbered for the APP-695 amino acid isotype, or at a corresponding site of an isotype or mutant thereof; for
10 inhibiting production of amyloid beta peptide (A beta) in a cell; for inhibiting the production of beta-amyloid plaque in an animal; and for treating or preventing a disease characterized by beta-amyloid deposits in the brain. These methods each include administration of a therapeutically effective amount of
15 a compound of formula I or a pharmaceutically acceptable salt or ester thereof.

 The invention also includes a method for inhibiting beta-secretase activity, including exposing said beta-secretase to an effective inhibitory amount of a compound of formula I
20 or a pharmaceutically acceptable salt or ester thereof.

 In an embodiment, this method includes exposing said beta-secretase to said compound *in vitro*.

 In an embodiment, this method includes exposing said beta-secretase to said compound in a cell.

25 In an embodiment, this method includes exposing said beta-secretase to said compound in a cell in an animal.

 In an embodiment, this method includes exposing said beta-secretase to said compound in a human.

 The invention also includes a method for inhibiting
30 cleavage of amyloid precursor protein (APP), in a reaction mixture, at a site between Met596 and Asp597, numbered for the APP-695 amino acid isotype; or at a corresponding site of an isotype or mutant thereof, including exposing said reaction mixture to an effective inhibitory amount of a compound of
35 formula I or a pharmaceutically acceptable salt or ester thereof.

5 In an embodiment, this method employs a cleavage site:
between Met652 and Asp653, numbered for the APP-751 isotype;
between Met 671 and Asp 672, numbered for the APP-770 isotype;
between Leu596 and Asp597 of the APP-695 Swedish Mutation;
between Leu652 and Asp653 of the APP-751 Swedish Mutation; or
10 between Leu671 and Asp672 of the APP-770 Swedish Mutation.

 In an embodiment, this method exposes said reaction mixture
in vitro.

 In an embodiment, this method exposes said reaction mixture
in a cell.

15 In an embodiment, this method exposes said reaction mixture
in an animal cell.

 In an embodiment, this method exposes said reaction mixture
in a human cell.

 The invention also includes a method for inhibiting
20 production of amyloid beta peptide (A beta) in a cell, including
administering to said cell an effective inhibitory amount of a
compound of formula I or a pharmaceutically acceptable salt or
ester thereof.

 In an embodiment, this method includes administering to an
25 animal.

 In an embodiment, this method includes administering to a
human.

 The invention also includes a method for inhibiting the
production of beta-amyloid plaque in an animal, including
30 administering to said animal an effective inhibitory amount of a
compound of formula I or a pharmaceutically acceptable salt or
ester thereof.

 In an embodiment, this method includes administering to a
human.

35 The invention also includes a method for treating or
preventing a disease characterized by beta-amyloid deposits in
the brain including administering to a patient an effective

5 therapeutic amount of a compound of formula I or a
pharmaceutically acceptable salt or ester thereof.

In an embodiment, this method employs a compound at a
therapeutic amount in the range of from about 0.1 to about 1000
mg/day.

10 In an embodiment, this method employs a compound at a
therapeutic amount in the range of from about 15 to about 1500
mg/day.

In an embodiment, this method employs a compound at a
therapeutic amount in the range of from about 1 to about 100
15 mg/day.

In an embodiment, this method employs a compound at a
therapeutic amount in the range of from about 5 to about 50
mg/day.

In an embodiment, this method can be used where said
20 disease is Alzheimer's disease.

In an embodiment, this method can be used where said
disease is Mild Cognitive Impairment, Down's Syndrome, or
Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch
Type.

25 The invention also includes a composition including beta-
secretase complexed with a compound of formula I or a
pharmaceutically acceptable salt or ester thereof.

The invention also includes a method for producing a beta-
secretase complex including exposing beta-secretase to a
30 compound of formula I or a pharmaceutically acceptable salt or
ester thereof, in a reaction mixture under conditions suitable
for the production of said complex.

In an embodiment, this method employs exposing *in vitro*.

In an embodiment, this method employs a reaction mixture
35 that is a cell.

The invention also includes a component kit including
component parts capable of being assembled, in which at least

5 one component part includes a compound of formula (I) enclosed in a container.

In an embodiment, this component kit includes lyophilized compound, and at least one further component part includes a diluent.

10 The invention also includes a container kit including a plurality of containers, each container including one or more unit dose of a compound of formula I or a pharmaceutically acceptable salt or ester thereof.

In an embodiment, this container kit includes each
15 container adapted for oral delivery and includes a tablet, gel, or capsule.

In an embodiment, this container kit includes each container adapted for parenteral delivery and includes a depot product, syringe, ampoule, or vial.

20 In an embodiment, this container kit includes each container adapted for topical delivery and includes a patch, medipad, ointment, or cream.

The invention also includes an agent kit including a compound of formula I or a pharmaceutically acceptable salt or
25 ester thereof; and one or more therapeutic agents selected from the group consisting of an antioxidant, an anti-inflammatory, a gamma secretase inhibitor, a neurotrophic agent, an acetyl cholinesterase inhibitor, a statin, an A beta peptide, and an anti-A beta antibody.

30 The invention also includes a composition including: a compound of formula I or a pharmaceutically acceptable salt or ester thereof; and an inert diluent or edible carrier.

In an embodiment, this composition includes a carrier that is an oil.

35 The invention also includes a composition including: a compound of formula I or a pharmaceutically acceptable salt or

5 ester thereof; and a binder, excipient, disintegrating agent, lubricant, or gildant.

The invention also includes a composition including: a compound of formula I or a pharmaceutically acceptable salt ester thereof; disposed in a cream, ointment, or patch.

10 The invention provides compounds, compositions, kits, and methods for inhibiting beta-secretase-mediated cleavage of amyloid precursor protein (APP). More particularly, the compounds, compositions, and methods of the invention are effective to inhibit the production of A beta peptide and to
15 treat or prevent any human or veterinary disease or condition associated with a pathological form of A beta peptide.

The compounds, compositions, and methods of the invention are useful for treating humans who have Alzheimer's Disease (AD), for helping prevent or delay the onset of AD, for treating
20 patients with mild cognitive impairment (MCI), and preventing or delaying the onset of AD in those patients who would otherwise be expected to progress from MCI to AD, for treating Down's syndrome, for treating Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type, for treating cerebral beta-
25 amyloid angiopathy and preventing its potential consequences such as single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, for treating dementia associated with Parkinson's disease, dementia associated with
30 progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type AD.

The compounds of the invention possess beta-secretase inhibitory activity. The inhibitory activities of the compounds of the invention are readily demonstrated, for example, using
35 one or more of the assays described herein or known in the art.

The invention includes a method for treating a patient who has, or in preventing a patient from getting, a disease or

5 condition selected from the group consisting of Alzheimer's
disease, for helping prevent or delay the onset of Alzheimer's
disease, for treating patients with mild cognitive impairment
(MCI) and preventing or delaying the onset of Alzheimer's
disease in those who would progress from MCI to AD, for treating
10 Down's syndrome, for treating humans who have Hereditary
Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for
treating cerebral amyloid angiopathy and preventing its
potential consequences, i.e. single and recurrent lobar
hemorrhages, for treating other degenerative dementias,
15 including dementias of mixed vascular and degenerative origin,
dementia associated with Parkinson's disease, dementia
associated with progressive supranuclear palsy, dementia
associated with cortical basal degeneration, or diffuse Lewy
body type of Alzheimer's disease and who is in need of such
20 treatment, comprising administering to such patient a
therapeutically effective amount of a compound of formula (I),
or a pharmaceutically acceptable salt or ester thereof, wherein
Z, R₁, R₂ and R₃ are as defined above and below.

The invention further encompasses a method for making a
25 compound of formula (I), or a pharmaceutically acceptable salt
or ester thereof, wherein Z, R₁, R₂ and R₃ are as defined as
above or below.

Detailed Description Of The Invention

The invention relates to compounds of formula I, or a
30 pharmaceutically acceptable salt or ester thereof. The
invention encompasses all stereoisomers of formula I and of the
other compounds disclosed herein.

Further in accordance with the embodiment of the invention
described above, compounds of Formula I include those where R₁
35 and R₃ are independently:

(I) $-(CH_2)_{n_1}-(R_{1-aryl})$, where n_1 is zero or one and where
R_{1-aryl} is phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl,

5 dihydronaphthalyl, or tetralinyl optionally substituted with one, two, three, or four of the following substituents on the aryl ring:

(A) C_1-C_6 alkyl optionally substituted with one, two or three substituents selected from the group consisting of
10 C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF₃, C_1-C_3 alkoxy, and -NR_{1-a}R_{1-b}, C_1-C_3 alkoxy-(R_{1-aryl}), C_1-C_3 alkoxy-(R_{1-heteroaryl}),

(B) C_2-C_6 alkenyl with one or two double bonds, optionally substituted with one, two or three substituents
15 selected from the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF₃, C_1-C_3 alkoxy, and -NR_{1-a}R_{1-b}, C_1-C_3 alkoxy-(R_{1-aryl}), C_1-C_3 alkoxy-(R_{1-heteroaryl}),

(C) C_2-C_6 alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents
20 selected from the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF₃, C_1-C_3 alkoxy, and -NR_{1-a}R_{1-b}, C_1-C_3 alkoxy-(R_{1-aryl}), C_1-C_3 alkoxy-(R_{1-heteroaryl}),

(D) -F, Cl, -Br, or -I,

(E) -C₁-C₆ alkoxy optionally substituted with
25 one, two, or three -F,

(F) -NR_{N-2}R_{N-3}, where R_{N-2} and R_{N-3} are independently selected from the group consisting of:

(1) -H,

(2) -C₁-C₆ alkyl optionally substituted with
30 one substituent selected from the group consisting of:

(a) -OH, and

(b) -NH₂,

(3) -C₁-C₆ alkyl optionally substituted with one to three -F, -Cl, -Br, or -I,

35 (4) -C₃-C₇ cycloalkyl,

(5) -(C₁-C₂ alkyl)-(C₃-C₇ cycloalkyl),

(6) -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl),

- 5 (7) $-C_2-C_6$ alkenyl with one or two double bonds,
- (8) $-C_2-C_6$ alkynyl with one or two triple bonds,
- (9) $-C_1-C_6$ alkyl chain with one double bond and one triple bond,
- 10 (10) $-R_{1-aryl}$, where R_{1-aryl} is as defined above, and
- (11) $-R_{1-heteroaryl}$,
- (G) $-OH$,
- 15 (H) $-C\equiv N$,
- (I) C_3-C_7 cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, $-NR_{1-a}R_{1-b}$, C_1-C_3 alkoxy, C_1-C_3 alkoxy- (R_{1-aryl}) , C_1-C_3 alkoxy- $(R_{1-heteroaryl})$,
- 20 (K) $-CO-(C_1-C_4 \text{ alkyl})$,
- (L) $-SO_2-NR_{1-a}R_{1-b}$,
- (M) $-CO-NR_{1-a}R_{1-b}$, or
- (N) $-SO_2-(C_1-C_4 \text{ alkyl})$, or
- (II) $-(CH_2)_{n1}-(R_{1-heteroaryl})$, where n_1 is zero or one and
- 25 where $R_{1-heteroaryl}$ is selected from the group consisting of:
- pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl,
- 30 indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl,
- where the $R_{1-heteroaryl}$ group is bonded to $-(CH_2)_{n1}-$ by any ring atom of the parent $R_{1-heteroaryl}$ group substituted by
- 35 hydrogen such that the new bond to the $R_{1-heteroaryl}$ group replaces the hydrogen atom and its bond, where heteroaryl is optionally substituted with one, two, three, or four of:

- 5 (1) C₁-C₆ alkyl optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),
- 10 (2) C₂-C₆ alkenyl with one or two double bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl, C₁-C₃ alkoxy, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),
- 15 (3) C₂-C₆ alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl, C₁-C₃ alkoxy, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),
- 20 (4) -F, Cl, -Br, or -I,
- (5) -C₁-C₆ alkoxy optionally substituted with one, two, or three -F,
- 25 (6) -NR_{N-2}R_{N-3},
- (7) -OH,
- (8) -C≡N,
- (9) C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl, C₁-C₃ alkoxy, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),
- 30 (10) -CO-(C₁-C₄ alkyl),
- (11) -SO₂-NR_{1-a}R_{1-b},
- 35 (12) -CO-NR_{1-a}R_{1-b}, or

5 (13) $-\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ alkyl})$, with the proviso that when n_1 is zero $\text{R}_{1\text{-heteroaryl}}$ is not bonded to the carbon chain by nitrogen.

In another embodiment, R_1 and R_3 are independently:

phenyl, 1-naphthyl, 2-naphthyl, tetralinyl,
10 indanyl, dihydronaphthyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl, each of which is optionally substituted with one, two or three of the following substituents which can be the same or different and are:

(1) C_1-C_6 alkyl, optionally substituted with
15 one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_3 alkoxy, and $-\text{NR}_{1-a}\text{R}_{1-b}$, C_1-C_3 alkoxy- $(\text{R}_{1\text{-aryl}})$, C_1-C_3 alkoxy- $(\text{R}_{1\text{-heteroaryl}})$,

(2) $-\text{OH}$,

20 (3) $-\text{NO}_2$,

(4) $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$,

(5) $-\text{CO}-\text{OH}$,

(6) $-\text{C}\equiv\text{N}$,

(7) $-(\text{CH}_2)_{0-4}-\text{CO}-\text{NR}_{N-2}\text{R}_{N-3}$,

25 (8) $-(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_1-\text{C}_{12} \text{ alkyl})$,

(9) $-(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_2-\text{C}_{12} \text{ alkenyl with one, two or three double bonds})$,

(10) $-(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_2-\text{C}_{12} \text{ alkynyl with one, two or three triple bonds})$,

30 (11) $-(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_3-\text{C}_7 \text{ cycloalkyl})$,

(12) $-(\text{CH}_2)_{0-4}-\text{CO}-\text{R}_{1\text{-aryl}}$,

(13) $-(\text{CH}_2)_{0-4}-\text{CO}-\text{R}_{1\text{-heteroaryl}}$,

(14) $-(\text{CH}_2)_{0-4}-\text{CO}-\text{R}_{1\text{-heterocycle}}$,

(15) $-(\text{CH}_2)_{0-4}-\text{CO}-\text{R}_{N-4}$ where R_{N-4} is selected
35 from the group consisting of morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide,

- 5 pyrrolinyl and pyrrolidinyl where each group is optionally substituted with one, two, three, or four of: C₁-C₆ alkyl,
- (16) - (CH₂)₀₋₄-CO-O-R_{N-5} where R_{N-5} is selected from the group consisting of:
- (a) C₁-C₆ alkyl,
- 10 (b) - (CH₂)₀₋₂- (R_{1-aryl}) ,
- (c) C₂-C₆ alkenyl containing one or two double bonds,
- (d) C₂-C₆ alkynyl containing one or two triple bonds,
- 15 (e) C₃-C₇ cycloalkyl, and
- (f) - (CH₂)₀₋₂- (R_{1-heteroaryl}) ,
- (17) - (CH₂)₀₋₄-SO₂-NR_{N-2}R_{N-3} ,
- (18) - (CH₂)₀₋₄-SO- (C₁-C₈ alkyl) ,
- (19) - (CH₂)₀₋₄-SO₂- (C₁-C₁₂ alkyl) ,
- 20 (20) - (CH₂)₀₋₄-SO₂- (C₃-C₇ cycloalkyl) ,
- (21) - (CH₂)₀₋₄-N(H or R_{N-5})-CO-O-R_{N-5} where R_{N-5} can be the same or different,
- (22) - (CH₂)₀₋₄-N(H or R_{N-5})-CO-N(R_{N-5})₂ , where R_{N-5} can be the same or different,
- 25 (23) - (CH₂)₀₋₄-N-CS-N(R_{N-5})₂ , where R_{N-5} can be the same or different,
- (24) - (CH₂)₀₋₄-N(-H or R_{N-5})-CO-R_{N-2} where R_{N-5} and R_{N-2} can be the same or different,
- (25) - (CH₂)₀₋₄-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} can be the same or different,
- 30 (26) - (CH₂)₀₋₄-R_{N-4} ,
- (27) - (CH₂)₀₋₄-O-CO- (C₁-C₆ alkyl) ,
- (28) - (CH₂)₀₋₄-O-P(O) - (OR_{N-aryl-1})₂ where R_{N-aryl-1} is -H or C₁-C₄ alkyl,
- 35 (29) - (CH₂)₀₋₄-O-CO-N(R_{N-5})₂ ,
- (30) - (CH₂)₀₋₄-O-CS-N(R_{N-5})₂ ,
- (31) - (CH₂)₀₋₄-O- (R_{N-5})₂ ,

- 5 (32) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{\text{N}-5})_2-\text{COOH}$,
 (33) $-(\text{CH}_2)_{0-4}-\text{S}-(\text{R}_{\text{N}-5})_2$,
 (34) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{C}_1-\text{C}_6 \text{ alkyl optionally}$
 substituted with one, two, three, four, or five -F),
 (35) $\text{C}_3-\text{C}_7 \text{ cycloalkyl}$,
 10 (36) $\text{C}_2-\text{C}_6 \text{ alkenyl}$ with one or two double
 bonds optionally substituted with $\text{C}_1-\text{C}_3 \text{ alkyl}$, -F, -Cl, -Br, -I,
 -OH, -SH, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1-\text{C}_3 \text{ alkoxy}$, or $-\text{NR}_{1-\text{a}}\text{R}_{1-\text{b}}$, $\text{C}_1-\text{C}_3 \text{ alkoxy}-(\text{R}_{1-\text{aryl}})$,
 $\text{C}_1-\text{C}_3 \text{ alkoxy}-(\text{R}_{1-\text{heteroaryl}})$,
 (37) $\text{C}_2-\text{C}_6 \text{ alkynyl}$ with one or two triple
 15 bonds optionally substituted with $\text{C}_1-\text{C}_3 \text{ alkyl}$, -F, -Cl, -Br, -I,
 -OH, -SH, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1-\text{C}_3 \text{ alkoxy}$, or $-\text{NR}_{1-\text{a}}\text{R}_{1-\text{b}}$, $\text{C}_1-\text{C}_3 \text{ alkoxy}-(\text{R}_{1-\text{aryl}})$,
 $\text{C}_1-\text{C}_3 \text{ alkoxy}-(\text{R}_{1-\text{heteroaryl}})$,
 (38) $-(\text{CH}_2)_{0-4}-\text{N}(-\text{H} \text{ or } \text{R}_{\text{N}-5})-\text{SO}_2-\text{R}_{\text{N}-2}$ where $\text{R}_{\text{N}-5}$
 and $\text{R}_{\text{N}-2}$ can be the same or different, or
 20 (39) $-(\text{CH}_2)_{0-4}-\text{C}_3-\text{C}_7 \text{ cycloalkyl}$.

In yet another embodiment, R_1 and R_3 are independently $\text{R}_{\text{N}-1}\text{C}(\text{O})-$; and

$\text{R}_{\text{N}-1}$ is $\text{R}_{\text{N}-\text{heteroaryl}}$ where $\text{R}_{\text{N}-\text{heteroaryl}}$ is selected from the group consisting of:

- 25 pyridinyl, pyrimidinyl, quinolinyl, benzothienyl,
 indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl,
 isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl,
 imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl,
 indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl,
 30 benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl,
 thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl,
 imidazopyridinyl, isothiazolyl, naphthyridinyl,
 cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanyl,
 tetrahydroisoquinolinyl,
 35 isoindolinyl, isobenzotetrahydrofuranlyl,
 isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl,

5 pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl,
purinyl,
benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl,
pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl,
dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl,
10 dihydrobenzisoquinazolinyl, benzopyranyl, benzothiopyranyl,
coumarinyl,

where the $R_{N\text{-heteroaryl}}$ group is bonded by any
atom of the parent $R_{N\text{-heteroaryl}}$ group substituted by hydrogen such
that the new bond to the $R_{N\text{-heteroaryl}}$ group replaces the hydrogen
15 atom and its bond, where heteroaryl is optionally substituted
with one, two, three, or four of:

(1) $C_1\text{-}C_6$ alkyl, optionally substituted with
one, two or three substituents selected from the group
consisting of $C_1\text{-}C_3$ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -
20 CF_3 , $C_1\text{-}C_3$ alkoxy, and - $NR_{1-a}R_{1-b}$, $C_1\text{-}C_3$ alkoxy- $(R_{1\text{-aryl}})$, $C_1\text{-}C_3$
alkoxy- $(R_{1\text{-heteroaryl}})$,

(2) -OH,

(3) -NO₂,

(4) -F, -Cl, -Br, or -I

25 (5) -CO-OH,

(6) -C $\equiv$ N,

(7) - $(CH_2)_{0-4}$ -CO-NR_{N-2}R_{N-3},

(8) - $(CH_2)_{0-4}$ -CO- $(C_1\text{-}C_{12}$ alkyl),

(9) - $(CH_2)_{0-4}$ -CO- $(C_2\text{-}C_{12}$ alkenyl with one, two
30 or three double bonds),

(10) - $(CH_2)_{0-4}$ -CO- $(C_2\text{-}C_{12}$ alkynyl with one,
two or three triple bonds),

(11) - $(CH_2)_{0-4}$ -CO- $(C_3\text{-}C_7$ cycloalkyl),

(12) - $(CH_2)_{0-4}$ -CO- $R_{1\text{-aryl}}$,

35 (13) - $(CH_2)_{0-4}$ -CO- $R_{1\text{-heteroaryl}}$,

(14) - $(CH_2)_{0-4}$ -CO- $R_{1\text{-heterocycle}}$,

(15) - $(CH_2)_{0-4}$ -CO- R_{N-4} ,

- 5 (16) $-(\text{CH}_2)_{0-4}-\text{CO}-\text{O}-\text{R}_{\text{N}-5}$,
 (17) $-(\text{CH}_2)_{0-4}-\text{SO}_2-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$,
 (18) $-(\text{CH}_2)_{0-4}-\text{SO}-(\text{C}_1-\text{C}_8 \text{ alkyl})$,
 (19) $-(\text{CH}_2)_{0-4}-\text{SO}_2-(\text{C}_1-\text{C}_{12} \text{ alkyl})$,
 (20) $-(\text{CH}_2)_{0-4}-\text{SO}_2-(\text{C}_3-\text{C}_7 \text{ cycloalkyl})$,
 10 (21) $-(\text{CH}_2)_{0-4}-\text{N}(\text{H or R}_{\text{N}-5})-\text{CO}-\text{O}-\text{R}_{\text{N}-5}$ where $\text{R}_{\text{N}-5}$
 can be the same or different,
 (22) $-(\text{CH}_2)_{0-4}-\text{N}(\text{H or R}_{\text{N}-5})-\text{CO}-\text{N}(\text{R}_{\text{N}-5})_2$, where
 $\text{R}_{\text{N}-5}$ can be the same or different,
 (23) $-(\text{CH}_2)_{0-4}-\text{N}-\text{CS}-\text{N}(\text{R}_{\text{N}-5})_2$, where $\text{R}_{\text{N}-5}$ can be
 15 the same or different,
 (24) $-(\text{CH}_2)_{0-4}-\text{N}(-\text{H or R}_{\text{N}-5})-\text{CO}-\text{R}_{\text{N}-2}$ where $\text{R}_{\text{N}-5}$
 and $\text{R}_{\text{N}-2}$ can be the same or different,
 (25) $-(\text{CH}_2)_{0-4}-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$ where $\text{R}_{\text{N}-2}$ and $\text{R}_{\text{N}-3}$ can
 be the same or different,
 20 (26) $-(\text{CH}_2)_{0-4}-\text{R}_{\text{N}-4}$,
 (27) $-(\text{CH}_2)_{0-4}-\text{O}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$,
 (28) $-(\text{CH}_2)_{0-4}-\text{O}-\text{P}(\text{O})-(\text{OR}_{\text{N-aryl-1}})_2$ where $\text{R}_{\text{N-aryl-1}}$
 is $-\text{H}$ or $\text{C}_1-\text{C}_4 \text{ alkyl}$,
 (29) $-(\text{CH}_2)_{0-4}-\text{O}-\text{CO}-\text{N}(\text{R}_{\text{N}-5})_2$,
 25 (30) $-(\text{CH}_2)_{0-4}-\text{O}-\text{CS}-\text{N}(\text{R}_{\text{N}-5})_2$,
 (31) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{\text{N}-5})_2$,
 (32) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{\text{N}-5})_2-\text{COOH}$,
 (33) $-(\text{CH}_2)_{0-4}-\text{S}-(\text{R}_{\text{N}-5})_2$,
 (34) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{C}_1-\text{C}_6 \text{ alkyl optionally}$
 30 substituted with one, two, three, four, or five $-\text{F}$),
 (35) $\text{C}_3-\text{C}_7 \text{ cycloalkyl}$,
 (36) $\text{C}_2-\text{C}_6 \text{ alkenyl}$ with one or two double
 bonds optionally substituted with $\text{C}_1-\text{C}_3 \text{ alkyl}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,
 $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1-\text{C}_3 \text{ alkoxy}$, or $-\text{NR}_{1-a}\text{R}_{1-b}$, $\text{C}_1-\text{C}_3 \text{ alkoxy}-(\text{R}_{1-}$
 35 $\text{aryl})$, $\text{C}_1-\text{C}_3 \text{ alkoxy}-(\text{R}_{1-\text{heteroaryl}})$,
 (37) $\text{C}_2-\text{C}_6 \text{ alkynyl}$ with one or two triple
 bonds optionally substituted with $\text{C}_1-\text{C}_3 \text{ alkyl}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,

5 -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, or -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R₁-aryl), C₁-C₃ alkoxy-(R₁-heteroaryl),

(38) -(CH₂)₀₋₄-N(-H or R_{N-5})-SO₂-R_{N-2} where R_{N-5} and R_{N-2} can be the same or different, or

(39) -(CH₂)₀₋₄- C₃-C₇ cycloalkyl.

10 In a further embodiment, R₁ and R₃ are independently R_{N-1}C(O)-; and R_{N-1} is phenyl, 1-naphthyl, or 2-naphthyl, each of which is optionally substituted with one, two or three of the following substituents which can be the same or different and are:

15 (1) C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R₁-aryl), C₁-C₃ alkoxy-(R₁-heteroaryl),

20 (2) -OH,

(3) -NO₂,

(4) -F, -Cl, -Br, or -I,

(5) -CO-OH,

(6) -C≡N,

25 (7) -(CH₂)₀₋₄-CO-NR_{N-2}R_{N-3},

(8) -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl),

(9) -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl with one, two or three double bonds),

30 (10) -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl with one, two or three triple bonds),

(11) -(CH₂)₀₋₄-CO-(C₃-C₇ cycloalkyl),

(12) -(CH₂)₀₋₄-CO-R₁-aryl,

(13) -(CH₂)₀₋₄-CO-R₁-heteroaryl,

(14) -(CH₂)₀₋₄-CO-R₁-heterocycle,

35 (15) -(CH₂)₀₋₄-CO-R_{N-4} where R_{N-4} is selected from the group consisting of morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl,

- 5 homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl where each group is optionally substituted with one, two, three, or four of: C₁-C₆ alkyl,
- (16) - (CH₂)₀₋₄-CO-O-R_{N-5} where R_{N-5} is selected from the group consisting of:
- 10 (a) C₁-C₆ alkyl,
- (b) - (CH₂)₀₋₂- (R_{1-aryl}),
- (c) C₂-C₆ alkenyl containing one or two double bonds,
- (d) C₂-C₆ alkynyl containing one or two
- 15 triple bonds,
- (e) C₃-C₇ cycloalkyl, and
- (f) - (CH₂)₀₋₂- (R_{1-heteroaryl}),
- (17) - (CH₂)₀₋₄-SO₂-NR_{N-2}R_{N-3},
- (18) - (CH₂)₀₋₄-SO- (C₁-C₈ alkyl),
- 20 (19) - (CH₂)₀₋₄-SO₂- (C₁-C₁₂ alkyl),
- (20) - (CH₂)₀₋₄-SO₂- (C₃-C₇ cycloalkyl),
- (21) - (CH₂)₀₋₄-N(H or R_{N-5})-CO-O-R_{N-5} where R_{N-5} can be the same or different,
- (22) - (CH₂)₀₋₄-N(H or R_{N-5})-CO-N(R_{N-5})₂, where
- 25 R_{N-5} can be the same or different,
- (23) - (CH₂)₀₋₄-N-CS-N(R_{N-5})₂, where R_{N-5} can be the same or different,
- (24) - (CH₂)₀₋₄-N(-H or R_{N-5})-CO-R_{N-2} where R_{N-5} and R_{N-2} can be the same or different,
- 30 (25) - (CH₂)₀₋₄-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} can be the same or different,
- (26) - (CH₂)₀₋₄-R_{N-4},
- (27) - (CH₂)₀₋₄-O-CO- (C₁-C₆ alkyl),
- (28) - (CH₂)₀₋₄-O-P(O) - (OR_{N-aryl-1})₂ where R_{N-aryl-1}
- 35 is -H or C₁-C₄ alkyl,
- (29) - (CH₂)₀₋₄-O-CO-N(R_{N-5})₂,
- (30) - (CH₂)₀₋₄-O-CS-N(R_{N-5})₂,

- 5 (31) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{\text{N}-5})_2$,
 (32) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{\text{N}-5})_2-\text{COOH}$,
 (33) $-(\text{CH}_2)_{0-4}-\text{S}-(\text{R}_{\text{N}-5})_2$,
 (34) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{C}_1-\text{C}_6 \text{ alkyl optionally}$
 substituted with one, two, three, four, or five $-\text{F}$),
 10 (35) $\text{C}_3-\text{C}_7 \text{ cycloalkyl}$,
 (36) $\text{C}_2-\text{C}_6 \text{ alkenyl}$ with one or two double
 bonds optionally substituted with $\text{C}_1-\text{C}_3 \text{ alkyl}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,
 $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1-\text{C}_3 \text{ alkoxy}$, or $-\text{NR}_{1-\text{a}}\text{R}_{1-\text{b}}$, $\text{C}_1-\text{C}_3 \text{ alkoxy}-(\text{R}_{1-\text{aryl}})$, $\text{C}_1-\text{C}_3 \text{ alkoxy}-(\text{R}_{1-\text{heteroaryl}})$,
 15 (37) $\text{C}_2-\text{C}_6 \text{ alkynyl}$ with one or two triple
 bonds optionally substituted with $\text{C}_1-\text{C}_3 \text{ alkyl}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,
 $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1-\text{C}_3 \text{ alkoxy}$, or $-\text{NR}_{1-\text{a}}\text{R}_{1-\text{b}}$, $\text{C}_1-\text{C}_3 \text{ alkoxy}-(\text{R}_{1-\text{aryl}})$, $\text{C}_1-\text{C}_3 \text{ alkoxy}-(\text{R}_{1-\text{heteroaryl}})$,
 (38) $-(\text{CH}_2)_{0-4}-\text{N}(-\text{H} \text{ or } \text{R}_{\text{N}-5})-\text{SO}_2-\text{R}_{\text{N}-2}$ where $\text{R}_{\text{N}-5}$
 20 and $\text{R}_{\text{N}-2}$ can be the same or different, or
 (39) $-(\text{CH}_2)_{0-4}-\text{C}_3-\text{C}_7 \text{ cycloalkyl}$.

In still another embodiment, R_1 and R_3 are independently $\text{R}_{\text{N}-1}\text{C}(\text{O})-$; and

$\text{R}_{\text{N}-1}$ is phenyl optionally substituted with one, two or three of
 25 the following substituents which can be the same or different
 and are:

- (1) $\text{C}_1-\text{C}_6 \text{ alkyl}$, optionally substituted with
 one, two or three substituents selected from the group
 consisting of $\text{C}_1-\text{C}_3 \text{ alkyl}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1-\text{C}_3 \text{ alkoxy}$, and $-\text{NR}_{1-\text{a}}\text{R}_{1-\text{b}}$, $\text{C}_1-\text{C}_3 \text{ alkoxy}-(\text{R}_{1-\text{aryl}})$, C_1-C_3
 30 $\text{alkoxy}-(\text{R}_{1-\text{heteroaryl}})$,
 (2) $-\text{OH}$,
 (3) $-\text{NO}_2$,
 (4) $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$,
 35 (5) $-\text{CO}-\text{OH}$,
 (6) $-\text{C}\equiv\text{N}$,

- 5 (7) - $(\text{CH}_2)_{0-4}-\text{CO}-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$,
 (8) - $(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_1-\text{C}_{12} \text{ alkyl})$,
 (9) - $(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_2-\text{C}_{12} \text{ alkenyl with one, two or three double bonds})$,
 (10) - $(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_2-\text{C}_{12} \text{ alkynyl with one, two or three triple bonds})$,
 10 (11) - $(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_3-\text{C}_7 \text{ cycloalkyl})$,
 (12) - $(\text{CH}_2)_{0-4}-\text{CO}-\text{R}_1\text{-aryl}$,
 (13) - $(\text{CH}_2)_{0-4}-\text{CO}-\text{R}_1\text{-heteroaryl}$,
 (14) - $(\text{CH}_2)_{0-4}-\text{CO}-\text{R}_1\text{-heterocycle}$,
 15 (15) - $(\text{CH}_2)_{0-4}-\text{CO}-\text{R}_{\text{N}-4}$ where $\text{R}_{\text{N}-4}$ is selected from the group consisting of morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl where each group is optionally
 20 substituted with one, two, three, or four of: C_1-C_6 alkyl,
 (16) - $(\text{CH}_2)_{0-4}-\text{CO}-\text{O}-\text{R}_{\text{N}-5}$ where $\text{R}_{\text{N}-5}$ is selected from the group consisting of:
 (a) C_1-C_6 alkyl,
 (b) - $(\text{CH}_2)_{0-2}-(\text{R}_1\text{-aryl})$,
 25 (c) C_2-C_6 alkenyl containing one or two double bonds,
 (d) C_2-C_6 alkynyl containing one or two triple bonds,
 (e) C_3-C_7 cycloalkyl, and
 30 (f) - $(\text{CH}_2)_{0-2}-(\text{R}_1\text{-heteroaryl})$,
 (17) - $(\text{CH}_2)_{0-4}-\text{SO}_2-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$,
 (18) - $(\text{CH}_2)_{0-4}-\text{SO}-(\text{C}_1-\text{C}_8 \text{ alkyl})$,
 (19) - $(\text{CH}_2)_{0-4}-\text{SO}_2-(\text{C}_1-\text{C}_{12} \text{ alkyl})$,
 (20) - $(\text{CH}_2)_{0-4}-\text{SO}_2-(\text{C}_3-\text{C}_7 \text{ cycloalkyl})$,
 35 (21) - $(\text{CH}_2)_{0-4}-\text{N}(\text{H or } \text{R}_{\text{N}-5})-\text{CO}-\text{O}-\text{R}_{\text{N}-5}$ where $\text{R}_{\text{N}-5}$ can be the same or different,

- 5 (22) $-(\text{CH}_2)_{0-4}-\text{N}(\text{H or } \text{R}_{\text{N}-5})-\text{CO}-\text{N}(\text{R}_{\text{N}-5})_2$, where $\text{R}_{\text{N}-5}$ can be the same or different,
- (23) $-(\text{CH}_2)_{0-4}-\text{N}-\text{CS}-\text{N}(\text{R}_{\text{N}-5})_2$, where $\text{R}_{\text{N}-5}$ can be the same or different,
- (24) $-(\text{CH}_2)_{0-4}-\text{N}(-\text{H or } \text{R}_{\text{N}-5})-\text{CO}-\text{R}_{\text{N}-2}$ where $\text{R}_{\text{N}-5}$ and $\text{R}_{\text{N}-2}$ can be the same or different,
- 10 (25) $-(\text{CH}_2)_{0-4}-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$ where $\text{R}_{\text{N}-2}$ and $\text{R}_{\text{N}-3}$ can be the same or different,
- (26) $-(\text{CH}_2)_{0-4}-\text{R}_{\text{N}-4}$,
- (27) $-(\text{CH}_2)_{0-4}-\text{O}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$,
- 15 (28) $-(\text{CH}_2)_{0-4}-\text{O}-\text{P}(\text{O})-(\text{OR}_{\text{N-aryl-1}})_2$ where $\text{R}_{\text{N-aryl-1}}$ is $-\text{H}$ or C_1-C_4 alkyl,
- (29) $-(\text{CH}_2)_{0-4}-\text{O}-\text{CO}-\text{N}(\text{R}_{\text{N}-5})_2$,
- (30) $-(\text{CH}_2)_{0-4}-\text{O}-\text{CS}-\text{N}(\text{R}_{\text{N}-5})_2$,
- (31) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{\text{N}-5})_2$,
- 20 (32) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{\text{N}-5})_2-\text{COOH}$,
- (33) $-(\text{CH}_2)_{0-4}-\text{S}-(\text{R}_{\text{N}-5})_2$,
- (34) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{C}_1-\text{C}_6 \text{ alkyl optionally substituted with one, two, three, four, or five } -\text{F})$,
- (35) $\text{C}_3-\text{C}_7 \text{ cycloalkyl}$,
- 25 (36) $\text{C}_2-\text{C}_6 \text{ alkenyl with one or two double bonds optionally substituted with } \text{C}_1-\text{C}_3 \text{ alkyl, } -\text{F, } -\text{Cl, } -\text{Br, } -\text{I, } -\text{OH, } -\text{SH, } -\text{C}\equiv\text{N, } -\text{CF}_3, \text{ C}_1-\text{C}_3 \text{ alkoxy, or } -\text{NR}_{1-\text{a}}\text{R}_{1-\text{b}}, \text{ C}_1-\text{C}_3 \text{ alkoxy-}(\text{R}_{1-\text{aryl}}), \text{ C}_1-\text{C}_3 \text{ alkoxy-}(\text{R}_{1-\text{heteroaryl}})$,
- (37) $\text{C}_2-\text{C}_6 \text{ alkynyl with one or two triple bonds optionally substituted with } \text{C}_1-\text{C}_3 \text{ alkyl, } -\text{F, } -\text{Cl, } -\text{Br, } -\text{I, } -\text{OH, } -\text{SH, } -\text{C}\equiv\text{N, } -\text{CF}_3, \text{ C}_1-\text{C}_3 \text{ alkoxy, or } -\text{NR}_{1-\text{a}}\text{R}_{1-\text{b}}, \text{ C}_1-\text{C}_3 \text{ alkoxy-}(\text{R}_{1-\text{aryl}}), \text{ C}_1-\text{C}_3 \text{ alkoxy-}(\text{R}_{1-\text{heteroaryl}})$,
- 30 (38) $-(\text{CH}_2)_{0-4}-\text{N}(-\text{H or } \text{R}_{\text{N}-5})-\text{SO}_2-\text{R}_{\text{N}-2}$ where $\text{R}_{\text{N}-5}$ and $\text{R}_{\text{N}-2}$ can be the same or different, or
- 35 (39) $-(\text{CH}_2)_{0-4}-\text{C}_3-\text{C}_7 \text{ cycloalkyl}$.

In another embodiment, R_1 and R_3 are independently $\text{R}_{\text{N}-1}\text{C}(\text{O})-$; and

5 R_{N-1} is phenyl of which is optionally substituted with one, two or three of the following substituents which can be the same or different and are:

(1) C_1-C_6 alkyl, optionally substituted with one, two or three substituents selected from the group
10 consisting of C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C_1-C_3 alkoxy, and -NR_{1-a}R_{1-b}, C_1-C_3 alkoxy-(R_{1-aryl}), C_1-C_3 alkoxy-(R_{1-heteroaryl}),

(2) -OH,

(3) -NO₂,

15 (4) -F, -Cl, -Br, or -I,

(5) -CO-OH,

(6) -C≡N,

(7) -(CH₂)₀₋₄-CO-NR_{N-2}R_{N-3},

(8) -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl),

20 (9) -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl with one, two or three double bonds),

(10) -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl with one, two or three triple bonds),

(11) -(CH₂)₀₋₄-CO-(C₃-C₇ cycloalkyl),

25 (12) -(CH₂)₀₋₄-CO-R_{1-aryl},

(13) -(CH₂)₀₋₄-CO-R_{1-heteroaryl},

(14) -(CH₂)₀₋₄-CO-R_{1-heterocycle},

(15) -(CH₂)₀₋₄-CO-R_{N-4} where R_{N-4} is selected from the group consisting of morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl where each group is optionally substituted with one, two, three, or four of: C_1-C_6 alkyl,

30 (16) -(CH₂)₀₋₄-CO-O-R_{N-5} where R_{N-5} is selected from the group consisting of:

(a) C_1-C_6 alkyl,

(b) -(CH₂)₀₋₂-(R_{1-aryl}),

5 (c) C₂-C₆ alkenyl containing one or two double bonds,

(d) C₂-C₆ alkynyl containing one or two triple bonds, and

(e) C₃-C₇ cycloalkyl,

10 (17) -(CH₂)₀₋₄-N(H or R_{N-5})-CO-O-R_{N-5} where R_{N-5} can be the same or different,

(18) -(CH₂)₀₋₄-N(H or R_{N-5})-CO-N(R_{N-5})₂, where R_{N-5} can be the same or different,

15 (19) -(CH₂)₀₋₄-N-CS-N(R_{N-5})₂, where R_{N-5} can be the same or different,

(20) -(CH₂)₀₋₄-N(-H or R_{N-5})-CO-R_{N-2} where R_{N-5} and R_{N-2} can be the same or different,

(21) -(CH₂)₀₋₄-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} can be the same or different,

20 (22) -(CH₂)₀₋₄-R_{N-4},

(23) -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl),

(24) -(CH₂)₀₋₄-O-CO-N(R_{N-5})₂,

(25) -(CH₂)₀₋₄-O-CS-N(R_{N-5})₂,

(26) -(CH₂)₀₋₄-O-(R_{N-5})₂,

25 (27) -(CH₂)₀₋₄-O-(R_{N-5})₂-COOH,

(28) -(CH₂)₀₋₄-O-(C₁-C₆ alkyl optionally substituted with one, two, three, four, or five -F),

(29) -(CH₂)₀₋₄-N(-H or R_{N-5})-SO₂-R_{N-2} where R_{N-5} and R_{N-2} can be the same or different, or

30 (30) -(CH₂)₀₋₄-C₃-C₇ cycloalkyl.

In another embodiment, R₁ and R₃ are independently R_{N-1}C(O)-; and

R₁ represents -(CH₂)_{n1}-phenyl where n₁ is zero or one and where phenyl is optionally substituted with one, two, or three of the following substituents which are the same or different:

(A) C₁-C₆ alkyl optionally substituted with one, two or three substituents selected from the group consisting of

5 C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(B) C₂-C₆ alkenyl with one or two double bonds, optionally substituted with one, two or three substituents
10 selected from the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(C) C₂-C₆ alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents
15 selected from the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(D) -F, Cl, -Br, or -I,

(E) -C₁-C₆ alkoxy optionally substituted with
20 one, two, or three -F,

(F) -NR_{N-2}R_{N-3}, where R_{N-2} and R_{N-3} are independently selected from the group consisting of:

(1) -H,

(2) -C₁-C₆ alkyl optionally substituted with
25 one substituent selected from the group consisting of:

(a) -OH, and

(b) -NH₂,

(3) -C₁-C₆ alkyl optionally substituted with one to three -F, -Cl, -Br, or -I,

30 (4) -C₃-C₇ cycloalkyl,

(5) -(C₁-C₂ alkyl)-(C₃-C₇ cycloalkyl),

(6) -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl),

(7) -C₂-C₆ alkenyl with one or two double
bonds,

35 (8) -C₂-C₆ alkynyl with one or two triple
bonds,

- 5 (9) $-C_1-C_6$ alkyl chain with one double bond
and one triple bond,
- (10) $-R_1\text{-aryl}$, , and
- (11) $-R_1\text{-heteroaryl}$, ,
- (G) $-\text{OH}$,
- 10 (H) $-\text{C}\equiv\text{N}$,
- (I) C_3-C_7 cycloalkyl, optionally substituted with
one, two or three substituents selected from the group
consisting of $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_3
alkoxy, and $-\text{NR}_{1-a}\text{R}_{1-b}$, C_1-C_3 alkoxy- $(R_1\text{-aryl})$, C_1-C_3 alkoxy- $(R_1\text{-}$
15 heteroaryl),
- (J) $-\text{CO}-(C_1-C_4 \text{ alkyl})$,
- (K) $-\text{SO}_2-\text{NR}_{1-a}\text{R}_{1-b}$,
- (L) $-\text{CO}-\text{NR}_{1-a}\text{R}_{1-b}$, or
- (M) $-\text{SO}_2-(C_1-C_4 \text{ alkyl})$.
- 20 In a further embodiment, R_1 and R_3 are independently
phenyl(C_1-C_6)alkyl groups where the phenyl is optionally
substituted with one or two groups independently selected from
- (A) C_1-C_6 alkyl optionally substituted with one,
two or three substituents selected from the group consisting of
- 25 C_1-C_3 alkyl, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_3
alkoxy, and $-\text{NR}_{1-a}\text{R}_{1-b}$, C_1-C_3 alkoxy- $(R_1\text{-aryl})$, C_1-C_3 alkoxy- $(R_1\text{-}$
heteroaryl),
- (B) $-\text{F}$, Cl , $-\text{Br}$, or $-\text{I}$,
- (C) $-C_1-C_6$ alkoxy optionally substituted with
- 30 one, two, or three $-\text{F}$,
- (D) $-\text{NR}_{N-2}\text{R}_{N-3}$, where R_{N-2} and R_{N-3} are independently
selected from the group consisting of:
- (1) $-\text{H}$,
- (2) $-C_1-C_6$ alkyl optionally substituted with
- 35 one substituent selected from the group consisting of:
- (a) $-\text{OH}$, and
- (b) $-\text{NH}_2$,

5 (3) -C₁-C₆ alkyl optionally substituted with
one to three -F, -Cl, -Br, or -I,

(4) -C₃-C₇ cycloalkyl,

(5) -(C₁-C₂ alkyl)-(C₃-C₇ cycloalkyl),

(6) -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl),

10 (9) -C₁-C₆ alkyl chain with one double bond
and one triple bond,

(E) -OH,

(F) -C≡N,

(G) C₃-C₇ cycloalkyl, optionally substituted with
15 one, two or three substituents selected from the group
consisting of -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃
alkoxy, and -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R₁₋
heteroaryl),

(H) -CO-(C₁-C₄ alkyl),

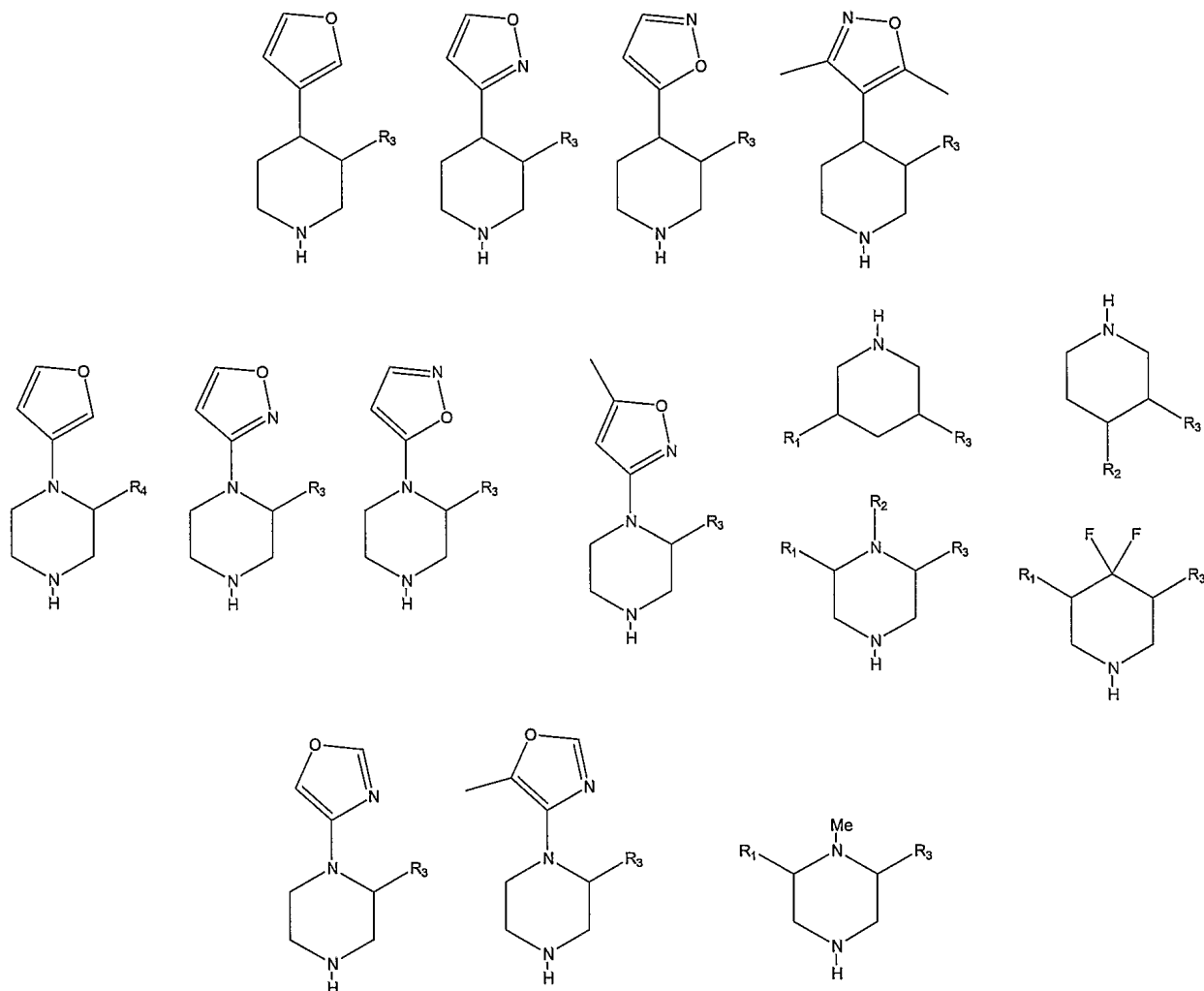
20 (I) -SO₂-NR_{1-a}R_{1-b}, where R_{1-a} and R_{1-b} are as
defined above, or

(J) -CO-NR_{1-a}R_{1-b}, where R_{1-a} and R_{1-b} are as defined
above.

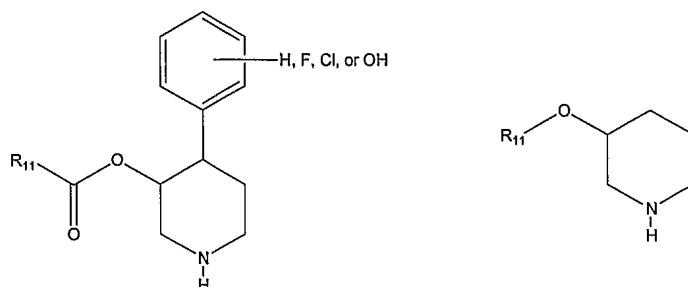
Representative R₁ and R₃ groups also independently include
25 benzyl, 4-hydroxybenzyl, 2-fluoro-4-propylbenzyl, 3-amino-4-
bromobenzyl; 3-chloro-5-methylphenethyl, 3,5-difluorobenzyl, 2-
methylphenylpropyl, 4-trifluoromethylbenzyl, 4-
trifluoromethylphenethyl, 2,3-dichlorobenzyl, and 2-chloro-4-
cyanobenzyl.

30 The invention encompasses compounds of formula I, which
includes those compounds shown below wherein R₁, R₂ and R₃ are as
defined above:

5



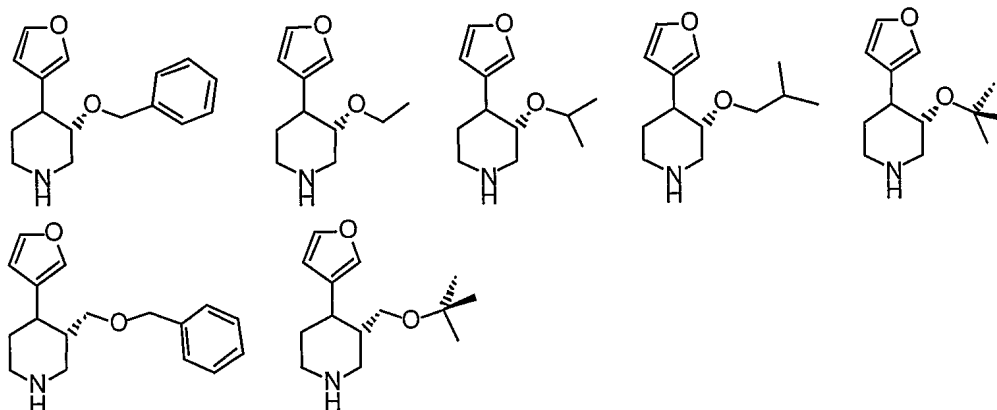
10 The invention encompasses compounds of formula I, which further includes compounds shown below, wherein R₁₁ is -(CH₂)_{n1}-(R₁-aryl), or -(CH₂)_{n1}-O-(R₁-aryl), wherein n1 and R₁-aryl are as defined above:



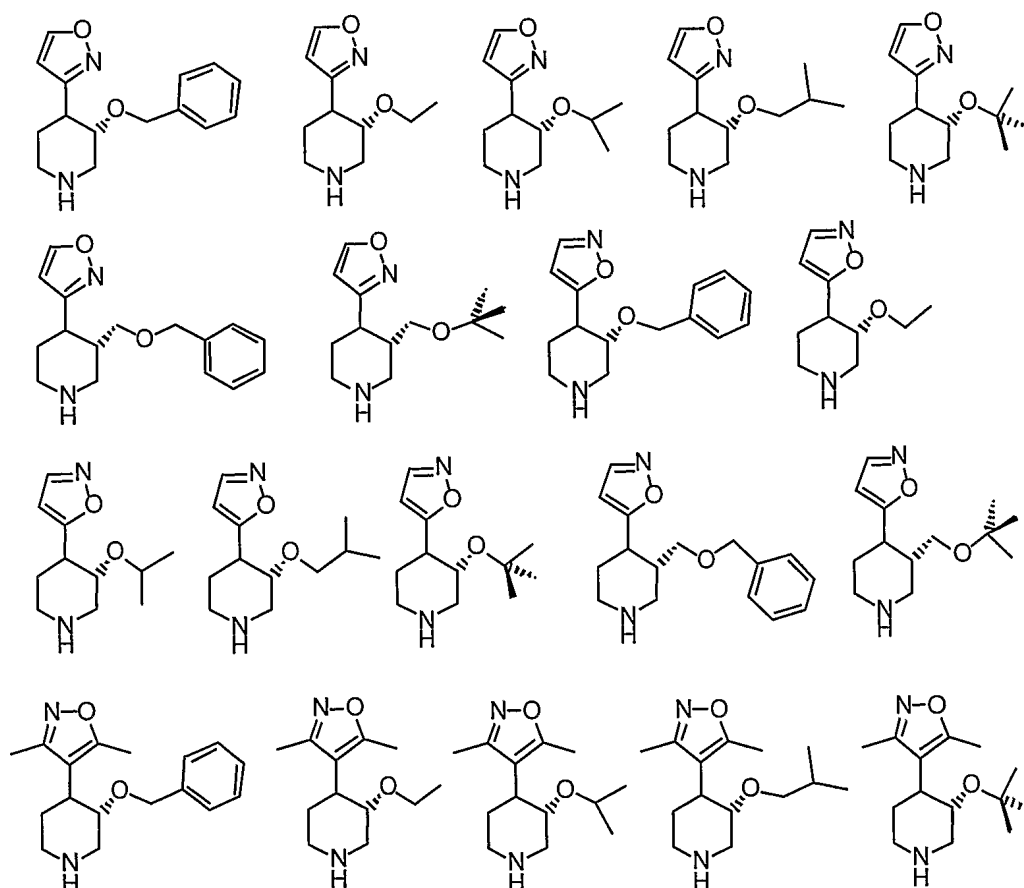
15

5 The invention encompasses compounds contemplated by Formula I, and more particularly those compounds shown below:

3-Alkyloxy-4-Furano-Piperidines

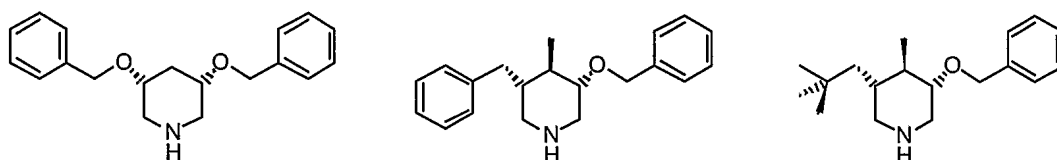
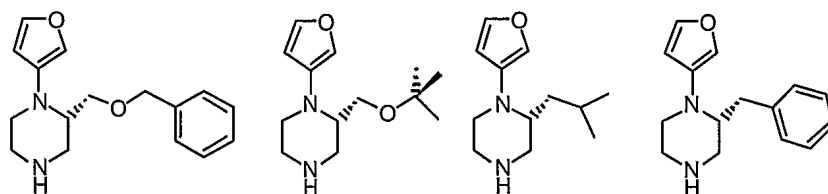
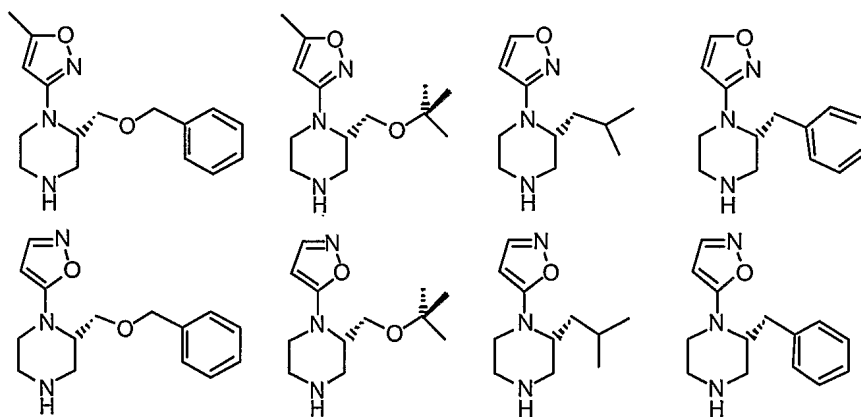
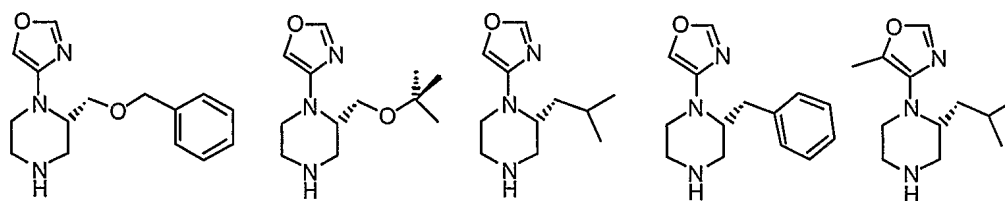


3-Alkyloxy-4-Isoxazolo-Piperidines



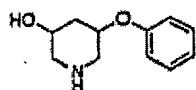
5

The invention encompasses compounds contemplated by Formula I, and more particularly those compounds shown below:

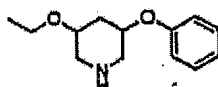
3,5-Alkyloxy-Piperidines**3-Alkyloxy- and 3-Alkyl-4-Furano-Piperazines****3-Alkyloxy- and 3-Alkyl-4-Isoxazolo-Piperazines****3-Alkyloxy- and 3-Alkyl-4-Oxazolo-Piperazines**

10

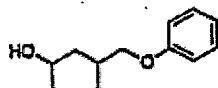
5 The invention encompasses compounds contemplated by Formula I, and more specifically those compounds shown below:



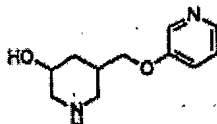
5-Phenoxy-piperidin-3-ol



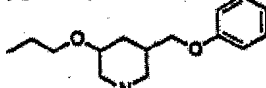
3-Ethoxy-5-phenoxy-piperidine



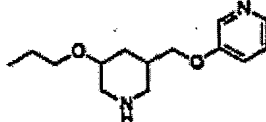
5-Phenoxymethyl-piperidin-3-ol



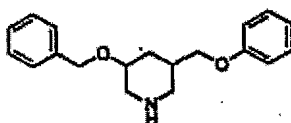
5-(Pyridin-3-yloxymethyl)-piperidin-3-ol



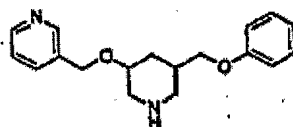
3-Phenoxymethyl-5-propoxy-piperidine



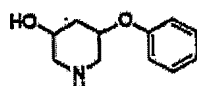
3-(5-Propoxy-piperidin-3-ylmethoxy)-pyridine



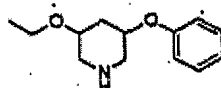
3-Benzoyloxy-5-phenoxy-methyl-piperidine



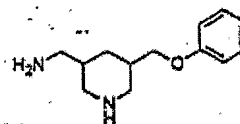
3-(5-Phenoxymethyl-piperidin-3-yloxymethyl)-pyridine



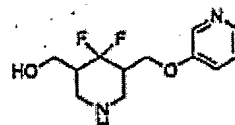
5-Phenoxy-piperidin-3-ol



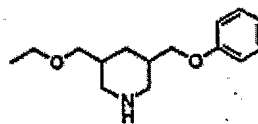
3-Ethoxy-5-phenoxy-piperidine



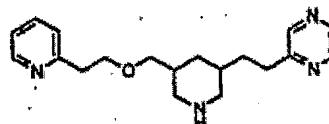
C-(5-Phenoxymethyl-piperidin-3-yl)-methylamine



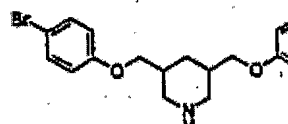
[4,4-Difluoro-5-(pyridin-3-yloxymethyl)-piperidin-3-yl]-methanol



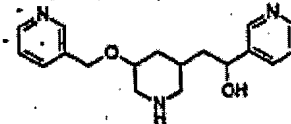
3-Ethoxymethyl-5-phenoxy-methyl-piperidine



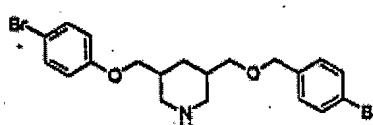
2-[5-(2-Pyridin-2-yl-ethoxymethyl)-piperidin-3-yl]-ethyl-pyrazine



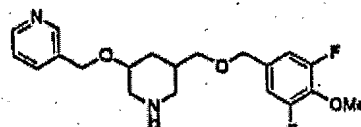
3-(4-Bromo-phenoxy-methyl)-5-(4-chloro-phenoxy-methyl)-piperidine



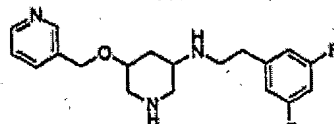
1-Pyridin-3-yl-2-[5-(pyridin-3-ylmethoxy)-piperidin-3-yl]-ethanol



3-(4-Bromo-benzoyloxymethyl)-5-(4-bromo-phenoxy-methyl)-piperidine

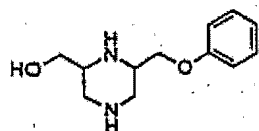


3-[5-(3,5-Difluoro-4-methoxy-benzoyloxymethyl)-piperidin-3-yloxymethyl]-pyridine

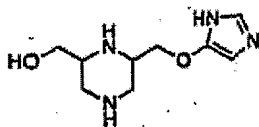


[2-(3,5-Difluoro-phenyl)-ethyl]-[5-(pyridin-3-ylmethoxy)-piperidin-3-yl]-amine

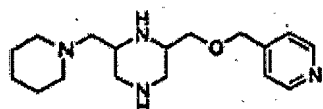
5 The invention encompasses compounds contemplated by Formula I, and more specifically those compounds shown below:



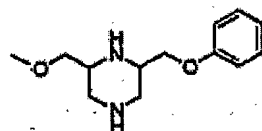
(6-Phenoxymethyl-piperazin-2-yl)-methanol



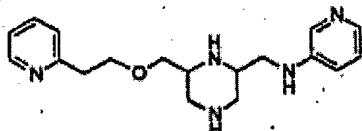
[6-(3H-imidazol-4-yloxymethyl)-piperazin-2-yl]-methanol



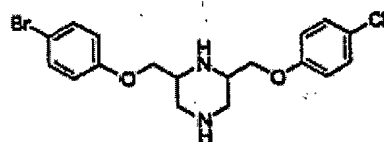
2-Piperidin-1-ylmethyl-6-(pyridin-4-ylmethoxymethyl)-piperazine



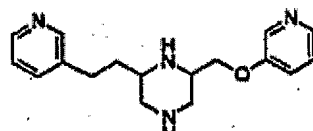
2-Methoxymethyl-6-phenoxymethyl-piperazine



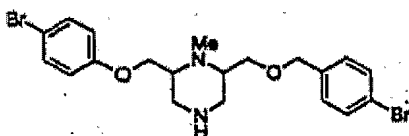
Pyridin-3-yl-[6-(2-pyridin-2-yl-ethoxymethyl)-piperazin-2-ylmethyl]-amine



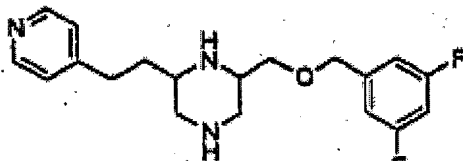
2-(4-Bromo-phenoxymethyl)-6-(4-chloro-phenoxymethyl)-piperazine



2-(2-Pyridin-3-yl-ethyl)-6-(pyridin-3-yloxymethyl)-piperazine



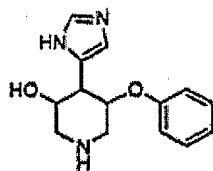
2-(4-Bromo-benzyloxymethyl)-8-(4-bromo-phenoxymethyl)-1-methyl-piperazine



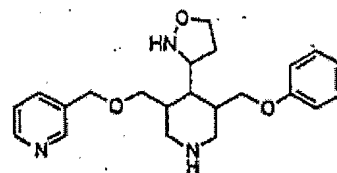
2-(3,5-Difluoro-benzyloxymethyl)-6-(2-pyridin-4-yl-ethyl)-piperazine

5

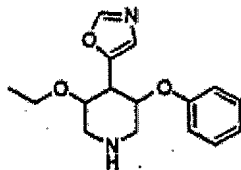
The invention encompasses compounds contemplated by Formula I, and more specifically those compounds shown below:



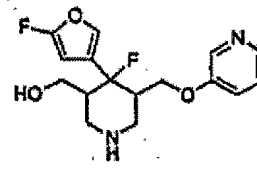
4-(3H-imidazol-4-yl)-5-phenoxy-piperidin-3-ol



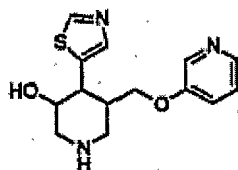
3-(4-isoxazolidin-3-yl)-5-phenoxy-methyl-piperidin-3-ylmethoxymethyl-pyridine



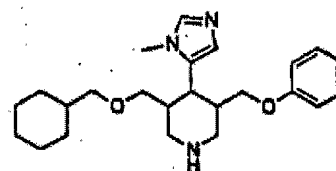
3-Ethoxy-4-oxazol-5-yl-5-phenoxy-piperidine



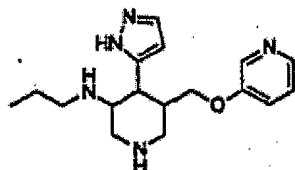
4-Fluoro-4-(5-fluoro-furan-3-yl)-5-(pyridin-3-ylmethoxymethyl)-piperidin-3-yl-methanol



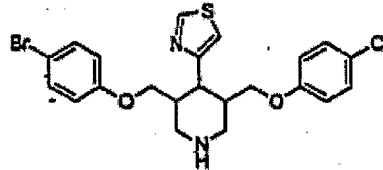
5-(Pyridin-3-ylmethoxymethyl)-4-thiazol-5-yl-piperidin-3-ol



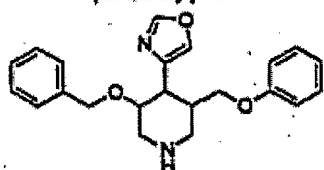
3-Cyclohexylmethoxymethyl-4-(3-methyl-3H-imidazol-4-yl)-5-phenoxy-methyl-piperidine



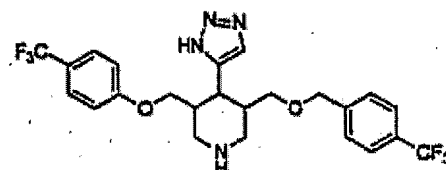
Propyl-[4-(2H-pyrazol-3-yl)-5-(pyridin-3-ylmethoxymethyl)-piperidin-3-yl]-amine



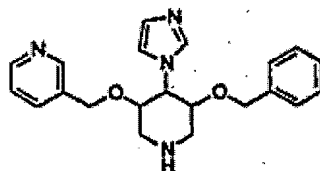
3-(4-Bromo-phenoxy-methyl)-5-(4-chloro-phenoxy-methyl)-4-thiazol-4-yl-piperidine



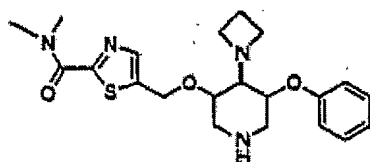
3-Benzoyloxy-4-oxazol-4-yl-5-phenoxy-methyl-piperidine



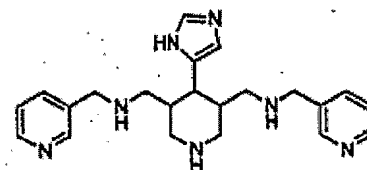
4-(3H-[1,2,3]Triazol-4-yl)-3-(4-trifluoromethyl-benzoyloxymethyl)-5-(4-trifluoromethyl-phenoxy-methyl)-piperidine



3-(5-Benzoyloxy-4-imidazol-1-yl-piperidin-3-ylmethoxymethyl)-pyridine



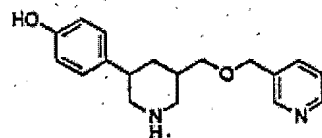
5-(4-Azetidin-1-yl-5-phenoxy-piperidin-3-ylmethoxymethyl)-thiazole-2-carboxylic acid dimethylamide



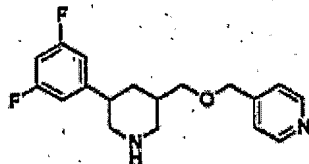
4-(3H-imidazol-4-yl)-5-(((pyridin-3-ylmethyl)-amino)-methyl)-piperidin-3-ylmethyl-pyridin-3-ylmethyl-amine

5

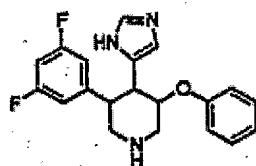
The invention encompasses compounds contemplated by Formula I, and more specifically those compounds shown below:



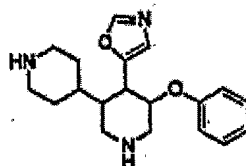
4-[5-(Pyridin-3-ylmethoxymethyl)-piperidin-3-yl]-phenol



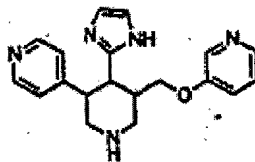
4-[5-(3,5-Difluoro-phenyl)-piperidin-3-ylmethoxymethyl]-pyridine



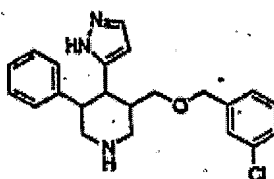
3-(3,5-Difluoro-phenyl)-4-(3H-imidazol-4-yl)-5-phenoxy-piperidine



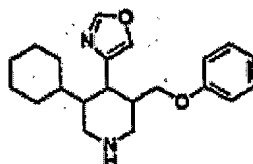
4-Oxazol-5-yl-5-phenoxy-[3,4'-bipiperidinyl]



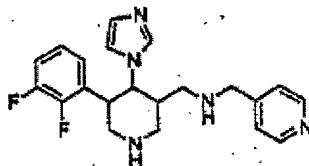
4-(1H-imidazol-2-yl)-5-(pyridin-3-ylloxymethyl)-1,2,3,4,5,6-hexahydro-[3,4'-bipyridinyl]



3-(3-Chloro-benzoyloxymethyl)-5-phenyl-4-(2H-pyrazol-3-yl)-piperidine



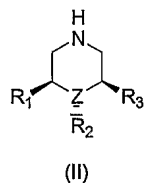
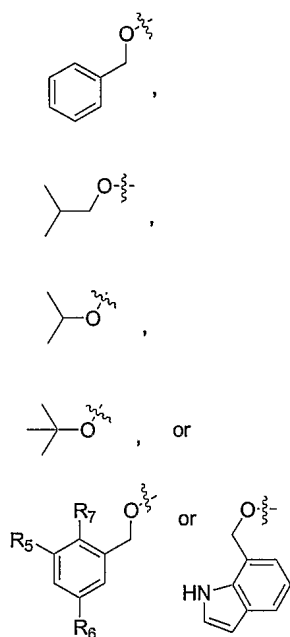
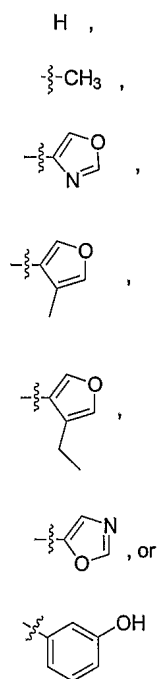
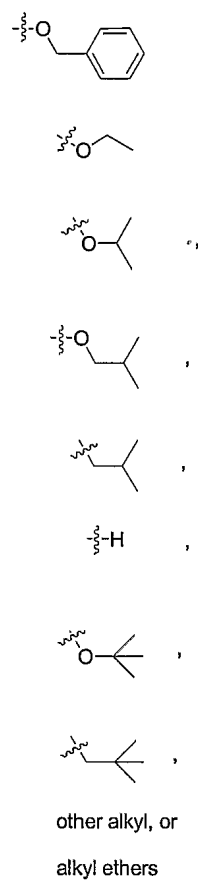
3-Cyclohexyl-4-oxazol-4-yl-5-phenoxy-methyl-piperidine



[5-(2,3-Difluoro-phenyl)-4-imidazol-1-yl-piperidin-3-ylmethyl]-pyridin-4-ylmethyl-amine

5

The invention encompasses compounds contemplated by Formula II, and more specifically those compounds represented by:

R₁ =R₆ = H, OH, NH₂R₄ = H, OH, NH₂, NHCH₃R₅ = H, OCH₃, CH₂CH₂OHR₂ =R₃ =

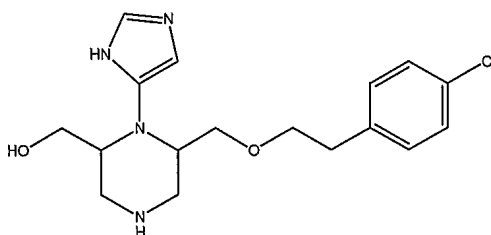
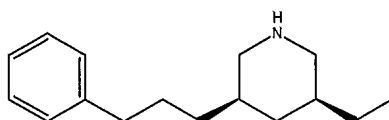
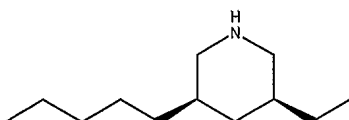
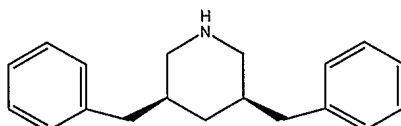
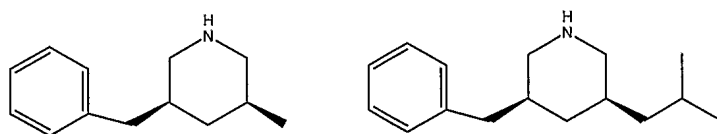
(wherein Z is CH or N)

10

15

5

The invention encompasses compounds contemplated by Formula I, and more specifically those compounds shown below:

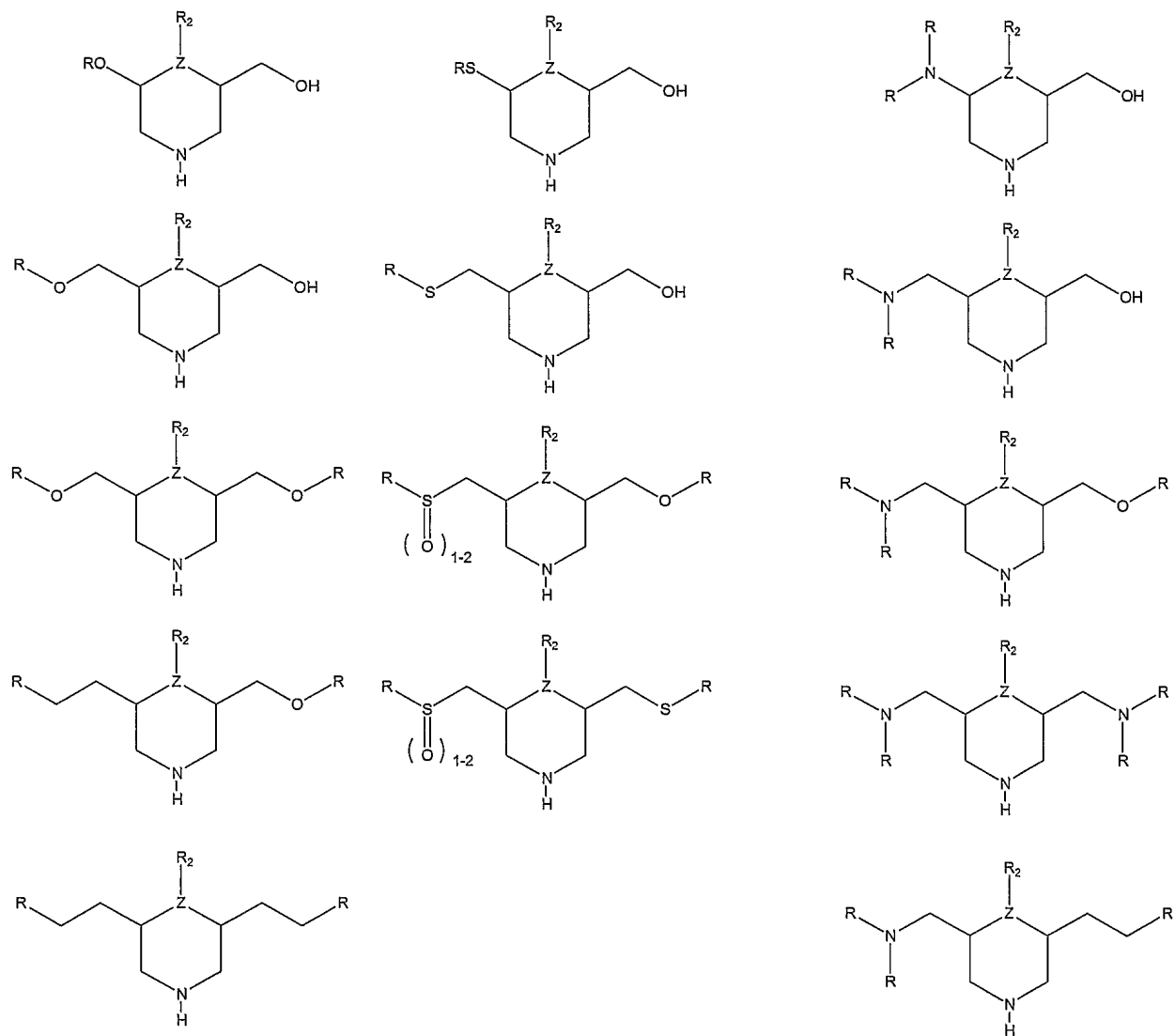


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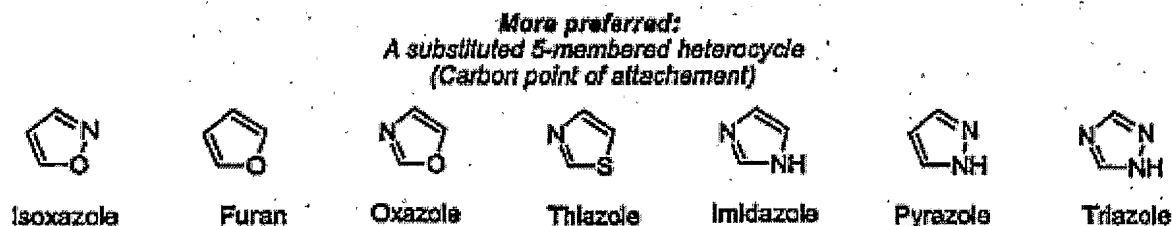
5 The invention encompasses compounds contemplated by Formula I, and more specifically those preferred compounds shown below, where R in each compound may independently be R_1 or R_3 , and wherein R_1 , R_2 , R_3 Z are as defined above.



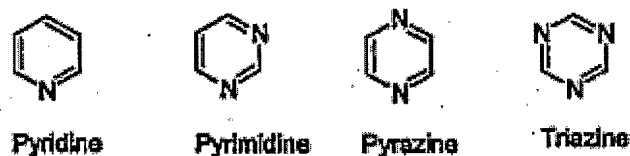
5

The invention encompasses compounds contemplated by Formula I, and more specifically those preferred R_2 groups as shown below. In another more preferred embodiment, R_2 is not a halogenated phenyl, benzyl, aryl or heteroaryl.

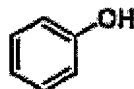
10



More preferred:
A substituted 6-membered heterocycle
(Carbon point of attachment)



More preferred:
A hydroxy substituted phenyl
(Carbon point of attachment)

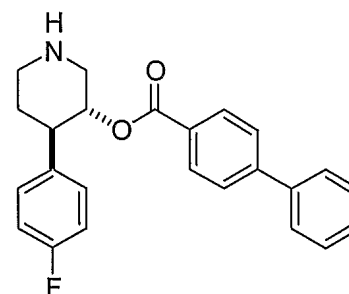
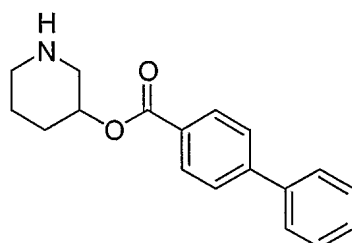
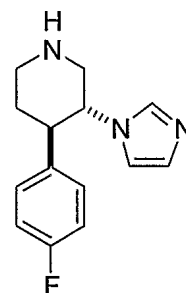
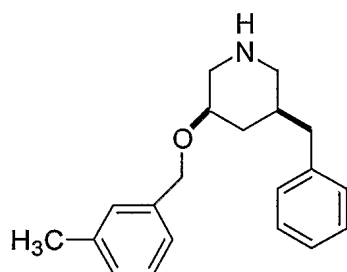
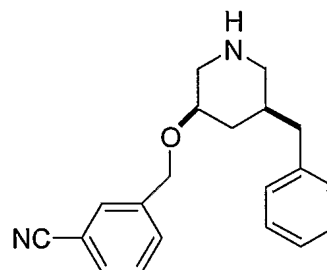
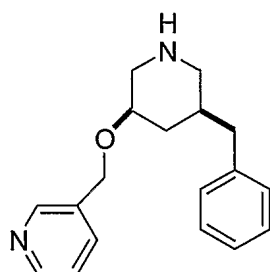
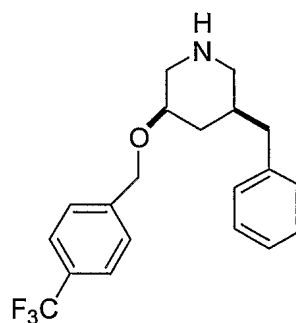
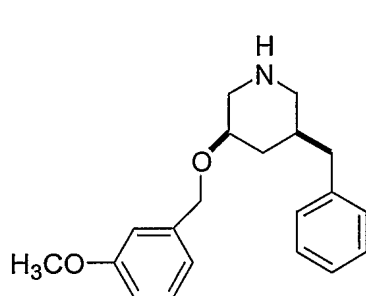


Where the aryl/heteroaryl substitution is "small"

Such as:
One or two, same or different:
Halogen (F, Cl, Br)
Substituted C_1-C_3 Alkyl (methyl, ethyl, trifluoromethyl ...)
Amino (NH_2)
 C_1-C_3 Alkylamino ($RHN-$)
Cyano

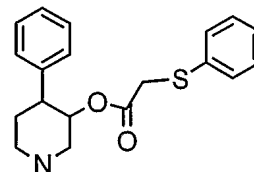
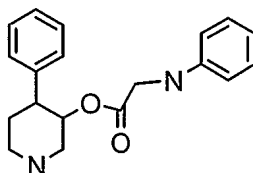
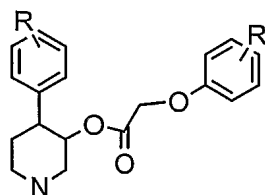
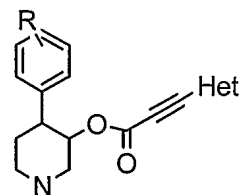
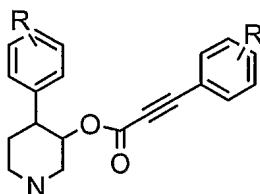
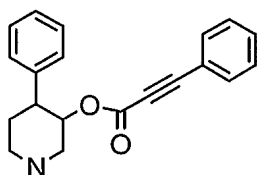
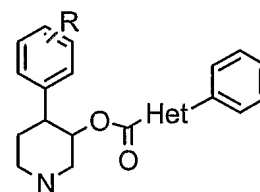
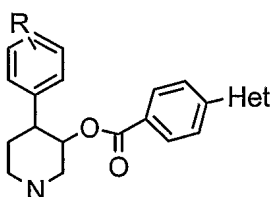
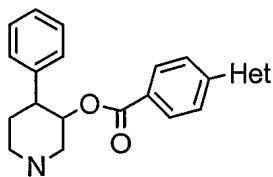
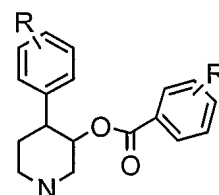
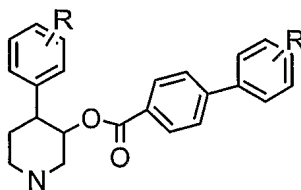
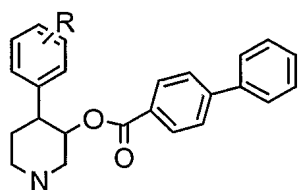
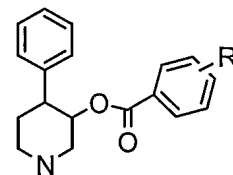
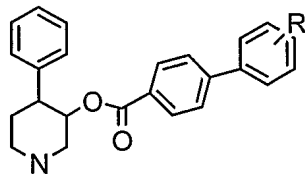
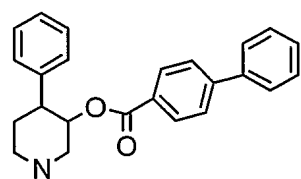
5

In yet another embodiment, the invention encompasses compounds contemplated by Formula I, and more specifically those preferred compounds as shown below. Possible substitutions off of the imidazole ring include aryl and alkyl groups.

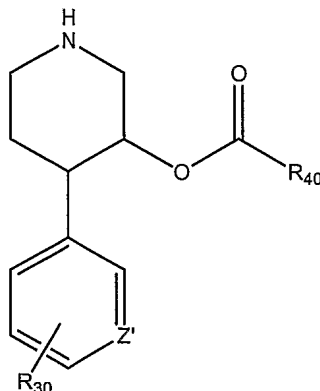


10

5 In yet another embodiment, the invention encompasses compounds contemplated by Formula I, and more specifically those preferred compounds as shown below.

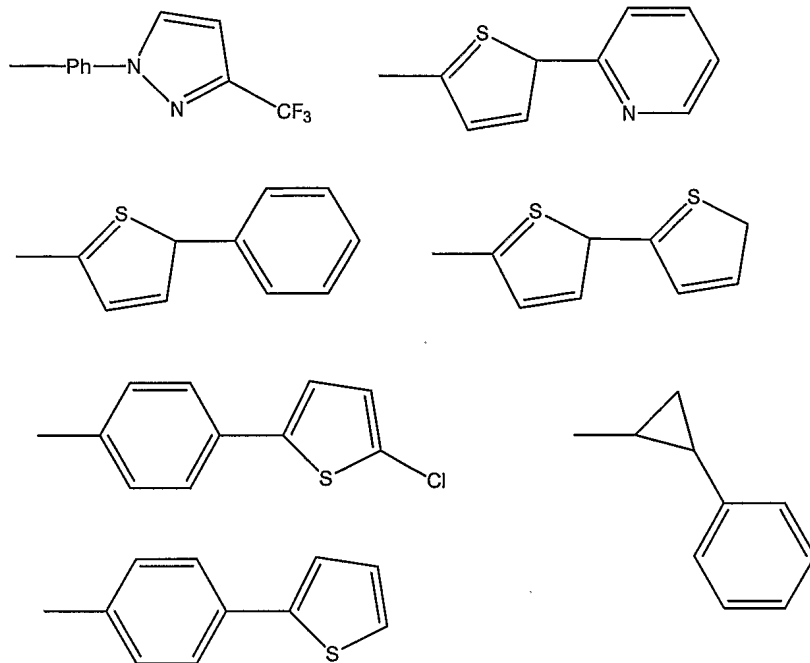


5 In another aspect, the invention provides compounds of the formula:



10 or a pharmaceutically acceptable salt or ester thereof,
wherein Z' is CH or N;
wherein R₃₀ is absent, -OH, or halo;
wherein R₄₀ is C₁₋₈ alkyl, C₁₋₈ alkoxy, aryl, substituted aryl,
heteroaryl, substituted heteroaryl, heterocycl, substituted
15 heterocycl, phenyl, substituted phenyl, C₁₋₈ alkyl-phenyl, or C₁₋₈
alkyl-substituted phenyl.

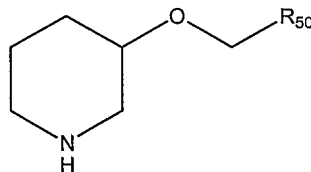
More preferably, R₃₀ is absent, -OH, or Cl, Br, I or F;
further R₄₀ is selected from the group consisting essentially of
-CH₃, -CH₂CH₂-Ph-O-CH₃, -Ph-Ph-CO₂H, -Ph-Ph-OCH₃, -Ph-Ph-C(CH₃)₃,
20 -Ph-Ph-OCF₃, -Ph-Ph-F, -Ph-C(=O)-Ph, -Ph-Ph-CN, -Ph-Ph-NH₂, -Ph-
C(CH₃)₃, -CH(CH₂CH₃)(CH₂CH₂CH₂CH₃), -CH₂CH₂Ph, -Ph-O-Ph,
naphthalene, -Ph-Ph-Cl, -Ph-(OCH₃)₂, -CH₂-Ph-OCH₃, -CH₂-Ph, -Ph-
Ph-S(=O)₂CH₃, -Ph-Ph, pyridyl, Ph, Ph-I, -Ph-Ph-S-CH₃, -Ph-
pyridyl, -Ph-NH₂, -Ph-NO₂, -Ph-CF₃, -Ph-CH₃, -Ph-Ph-CF₃, -Ph-Ph-
25 (OCH₃)₂, -Ph-OCH₃, -Ph-CN, -CH₂-O-Ph, -Ph-OCF₃, -CH₂-PhF₂,



5

In a more preferred embodiment Z is CH. In accordance with this embodiment, a single substituent attached to a Ph-ring is in the ortho position; alternatively, a single substituent attached to a Ph-ring is in the meta position; also alternatively, a single substituent attached to a Ph-ring is in the para position. Further, di-substituents attached to a Ph-ring are in di-meta positions; alternatively, di-substituents attached to a Ph-ring are in a meta and para position.

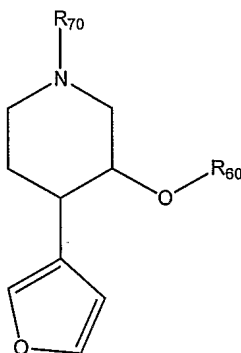
In another aspect, the invention includes compounds of the formula



wherein R₅₀ is aryl or substituted aryl. More preferably, R₅₀ is selected from the group consisting of -Ph, -PhBr, -Ph-C(CH₃)₃, -PhF, -PhCl, -PhCN, naphthyl, -Ph(CH₃)₂, -Ph-Ph, -PhI, -Ph-OCH₃, -PhCl₂, -Ph-PhCN, and -Ph-(OCH₃)₂. In accordance with this embodiment, a single substituent attached to a Ph-ring is in the

5 ortho position; alternatively, a single substituent attached to a Ph-ring is in the meta position; also alternatively, a single substituent attached to a Ph-ring is in the para position. Further, di-substituents attached to a Ph-ring are in di-meta positions; alternatively, di-substituents attached to a Ph-ring
10 are in a meta and para position.

In yet another embodiment, the invention includes compounds of the formula



15 wherein R₆₀ is aryl, substituted aryl, C₁₋₆ alkyl, C₁₋₆ alkenyl, C₁₋₆ cycloalkyl, C₁₋₆ alkyl-C₁₋₆ cycloalkyl; and wherein R₇₀ is t-butoxycarbonyl or H. More preferably, R₆₀ is selected from the group consisting of -Ph, -Ph-Ph, naphthyl, -Ph-
20 O-Ph, -PhC(CH₃)₃, anthracinyl, -PhCH₃, -Ph(OCH₃)₂, -PhBr, -PhS(=O)₂CH₃, C(=CH₂)CH₃, cyclohexyl, -CH₂-cyclohexyl, -CH(CH₃)₂, and -CH(CH₂CH₃)₂. In accordance with this embodiment, a single substituent attached to a Ph-ring is in the ortho position; alternatively, a single substituent attached to a Ph-ring is in
25 the meta position; also alternatively, a single substituent attached to a Ph-ring is in the para position. Further, di-substituents attached to a Ph-ring are in di-meta positions; alternatively, di-substituents attached to a Ph-ring are in a meta and para position.

30 The compounds of the present invention, and pharmaceutically acceptable salts or esters thereof, are useful

5 for treating humans who have Alzheimer's disease, for helping
prevent or delay the onset of Alzheimer's disease, for treating
patients with mild cognitive impairment (MCI) and preventing or
delaying the onset of Alzheimer's disease in those who would
progress from MCI to AD, for treating Down's syndrome, for
10 treating humans who have Hereditary Cerebral Hemorrhage with
Amyloidosis of the Dutch-Type, for treating cerebral amyloid
angiopathy and preventing its potential consequences, i.e.
single and recurrent lobar hemorrhages, for treating other
degenerative dementias, including dementias of mixed vascular
15 and degenerative origin, dementia associated with Parkinson's
disease, dementia associated with progressive supranuclear
palsy, dementia associated with cortical basal degeneration,
diffuse Lewy body type of Alzheimer's disease. It is preferred
that the disease is Alzheimer's disease.

20 The compounds of the present invention are also useful to
inhibit beta-secretase and reduce or inhibit the formation of
plaque.

When treating these diseases, compounds of the present
invention can either be used individually or together as is best
25 for the patient.

With regard to these diseases the term "treating" means
that compounds of the present invention can be used in humans
with existing disease. The compounds of the present invention
will not necessarily cure the patient who has the disease but
30 will delay or slow the progression of the disease thereby giving
the individual a more useful life span.

The term "preventing" means that that if the compounds of
the present invention are administered to those who do not now
have the disease but who would normally get the disease or be at
35 increased risk for the disease, they will not get the disease.
In addition, "preventing" also includes delaying the development
of the disease in an individual who will ultimately get the

5 disease or would be at risk for the disease. By delaying the onset of the disease, compounds of the present invention have prevented the individual from getting the disease during the period in which the individual would normally have gotten the disease or reduce the rate of development of the disease or some
10 of its effects but for the administration of compounds of the present invention up to the time the individual ultimately gets the disease.

In treating or preventing the above diseases the compounds of the present invention are administered in a therapeutically
15 effective amount. The therapeutically effective amount will vary depending on the particular compound used and the route of administration as is known to those skilled in the art.

In treating a patient with any of the diagnosed above conditions a physician should begin administration of one or
20 more of the compounds of the present invention immediately and continue indefinitely.

In treating patients who do not at the present have Alzheimer's disease, but who are believed to be at substantial risk for getting Alzheimer's disease in the future, the
25 physician should start treatment when the patient first experiences early pre-Alzheimer's symptoms such as, memory or cognitive problems associated with aging. In addition, there are some patients who are at high risk because of having the genetic marker APOE4 which is predictive for Alzheimer's disease. In
30 these situations, even though the patient does not have the disease, the administration of the compounds of the present invention should be started before disease symptoms appear and treatment continued indefinitely to prevent or delay them from possibly getting the disease.

35 The compounds of the present invention can be administered orally, parenterally (IV, IM, depo-IM, SQ and depo-SQ), sublingually, intranasally (inhalation), intrathecally,

5 topically and rectally. The invention here is the compounds of the present invention. There is nothing new about the routes of administration nor the dosage forms. Dosage forms known to those skilled in the art are suitable for delivery of the compounds of the present invention.

10 When administered orally, the compounds of the present invention can be administered in usual dosage forms for oral administration as is well known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as
15 solutions, suspensions and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained release type so that the compounds of the present invention need to be administered only once or twice daily.

The oral dosage forms are administered to the patient one
20 thru four times daily. It is preferred that the compounds of the present invention be administered either three or fewer time, more preferably once or twice daily. Hence, it is preferred that the compounds of the present invention be administered in solid dosage form and further it is preferred that the solid dosage
25 form be a sustained release form which permits once or twice daily dosing. It is preferred that whatever dosage form is used, that it be designed so as to protect the compounds of the present invention from the acidic environment of the stomach. Enteric coated tablets are well known to those skilled in the
30 art. In addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also well known to those skilled in the art. When administered orally the therapeutically effective amount is from about 0.1 mg/day to about 3,000 mg/day, preferably about 1,000 mg/day. It is more preferred that the
35 oral dosage is from about 1 mg/day to about 100 mg/day. It is more preferred that the oral dosage is from about 5 mg/day to about 50 mg/day. It is understood that while a patient may be

5 started on one dose, that dose may have to be varied over time as the patient's condition changes.

In addition, the compounds of the present invention can be administered parenterally. When administered parenterally they can be administered IV, IM, depo-IM, SQ or depo-SQ. When
10 administered parenterally, the compounds of the present invention should deliver a therapeutically effective amount about 0.5 to about 100 mg/day, preferably from about 5 to about 50 mg daily. When a depo formulation is used for injection once a month or once every two weeks, the
15 dose should be about 0.5 mg/day to about 50 mg/day or on a monthly amount the dose for one month should be from about 15 mg to about 1,500 mg. Because of the forgetfulness of the patients with Alzheimer's disease, it is preferred that the parenteral dosage form be a depo-IM injection.

20 The compounds of the present invention can be given sublingually. When given sublingually, the compounds of the present invention should be given one thru four times daily in the same amount as for IM administration.

The compounds of the present invention can be given
25 intranasally. When given by this route of administration, the appropriate dosage forms are a nasal spray or dry powder as is known to those skilled in the art. The dosage of the compounds of the present invention for intranasal administration is the same as for IM administration.

30 The compounds of the present invention can be given intrathecally. When given by this route of administration the appropriate dosage form can be a parenteral dosage form as is known to those skilled in the art. The dosage of the compounds of the present invention for intrathecal administration is the
35 same as for IM administration.

The compounds of the present invention can be given topically. When given by this route of administration, the

5 appropriate dosage form is a cream, ointment or patch. Because
of the amount of the compounds of the present invention needed
to administered the patch is preferred. Further, two or more
patches may be needed. When administered topically, the dosage
is from about 0.5 mg/day to about 200
10 mg/day. However, the amount that can be delivered by a patch is
limited. Therefore, two or more patches may be required. The
number and size of the patch is not important, what is important
is that a therapeutically effective amount of the compounds of
the present invention be delivered as is known to those skilled
15 in the art. The compounds of the present invention can be
administered rectally by suppository as is known to those
skilled in the art. When administered by suppository, the
therapeutically effective amount is from about 0.5 mg to about
500 mg.

20 The compounds of the present invention can be administered
by implants as is known to those skilled in the art. When
administering a compound of the present invention by implant,
the therapeutically effective amount is the same as for depot
administration.

25 Again, the invention here is the compounds of the present
invention of the present invention. There is nothing novel about
the route of administration nor the dosage forms for
administering the compounds of the present invention. Given a
particular compounds of the present invention, and a desired
30 dosage form, one skilled in the art would know how to prepare
the appropriate dosage form for the compounds of the present
invention.

The compounds of the present invention are used in the same
manner by the same routes of administration using the same
35 pharmaceutical dosage forms and at the same dosing schedule for
treating patients with MCI (mild cognitive impairment) and
preventing or delaying the onset of Alzheimer's disease in those

5 who would progress from MCI to AD, for treating Down's syndrome,
for treating humans who have Hereditary Cerebral Hemorrhage with
Amyloidosis of the Dutch-Type, for treating cerebral amyloid
angiopathy and preventing its potential consequences, i.e.
single and recurrent lobar hemorrhages, for treating other
10 degenerative dementias, including dementias of mixed vascular
and degenerative origin, dementia associated with Parkinson's
disease, dementia associated with progressive supranuclear
palsy,
dementia associated with cortical basal degeneration, diffuse
15 Lewy body type of Alzheimer's disease.

The compounds of the present invention can be used with
each other or with other agents used to treat or prevent the
conditions listed above. Such agents include gamma-secretase
inhibitors, anti-amyloid vaccines and pharmaceutical agents such
20 as donepezil hydrochloride (ARICEPT Tablets), tacrine
hydrochloride (COGNEX Capsules) or other acetylcholine esterase
inhibitors and with direct or indirect
neurotropic agents of the future.

In addition, the compounds of the present invention can
25 also be used with inhibitors of P-glycoprotein (P-gp). The use of
P-gp inhibitors is known to those skilled in the art. See for
example, Cancer Research, 53, 4595-4602 (1993), Clin. Cancer
Res., 2, 7-12 (1996), Cancer Research, 56, 4171-4179 (1996),
International Publications WO99/64001 and WO01/10387. The
30 important thing is that the blood level of the P-gp inhibitor be
such that it exerts its effect in inhibiting P-gp from
decreasing brain blood levels of the compounds of the present
invention. To that end the P-gp inhibitor and the compounds of
the present invention can be administered at the same time, by
35 the same or different route of administration, or at different
times. The important thing is not the time of administration
but having an effective blood level of the P-gp inhibitor.

5 Suitable P-gp inhibitors include cyclosporin A, verapamil, tamoxifen, quinidine, Vitamin E-TGPS, ritonavir, megestrol acetate, progesterone, rapamycin, 10,11-methanodibenzosuberane, phenothiazines, acridine derivatives such as GF120918, FK506, VX-710, LY335979, PSC-833, GF-102,918 and other steroids. It is
10 to be understood that additional agents will be found that do the same function and are also considered to be useful.

 The P-gp inhibitors can be administered orally, parenterally, (IV, IM, IM-depo, SQ, SQ-depo), topically, sublingually, rectally, intranasally, intrathecally and by
15 implant.

 The therapeutically effective amount of the P-gp inhibitors is from about 0.1 to about 300 mg/kg/day, preferably about 0.1 to about 150 mg/kg daily. It is understood that while a patient may be started on one dose, that dose may have to be varied over
20 time as the patient's condition changes.

 When administered orally, the P-gp inhibitors can be administered in usual dosage forms for oral administration as is known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as
25 well as liquid dosage forms such as solutions, suspensions and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained release type so that the P-gp inhibitors need to be administered only once or twice daily. The oral dosage forms are administered to the patient one thru
30 four times daily. It is preferred that the P-gp inhibitors be administered either three or fewer times a day, more preferably once or twice daily. Hence, it is preferred that the P-gp inhibitors be administered in solid dosage form and further it is preferred that the solid dosage form be a sustained release
35 form which permits once or twice daily dosing. It is preferred that what ever dosage form is used, that it be designed so as to protect the P-gp inhibitors from the acidic environment of the

5 stomach. Enteric coated tablets are well known to those skilled in the art. In addition, capsules filled with small spheres each coated to protect From the acidic stomach, are also well known to those skilled in the art.

10 In addition, the P-gp inhibitors can be administered parenterally. When administered parenterally they can be administered IV, IM, depo-IM, SQ or depo-SQ. The P-gp inhibitors can be given sublingually. When given sublingually, the P-gp inhibitors should be given one thru four times daily in the same amount as for IM administration.

15 The P-gp inhibitors can be given intranasally. When given by this route of administration, the appropriate dosage forms are a nasal spray or dry powder as is known to those skilled in the art. The dosage of the P-gp inhibitors for intranasal administration is the same as for IM administration.

20 The P-gp inhibitors can be given intrathecally. When given by this route of administration the appropriate dosage form can be a parenteral dosage form as is known to those skilled in the art.

The P-gp inhibitors can be given topically. When given by
25 this route of administration, the appropriate dosage form is a cream, ointment or patch. Because of the amount of the P-gp inhibitors needed to be administered the patch is preferred. However, the amount that can be delivered by a patch is limited. Therefore, two or more patches may be required. The number and
30 size of the patch is not important, what is important is that a therapeutically effective amount of the P-gp inhibitors be delivered as is known to those skilled in the art.

The P-gp inhibitors can be administered rectally by suppository as is known to those skilled in the art.

35 The P-gp inhibitors can be administered by implants as is known to those skilled in the art.

5 There is nothing novel about the route of administration nor the dosage forms for administering the P-gp inhibitors. Given a particular P-gp inhibitor, and a desired dosage form, one skilled in the art would know how to prepare the appropriate dosage form for the P-gp inhibitor.

10 It should be apparent to one skilled in the art that the exact dosage and frequency of administration will depend on the particular compounds of the present invention administered, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical
15 condition of the particular patient, other medication the individual may be taking as is well known to those skilled in the art.

 The compounds of the present invention are also useful to inhibit beta-secretase and reduce or inhibit the formation of
20 plaque.

Inhibition of APP Cleavage

 The compounds of the invention inhibit cleavage of APP between Met595 and Asp596 numbered for the APP695 isoform, or a mutant thereof, or at a corresponding site of a different
25 isoform, such as APP751 or APP770, or a mutant thereof (sometimes referred to as the "beta secretase site". While not wishing to be bound by a particular theory, inhibition of beta-secretase activity is thought to inhibit production of beta amyloid peptide (A-beta or Abeta). Inhibitory activity is
30 demonstrated in one of a variety of inhibition assays, whereby cleavage of an APP substrate in the presence of A-beta-secretase enzyme is analyzed in the presence of the inhibitory compound, under conditions normally sufficient to result in cleavage at the beta-secretase cleavage site. Reduction of APP cleavage at
35 the beta-secretase cleavage site compared with an untreated or inactive control is correlated with inhibitory activity. Assay systems that can be used to demonstrate efficacy of the compound

5 inhibitors of the invention are known. Representative assay systems are described, for example, in U.S. Patents No. 5,942,400, 5,744,346, as well as in the examples below.

The enzymatic activity of beta-secretase and the production of Abeta can be analyzed in vitro or in vivo, using natural,
10 mutated, and/or synthetic APP substrates, natural, mutated, and/or synthetic enzyme, and the test compound. The analysis may involve primary or secondary cells expressing native, mutant, and/or synthetic APP and enzyme, or may utilize transgenic animal models expressing the substrate and
15 enzyme. Detection of enzymatic activity can be by analysis of one or more of the cleavage products, for example, by immunoassay, flurometric or chromogenic assay, HPLC, or other means of detection. Inhibitory compounds are determined as those having the ability to decrease the amount of beta-secretase
20 cleavage product produced in comparison to a control, where beta-secretase mediated cleavage in the reaction system is observed and measured in the absence of inhibitory compounds.

Beta-secretase

Various forms of beta-secretase enzyme are known, and are
25 available and useful for assay of enzyme activity and inhibition of enzyme activity. These include native, recombinant, and synthetic forms of the enzyme. Human beta-secretase is known as Beta Site APP Cleaving Enzyme (BACE), Asp2, and memapsin 2, and has been characterized, for example, in U.S. Patent 5,744,346
30 and published PCT patent applications WO98/22597, WO00/03819, WO01/23533, and WO00/17369, as well as in literature publications (Mol.Cell.Neurosci. 14:419-427 (1999); Science 286:735-741 (1999); Nature 402:533-537 (1999); Nature 40:537-540 (1999); and PNAS USA 97:1456-1460 (2000)). Synthetic forms of
35 the enzyme have also been described (WO98/22597 and WO00/17369). Beta-secretase can be extracted and purified from human brain .

5 tissue and can be produced in cells, for example mammalian cells expressing recombinant enzyme.

Preferred compounds are effective to inhibit 50% of beta-secretase enzymatic activity at a concentration of less than about 50 micromolar, preferably at a concentration of less than
10 about 10 micromolar, more preferably less than about 1 micromolar, and most preferably less than about 10 nanomolar.

APP substrate

Assays that demonstrate inhibition of beta-secretase-mediated cleavage of APP can utilize any of the known forms of
15 APP, including the 695 amino acid "normal" isotype described in Nature 325:733-6 (1987), the 770 amino acid isotype described Nature 331:530-532 (1981), and variants such as the Swedish Mutation (KM670-1NL) (APP-SW), the London Mutation (V7176F), and others. See, for example U.S. Patent 5,766,846 and also Nature
20 Genet. 1:233-234 (1992), for a review of known variant mutations. Additional useful substrates include the dibasic amino acid modification, APP-KK disclosed, for example, in WO 00/17369, fragments of APP, and synthetic peptides containing the beta-secretase cleavage site, wild type (WT) or mutated
25 form, e.g., SW, as described, for example, in U.S. Patent 5,942,400 and WO00/03819.

The APP substrate contains the beta-secretase cleavage site of APP (KM-DA or NL-DA) for example, a complete APP peptide or variant, an APP fragment, a recombinant or synthetic APP, or a
30 fusion peptide. Preferably, the fusion peptide includes the beta-secretase cleavage site fused to a peptide having a moiety useful for enzymatic assay, for example, having isolation and/or detection properties. A useful moiety may be an antigenic epitope for antibody binding, a label or other detection moiety,
35 a binding substrate, and the like.

5 Antibodies

Products characteristic of APP cleavage can be measured by immunoassay using various antibodies, as described, for example, in Neuro. Lett. 249:21-4 (1999) and in U.S. Patent 5,612,486. Useful antibodies to detect Abeta include, for example, the
10 monoclonal antibody 6E10 (Senetek, St. Louis, MO) that specifically recognizes an epitope on amino acids 1-16 of the Abeta peptide; antibodies 162 and 164 (New York State Institute for Basic Research, Staten Island, NY) that are specific for human A-beta 1-40 and 1-42, respectively; and antibodies that
15 recognize the junction region of beta-amyloid peptide, the site between residues 16 and 17, as described in U.S. Patent 5,593,846. Antibodies raised against a synthetic peptide of residues 591 to 596 of APP and SW192 antibody raised against 590-596 of the Swedish mutation are also useful in immunoassay
20 of APP and its cleavage products, as described in U.S. Patents 5,604,102 and 5,721,130.

Assay Systems

Assays for determining APP cleavage at the beta-secretase cleavage site are well known in the art. Exemplary assays, are
25 described, for example, in U.S. Patent 5,744,346 and 5,942,400, and described in the EXAMPLES below.

Cell free assays

Exemplary assays that can be used to demonstrate the inhibitory activity of the compounds of the invention are
30 described, for example, in WO00/17369, WO 00/03819, and U.S. Patents 5,942,400 and 5,744,346. Such assays can be performed in cell-free incubations or in cellular incubations using cells expressing A-beta- secretase and an APP substrate having A-beta-secretase cleavage site.

35 An APP substrate containing the beat-secretase cleavage site of APP, for example, a complete APP or variant, an APP fragment, or a recombinant or synthetic APP substrate containing

5 the amino acid sequence: KM-DA or NL-DA, is incubated in the presence of beta-secretase enzyme, a fragment thereof, or a synthetic or recombinant polypeptide variant having beta-secretase activity and effective to cleave the beta-secretase cleavage site of APP, under incubation conditions suitable for
10 the cleavage activity of the enzyme. Suitable substrates optionally include derivatives that may be fusion proteins or peptides that contain the substrate peptide and a modification useful to facilitate the purification or detection of the peptide or its beta-secretase cleavage products. Useful
15 modifications include the insertion of a known antigenic epitope for antibody binding; the linking of a label or detectable moiety, the linking of a binding substrate, and the like.

Suitable incubation conditions for a cell-free in vitro
20 assay include, for example: approximately 200 nanomolar to 10 micromolar substrate, approximately 10 to 200 picomolar enzyme, and approximately 0.1 nanomolar to 10 micromolar inhibitor compound, in aqueous solution, at an approximate pH of 4-7, at approximately 37°C, for a time period of approximately 10
25 minutes to 3 hours. These incubation conditions are exemplary only, and can be varied as required for the particular assay components and/or desired measurement system. Optimization of the incubation conditions for the particular assay components should account for the specific beta-secretase enzyme used and
30 its pH optimum, any additional enzymes and/or markers that might be used in the assay, and the like. Such optimization is routine and will not require undue experimentation.

One useful assay utilizes a fusion peptide having maltose binding protein (MBP) fused to the C-terminal 125 amino acids of
35 APP-SW. The MBP portion is captured on an assay substrate by anti-MBP capture antibody. Incubation of the captured fusion protein in the presence of beta-secretase results in cleavage of

5 the substrate at the beta-secretase cleavage site. Analysis of
the cleavage activity can be,
for example, by immunoassay of cleavage products. One such
immunoassay detects a unique epitope exposed at the carboxy
terminus of the cleaved fusion protein, for example, using the
10 antibody SW192. This assay is described, for example, in U.S.
Patent 5,942,400.

Cellular assay

Numerous cell-based assays can be used to analyze beta-
secretase activity and/or processing of APP to release A-beta.
15 Contact of an APP substrate with A-beta- secretase enzyme within
the cell and in the presence or absence of a compound inhibitor
of the invention can be used to demonstrate beta-secretase
inhibitory activity of the compound. Preferably, assay in the
presence of a useful inhibitory compound provides at least about
20 30%, most preferably at least about 50% inhibition of the
enzymatic activity, as compared with a non-inhibited control.

In one embodiment, cells that naturally express beta-
secretase are used. Alternatively, cells are modified to express
a recombinant beta-secretase or synthetic variant enzyme as
25 discussed above. The APP substrate may be added to the culture
medium and is preferably expressed in the cells. Cells that
naturally express APP, variant or mutant forms of APP, or cells
transformed to express an isoform of APP, mutant or variant APP,
recombinant or synthetic APP, APP fragment, or synthetic APP
30 peptide or fusion protein containing the beta-secretase APP
cleavage site can be used, provided that the expressed APP is
permitted to contact the enzyme and enzymatic cleavage activity
can be analyzed.

Human cell lines that normally process Abeta from APP
35 provide a useful means to assay inhibitory activities of the
compounds of the invention. Production and release of A-beta
and/or other cleavage products into the culture medium can be

5 measured, for example by immunoassay, such as Western blot or enzyme-linked immunoassay (EIA) such as by ELISA.

Cells expressing an APP substrate and an active beta-secretase can be incubated in the presence of a compound inhibitor to demonstrate inhibition of enzymatic activity as
10 compared with a control. Activity of beta-secretase can be measured by analysis of one or more cleavage products of the APP substrate. For example, inhibition of beta-secretase activity against the substrate APP would be expected to decrease release of specific beta-secretase induced
15 APP cleavage products such as Abeta.

Although both neural and non-neural cells process and release A-beta, levels of endogenous beta-secretase activity are low and often difficult to detect by EIA. The use of cell types known to have enhanced beta-secretase activity, enhanced
20 processing of APP to Abeta, and/or enhanced production of A-beta are therefore preferred. For example, transfection of cells with the Swedish Mutant form of APP (APP-SW); with APP-KK; or with APP-SW-KK provides cells having enhanced beta-secretase activity and producing amounts of A-beta that can be readily measured.

25 In such assays, for example, the cells expressing APP and beta-secretase are incubated in a culture medium under conditions suitable for beta-secretase enzymatic activity at its cleavage site on the APP substrate. On exposure of the cells to the compound inhibitor, the amount of Abeta released into the
30 medium and/or the amount of CTF99 fragments of APP in the cell lysates is reduced as compared with the control. The cleavage products of APP can be analyzed, for example, by immune reactions with specific antibodies, as discussed above.

Preferred cells for analysis of beta-secretase activity
35 include primary human neuronal cells, primary transgenic animal neuronal cells where the transgene is APP,

5 and other cells such as those of a stable 293 cell line
expressing APP, for example,
APP-SW.

In vivo assays: animal models

Various animal models can be used to analyze beta-secretase
10 activity and /or processing of APP to release Abeta, as
described above. For example, transgenic animals expressing APP
substrate and beta-secretase enzyme can be used to demonstrate
inhibitory activity of the compounds of the invention. Certain
transgenic animal models have been described, for example, in
15 U.S. Patents 5,877,399, 5,612,486, 5,387,742, 5,720,936,
5,850,003, 5,877,015 and 5,811,633, and Nature 373:523 (1995)).
Preferred are animals that exhibit characteristics associated
with the pathophysiology of AD. Administration of the compound
inhibitors of the invention to the transgenic mice described
20 herein provides an alternative method for demonstrating the
inhibitory activity of the compounds. Administration of the
compounds in a pharmaceutically effective carrier and via an
administrative route that reaches the target tissue in an
appropriate therapeutic amount is also preferred.

25 Inhibition of beta-secretase mediated cleavage of APP at
the beta-secretase cleavage site and of Abeta release can be
analyzed in these animals by measure of cleavage fragments in
the animal's body fluids such as cerebral fluid or tissues.
Analysis of brain tissues for Abeta deposits or plaques is
30 preferred.

On contacting an APP substrate with A-beta-secretase enzyme
in the presence of an inhibitory compound of the invention and
under conditions sufficient to permit enzymatic mediated
cleavage of APP and/or release of Abeta from the substrate, the
35 compounds of the invention are effective to reduce beta-
secretase-mediated cleavage of APP at the beta-secretase
cleavage site and/or effective to reduce released amounts of

5 Abeta. Where such contacting is the administration of the
inhibitory compounds of the invention to an animal model, for
example, as described above, the compounds are effective to
reduce Abeta deposition in brain tissues of the animal, and to
reduce the number and/or size of beta amyloid plaques. Where
10 such administration is to a human subject, the compounds are
effective to inhibit or slow the progression of disease
characterized by enhanced amounts of Abeta to slow the
progression of AD in the, and/or to prevent onset or development
of AD in a patient at risk for the disease.

15 Unless defined otherwise, all scientific and technical
terms used herein have the same meaning as commonly understood
by one of skill in the art to which this invention belongs.

Definitions And Conventions

The definitions and explanations below are for the terms as
20 used throughout this entire document including both the
specification and the claims.

Definitions

Pharmaceutically acceptable refers to those properties
and/or substances which are acceptable to the patient from a
25 pharmacological/toxicological point of view and to the
manufacturing pharmaceutical chemist from a physical/chemical
point of view regarding composition, formulation, stability,
patient acceptance and bioavailability.

AD refers to Alzheimer's disease.

30 APP, amyloid precursor protein, is defined as any APP
polypeptide, including APP variants, mutations, and isoforms,
for example, as disclosed in U.S. Patent 5,766,846.

A-beta (or Abeta), amyloid beta peptide, is defined as any
peptide resulting from beta-secretase mediated cleavage of APP,
35 including peptides of 39, 40, 41, 42, and 43 amino acids, and
extending from the beta-secretase cleavage site to amino acids
39, 40, 41, 42, or 43.

5 Beta-secretase (beta-secretase, BACE1, Asp2, Memapsin 2) is an aspartyl protease that mediates cleavage of APP at the amino-terminal edge of Abeta. Human beta-secretase is described, for example, in WO00/17369.

DMSO refers to dimethyl sulfoxide.

10 All temperatures are in degrees Centigrade.

HPLC refers to high pressure liquid chromatography.

BOC refers to 1,1-dimethylethoxy carbonyl or *t*-butoxycarbonyl, -CO-O-C(CH₃)₃.

Protecting group refers to *t*-butoxycarbonyl,

15 benzyloxycarbonyl, formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-ethoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-
20 chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-
25 (*p*-toluyl)prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-
30 (triphenylphosphino)ethoxycarbonyl, fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl,
35 cyclopropylmethoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl and 1-piperidyloxycarbonyl, 9-fluorenylmethyl carbonate,

5 -CH-CH=CH₂ and phenyl-C(=N-)-H.

Saline refers to an aqueous saturated sodium chloride solution.

Chromatography (column and flash chromatography) refers to purification/separation of compounds expressed as (support,
10 eluent). It is understood that the appropriate fractions are pooled and concentrated to give the desired compound(s).

Pharmaceutically acceptable refers to those properties and/or substances that are acceptable to the patient from a pharmacological/toxicological point of view and to the
15 manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

A therapeutically effective amount is defined as an amount effective to reduce or lessen at least one symptom of the
20 disease being treated or to reduce or delay onset of one or more clinical markers or symptoms of the disease.

It should be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates
25 otherwise. Thus, for example, reference to a composition containing "a compound" includes a mixture of two or more compounds. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

30 Unless defined otherwise, all scientific and technical terms used herein have the same meaning as commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are hereby incorporated by reference for all purposes.

35 By "alkyl" and "C₁-C₆ alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, n-butyl, sec-

5 butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. It is understood that in cases where an alkyl chain of a substituent (e.g. of an alkyl, alkoxy or alkenyl group) is shorter or longer than 6 carbons, it will be so indicated in the second "C" as, for
10 example, "C₁-C₁₀" indicates a maximum of 10 carbons.

By "alkoxy" and "C₁-C₆ alkoxy" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, attached through at least one divalent oxygen atom, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy,
15 sec-butoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, hexoxy, and 3-methylpentoxy.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

"Alkenyl" and "C₂-C₆ alkenyl" means straight and branched
20 hydrocarbon radicals having from 2 to 6 carbon atoms and from one to three double bonds and includes, for example, ethenyl, propenyl, 1-but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl and the like.

"Alkynyl" and "C₂-C₆ alkynyl" means straight and branched
25 hydrocarbon radicals having from 2 to 6 carbon atoms and one or two triple bonds and includes ethynyl, propynyl, butynyl, pentyn-2-yl and the like.

As used herein, the term "cycloalkyl" refers to saturated carbocyclic radicals having three to twelve carbon atoms. The
30 cycloalkyl can be monocyclic, or a polycyclic fused system. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Preferred cycloalkyl groups are cyclopentyl, cyclohexyl, and cycloheptyl. The cycloalkyl groups herein are unsubstituted or, as specified, substituted in one or
35 more substitutable positions with various groups. For example, such cycloalkyl groups may be optionally substituted with, for example, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano,

5 nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl or di(C₁-C₆)alkylamino(C₁-C₆)alkyl.

By "aryl" is meant an aromatic carbocyclic group having a
10 single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl), which is optionally mono-, di-, or trisubstituted. Preferred aryl groups of the present invention are phenyl, 1-naphthyl, 2-naphthyl,
15 indanyl, indenyl, dihydronaphthyl, tetralinyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl. The aryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such aryl groups may be optionally substituted with, for example, C₁-
20 C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl or di(C₁-C₆)alkylamino(C₁-C₆)alkyl.

25 By "heteroaryl" is meant one or more aromatic ring systems of 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Preferred heteroaryl groups of the present invention include pyridinyl, pyrimidinyl,
30 quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl,
35 oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanlyl,

5 chromanyl, tetrahydroisoquinolinyl, isoindolinyl,
isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl,
isobenzothienyl, benzoxazolyl, pyridopyridinyl,
benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl,
benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl,
10 pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl,
dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl,
dihydrobenzisoethiazinyl, benzopyranyl, benzothiopyranyl,
coumarinyl, isocoumarinyl, chromonyl, chromanonyl, pyridinyl-N-
oxide, tetrahydroquinolinyl, dihydroquinolinyl,
15 dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl,
dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl,
benzoxazolinonyl, pyrrolyl N-oxide,, pyrimidinyl N-oxide,
pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide,
indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide,
20 quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-
oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide,
thiazolyl N-oxide, indoliziny N-oxide, indazolyl N-oxide,
benzothiazolyl N-oxide, benzimidazolyl N-oxide, pyrrolyl N-
oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl N-
25 oxide, tetrazolyl N-oxide, benzothiopyranyl S-oxide,
benzothiopyranyl S,S-dioxide. The heteroaryl groups herein are
unsubstituted or, as specified, substituted in one or more
substitutable positions with various groups. For example, such
heteroaryl groups may be optionally substituted with, for
30 example, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano,
nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-
C₆alkenyl, C₂-C₆alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy,
amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl or di(C₁-
C₆)alkylamino(C₁-C₆)alkyl.

35 By "heterocycle", "heterocycloalkyl" or "heterocyclyl" is
meant one or more carbocyclic ring systems of 4-, 5-, 6-, or 7-
membered rings which includes fused ring systems of 9-11 atoms

5 containing at least one and up to four heteroatoms selected from
nitrogen, oxygen, or sulfur. Preferred heterocycles of the
present invention include morpholinyl, thiomorpholinyl,
thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide,
piperazinyl, homopiperazinyl, pyrrolidinyl, pyrrolinyl,
10 tetrahydropyranyl, piperidinyl, tetrahydrofuranyl,
tetrahydrothienyl, homopiperidinyl, homomorpholinyl,
homothiomorpholinyl, homothiomorpholinyl S,S-dioxide,
oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl,
dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl,
15 dihydrofuryl, dihydropyranyl, tetrahydrothienyl S-oxide,
tetrahydrothienyl S,S-dioxide and homothiomorpholinyl S-oxide.
The heterocycle groups herein are unsubstituted or, as
specified, substituted in one or more substitutable positions
with various groups. For example, such heterocycle groups may
20 be optionally substituted with, for example, C₁-C₆ alkyl, C₁-C₆
alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-
C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆alkenyl, C₂-C₆alkynyl,
C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-
C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl or =O.

25 Modes of Preparation

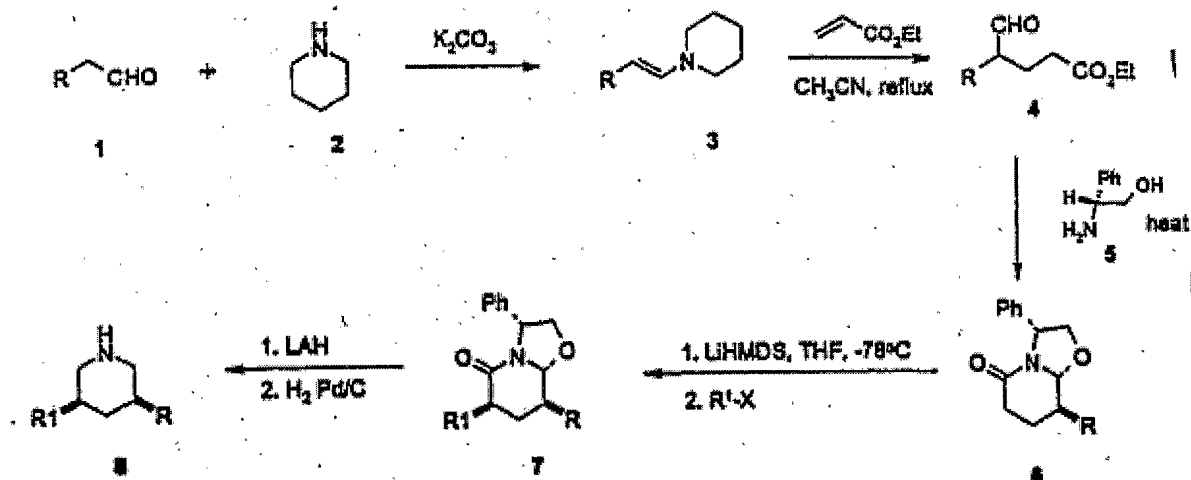
Compounds of the invention can be prepared utilizing a
variety of known chemical transformations. The compounds of the
invention can be prepared by one skilled in the art without more
just by knowing the chemical structure of the compound. The
30 chemistry is known to those skilled in the art. In fact, there
is more than one process to prepare the compounds of the
invention. Exemplary methods of preparation can be found in the
art. For example, see *A Short Formal Synthesis of Paroxetine*.
Diastereoselective Cuprate Addition of a Chiral Racemic Olefinic
35 *Amido Ester*, Coss, J., et al., Tetrahedron Letters, 42 (2001,
7805-7807; *Solid-Phase Synthesis of Aspartic Peptidase Inhibitors*:
3-Alkoxy-4-Aryl Piperidines, Bursavich, Matthew, et. al.,

5 Organic Letters, 2001, Vol. 3, No. 17, 2625-2628; and *From Peptides to Non-Peptide Peptidomimetics: Design and Synthesis of New Piperidine Inhibitors of Aspartic Peptidases*, Bursavich, Matthew, et. al., Organic Letters, 2001, Vol. 3, No. 15, 2317-2320; and the references cited therein, all incorporated in by
10 the entirety.

In addition to the methods above, a variety of additional synthetic routes may be utilized to prepare the compounds of the invention as shown in more detail below. Representative procedures for the preparation of compounds are set forth below
15 in the various schemes. The R-groups shown in the schemes are generally representative of R₁, R₂, R₃, and R₄ as set forth herein.

Synthetic Routes to 3,5-Disubstituted-piperidines

Scheme 1



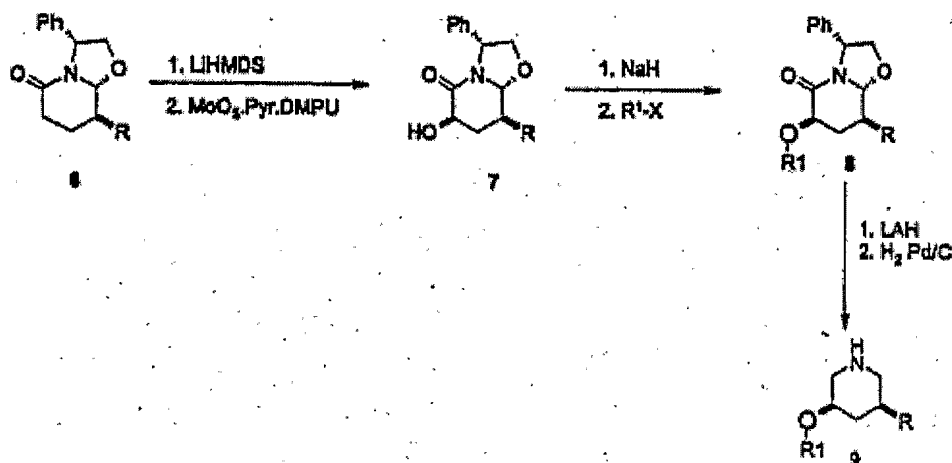
20

Any enolizable aldehyde capable of forming an enamine should react to form 3, leading to a wide variety of substituents which end up at C-3. R can be alkyl chain of 1-6
25 carbons, straight-chained or branched, cycloalkylmethyl, phenylmethyl, or phenyl-substituted alkyl chain of 1-6 carbons, either straight-chained or branched. Both enantiomers of 5, commercially available, which can therefore give rise to both enantiomers of 6. R¹ can be the same or different as R, defined

5 above, where X is a "good leaving" group such as, Br, Cl, I, Tosyl, Mesyl, etc. Other electrophilic reagents such as acid chlorides, sulfonyl chlorides, chloroformates and also make up R^1-X .

Scheme 2

10

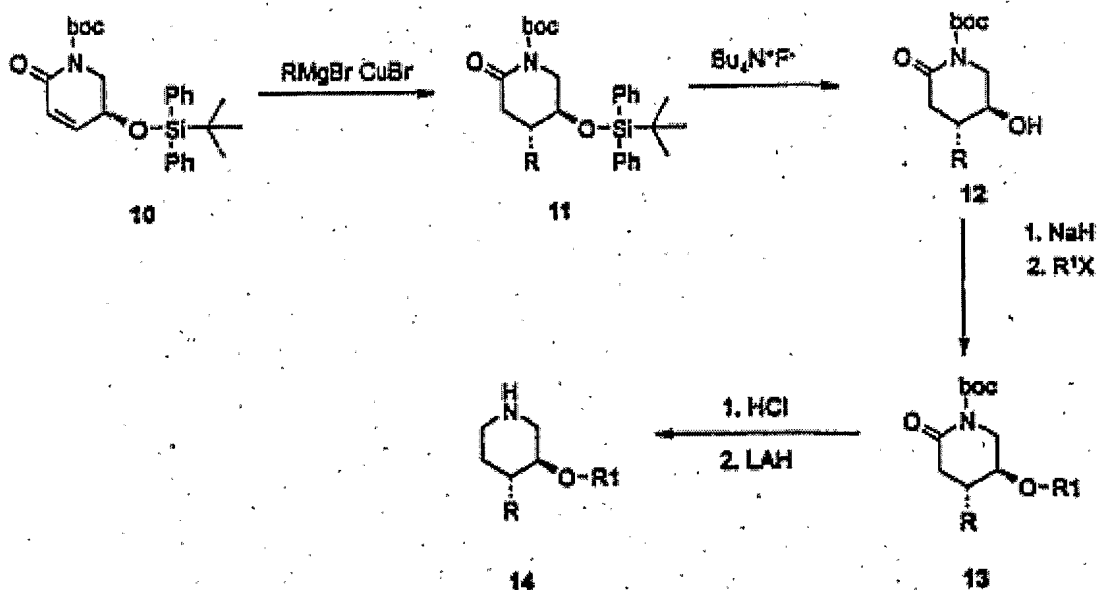


There are numerous ways to introduce an oxygen α to the amide carbonyl. Only one such method is shown. R is defined as above. R^1-X defined as above.

15

Synthetic Routes to 3,4-disubstituted and 3,4,5-trisubstituted piperidines

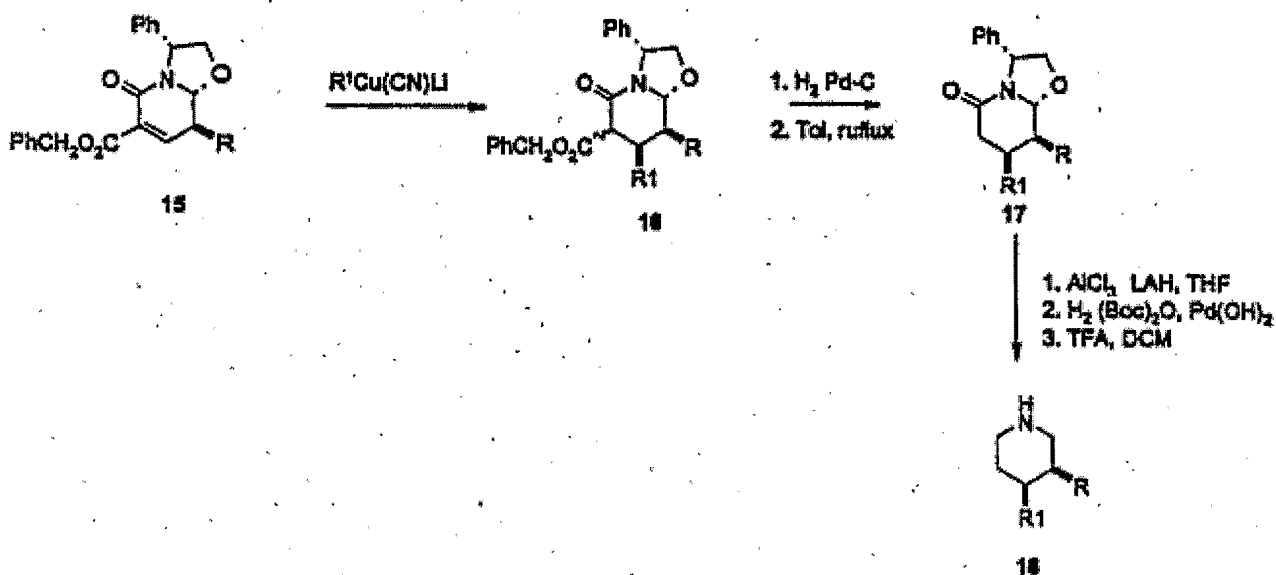
Scheme 3



5

Compound 10 is known in the literature (Tet.Asymm, 1996, 7, 867). R is defined as above, with the addition of being phenyl, substituted phenyl, heteroaromatic rings, cycloalkyl rings, or substituted cycloalkyl rings of 3-8 members. The reaction sequence will also work if alkyl lithium cuprates are substituted for the Grignard reagent, RMgBr.

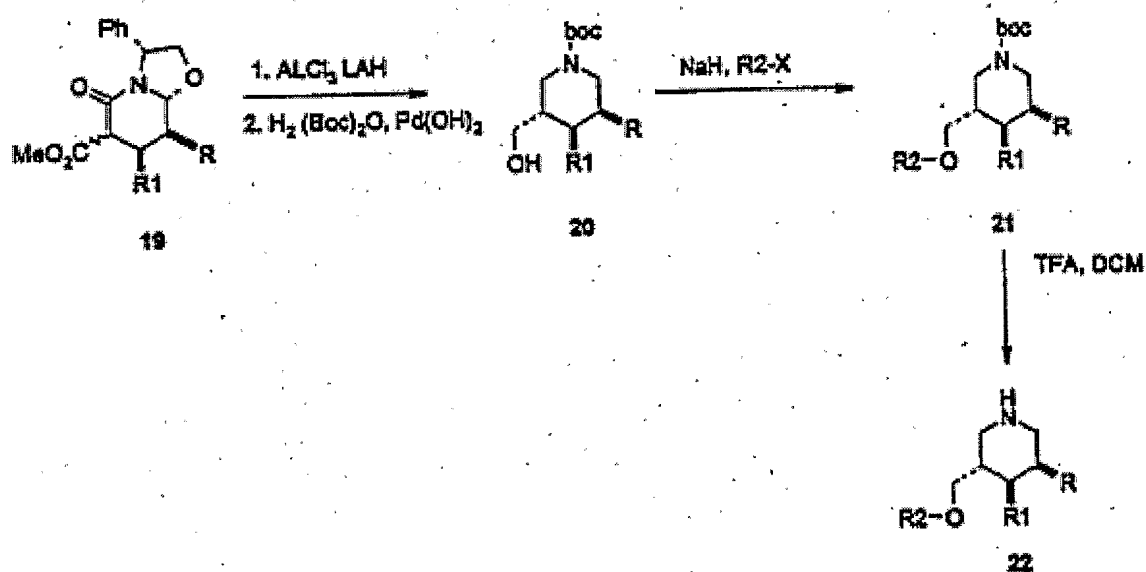
Scheme 4



Compound 15 is known in the literature where R - Ethyl (Org Lett, 2001, 3, 611). It can be prepared readily from 6, where R is defined as above. R¹ can be the same as or different from R and defined as above. R is defined as above, with the addition of being phenyl, substituted phenyl, heteroaromatic rings, cycloalkyl rings, or substituted cycloalkyl rings of 3-8 members.

5

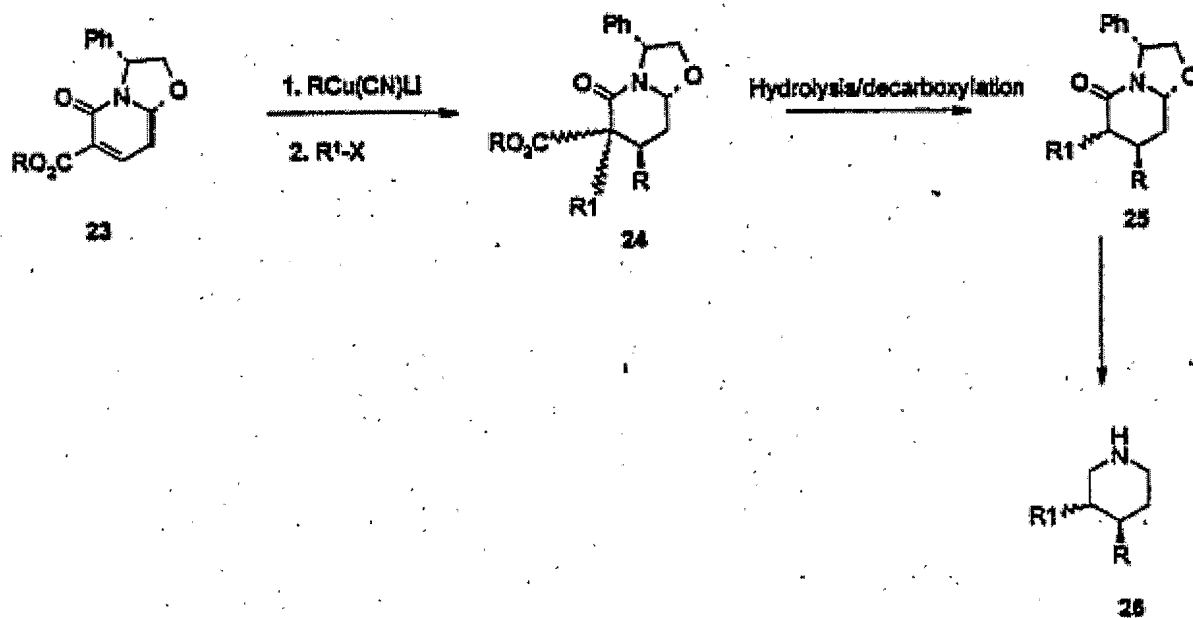
Scheme 5



Compound 19 can be prepared analogously to 16 above. R and R₁ are defined above. R₂ can be the same or different as R or R₁.

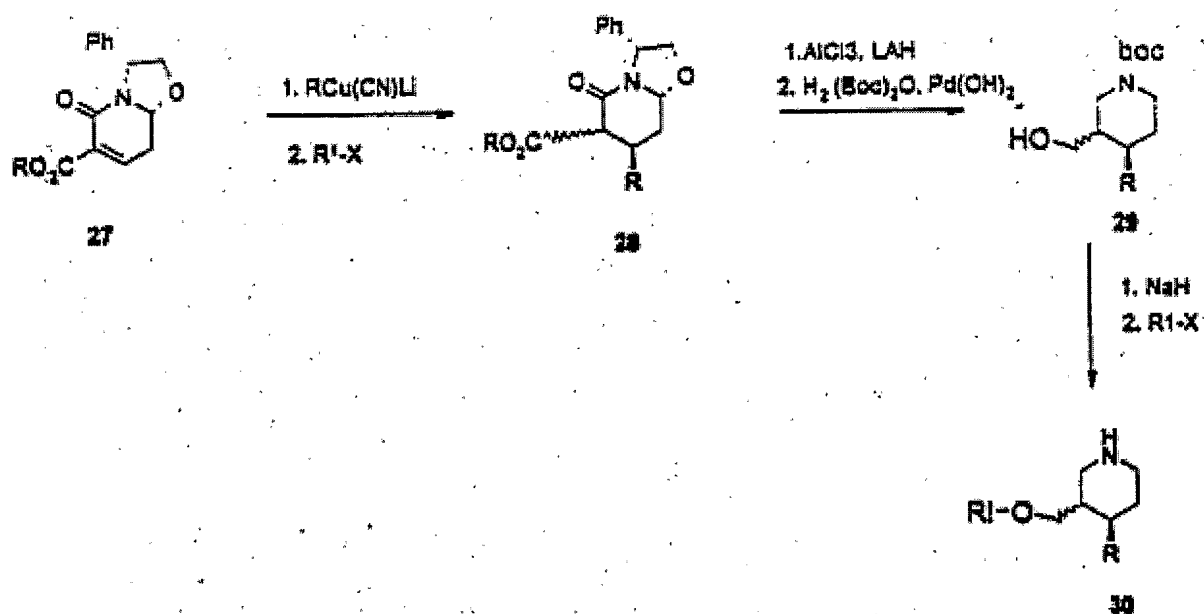
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Scheme 6

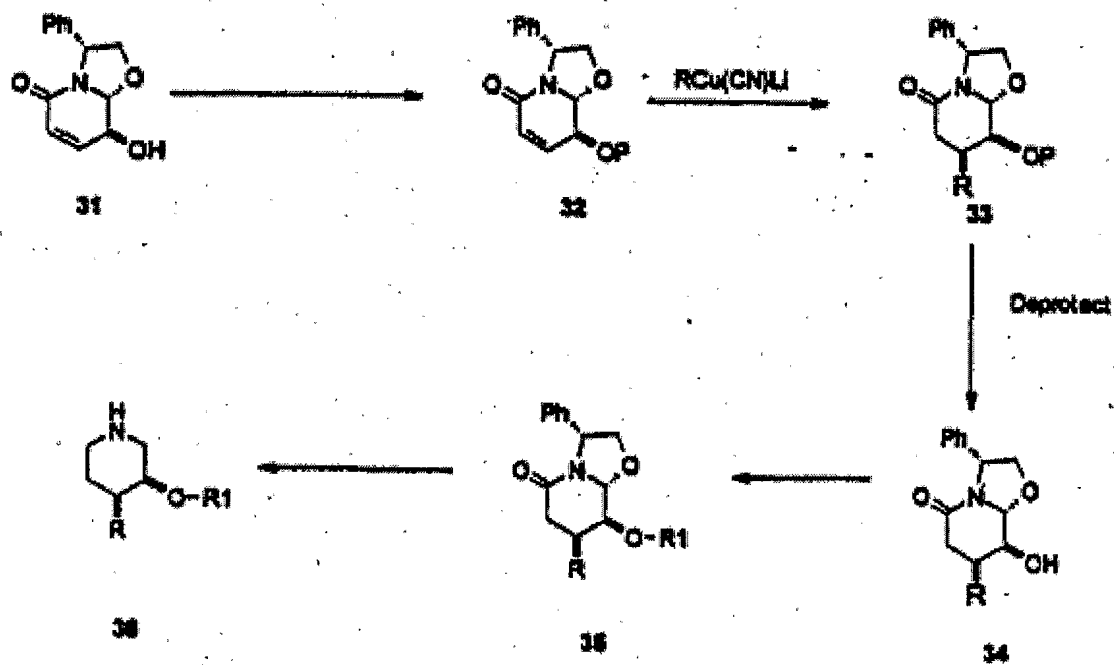


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Scheme 7

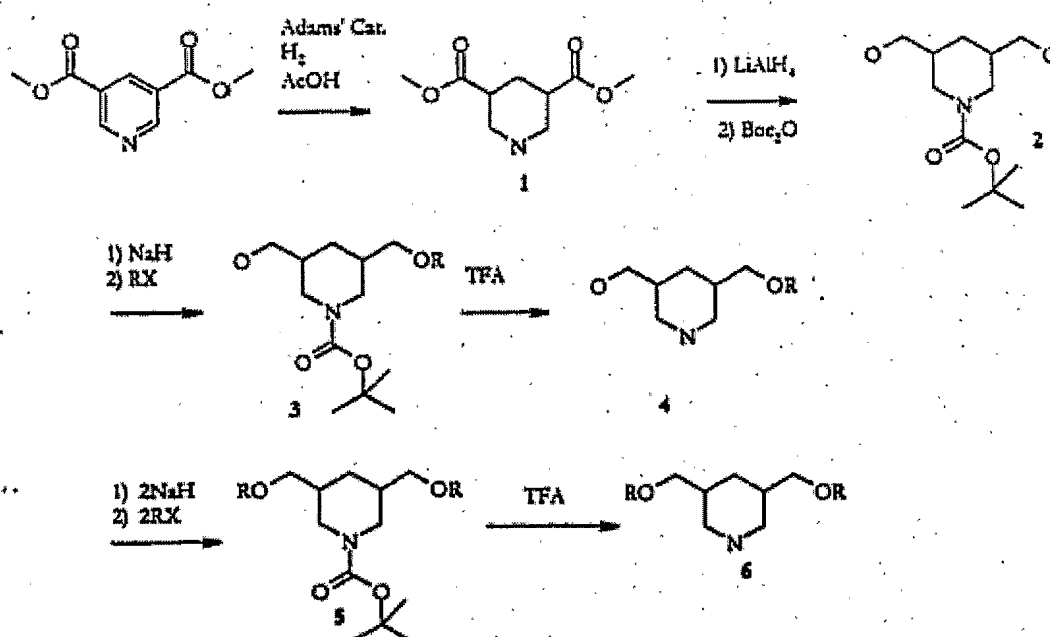


Scheme 8

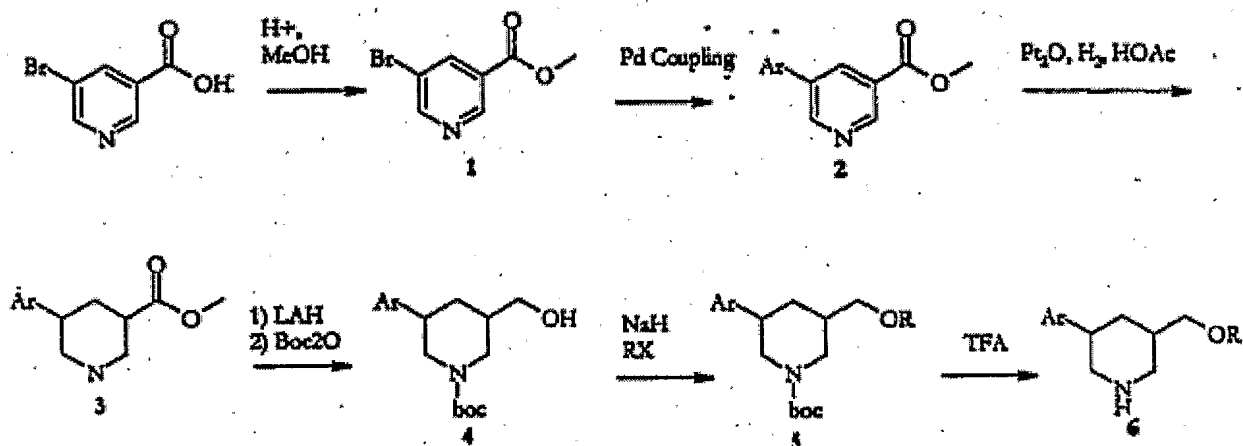


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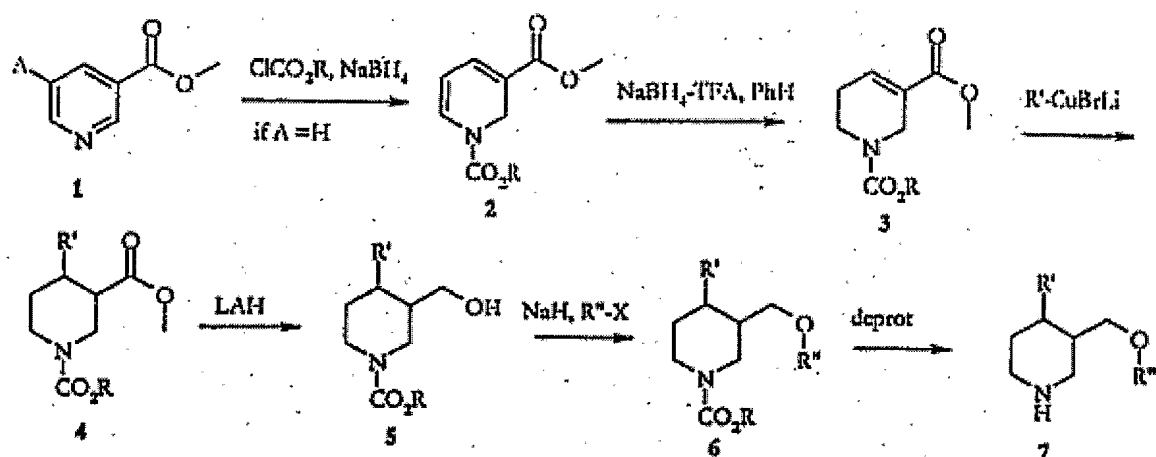
15

Complimentary Methods of Piperidine Synthesis:

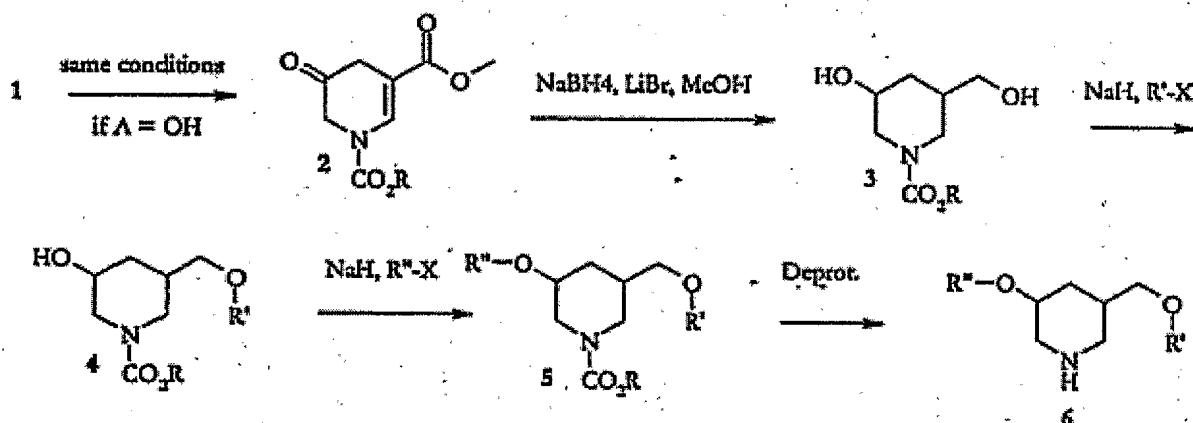
Dimethyldinicotinate is hydrogenated over Adam's catalyst in AcOH to give the piperidine 1. The esters are then reduced by LAH, then protected with Boc anhydride to give the diol 2, which is alkylated under Williamson-type conditions to give either mono-alkyl 3, or bis-alkyl 4. Removal of the Boc group yields the final compound.



Fischer esterification of 5-bromonicotinic acid gives the ester 1, which can be coupled with an arylmetaloid under Pd catalyzed conditions to give 2. Reduction of the nicotinate ester may be accomplished by Adam's catalyst to give 3. This can be further reduced by the action of LAH on the ester, and the resulting compound N-protected to give 4. Alkylation gives 5, and the removal of the carbamate gives the desired 6.



Nicotinic acid, 1, is subjected to a Fowler reduction, giving compound 2. Further reduction gives the enoate 3. Addition of an alkyl cuprate will substitute the 4-position of the piperidine to give 4 (if H is desired, Rh catalyzed hydrogenation is used), the ester of which can be reduced by LAH to give the primary alcohol, 5. The alcohol can be alkylated to give 6, and the amine deprotected to give 7. (*Org. Lett.*, 2001, 3, 210)



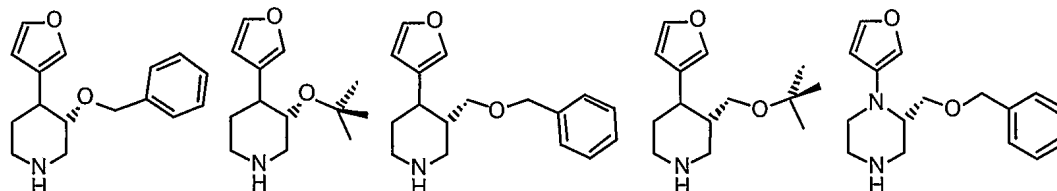
5-Hydroxynicotinic acid is subjected to Fowler reduction to give the keto-enoate 2, and reduction of the carbonyls gives the diol 3. alkylation of the primary alcohol to give 4 s followed by further alkylation to give 5. Deprotection of the amine gives compound 6. (*Org. Lett.* 2001, 3, 210)

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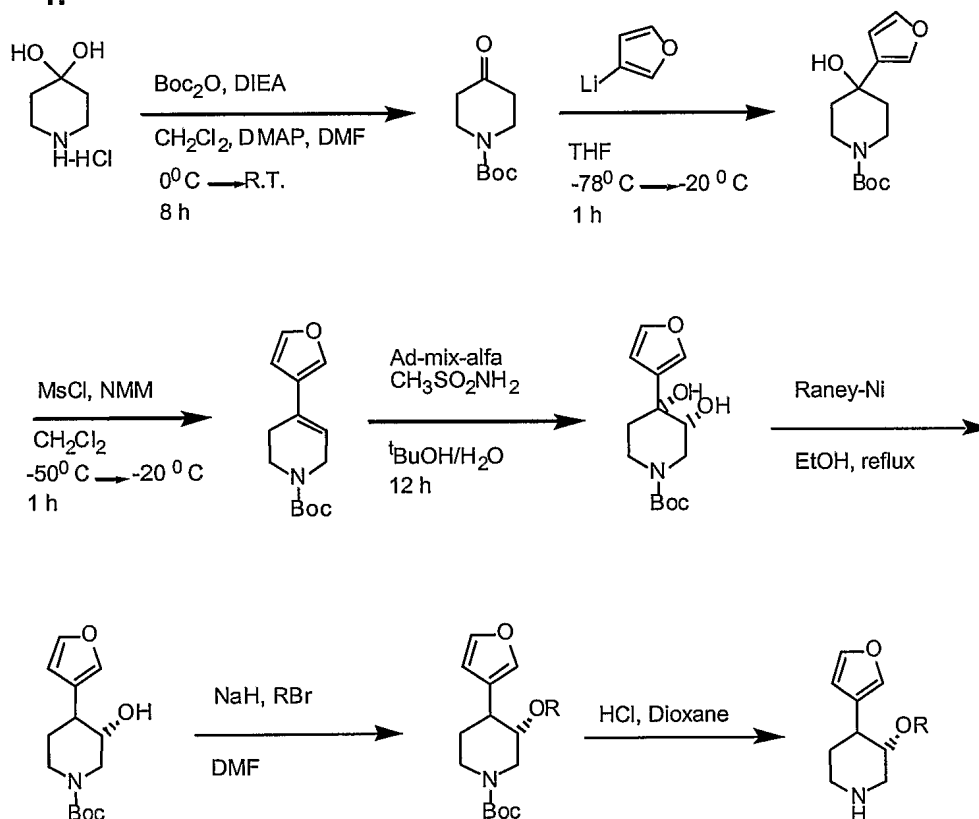
- 5 Additional alternatives methods of synthesis of the compounds are contemplated by the invention as shown in more detail below, for the subject compounds indicated.

3-Alkyloxy-4-Furano-Piperidines and Piperazines:



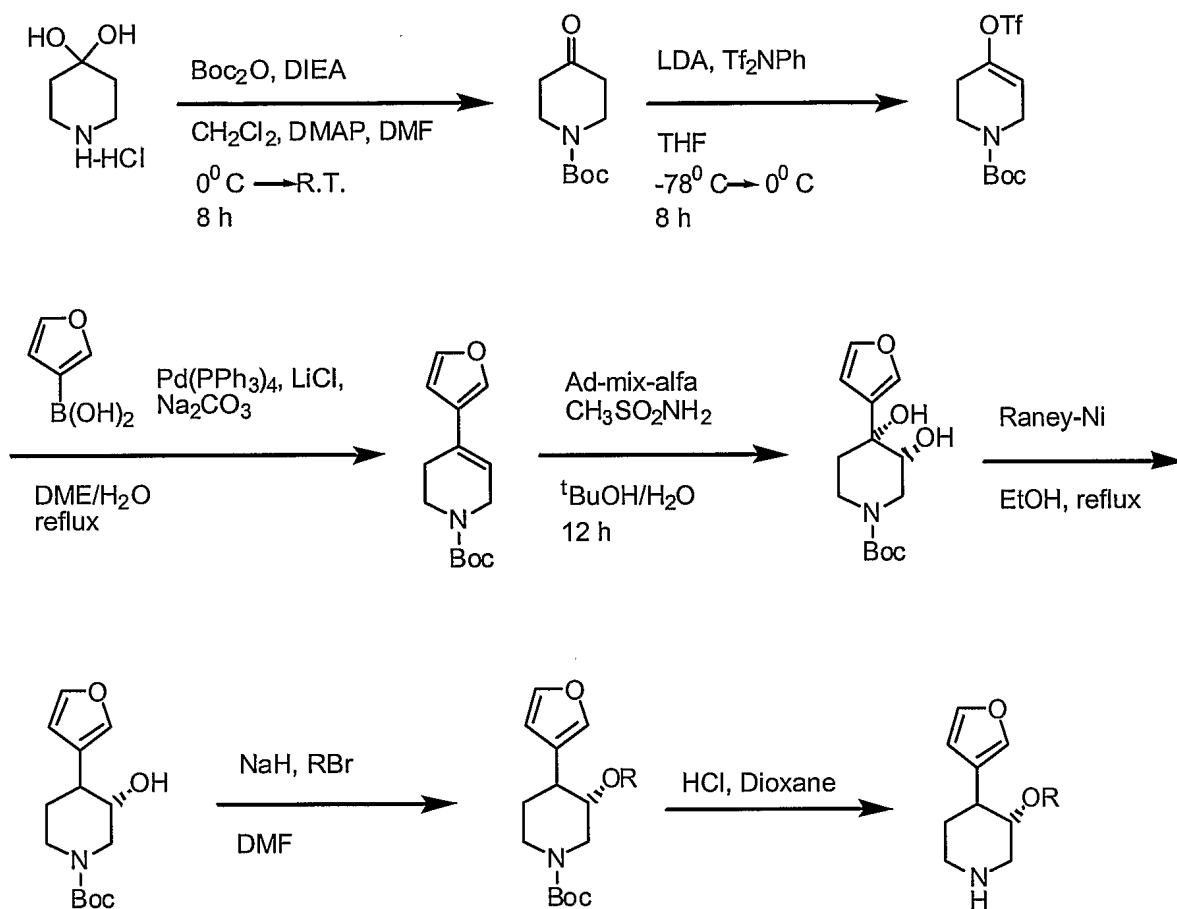
Synthetic Routes:

1.



R = Bn, Et, ⁱPr, ⁱBu, ^tBu

2.



R = Bn, Et, $i\text{Pr}$, $i\text{Bu}$, $t\text{Bu}$

Ref: *Org. Lett.* **2001**, 3(15), 2317-2320.

5

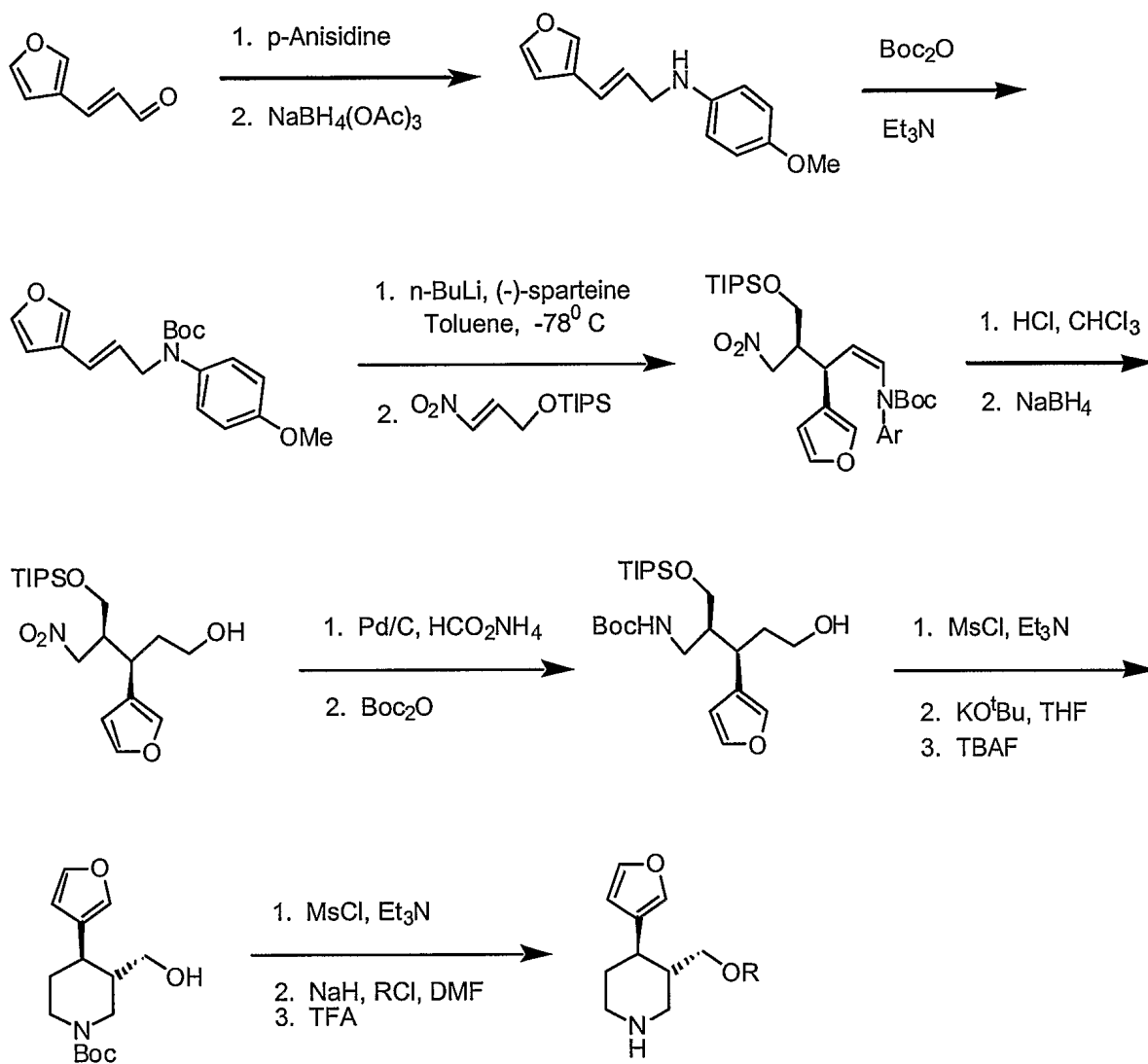
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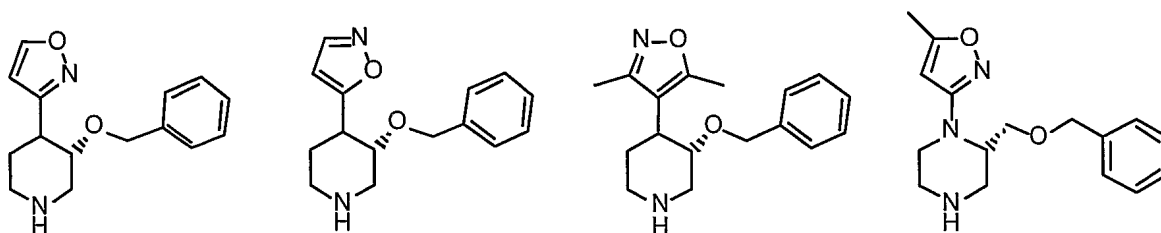
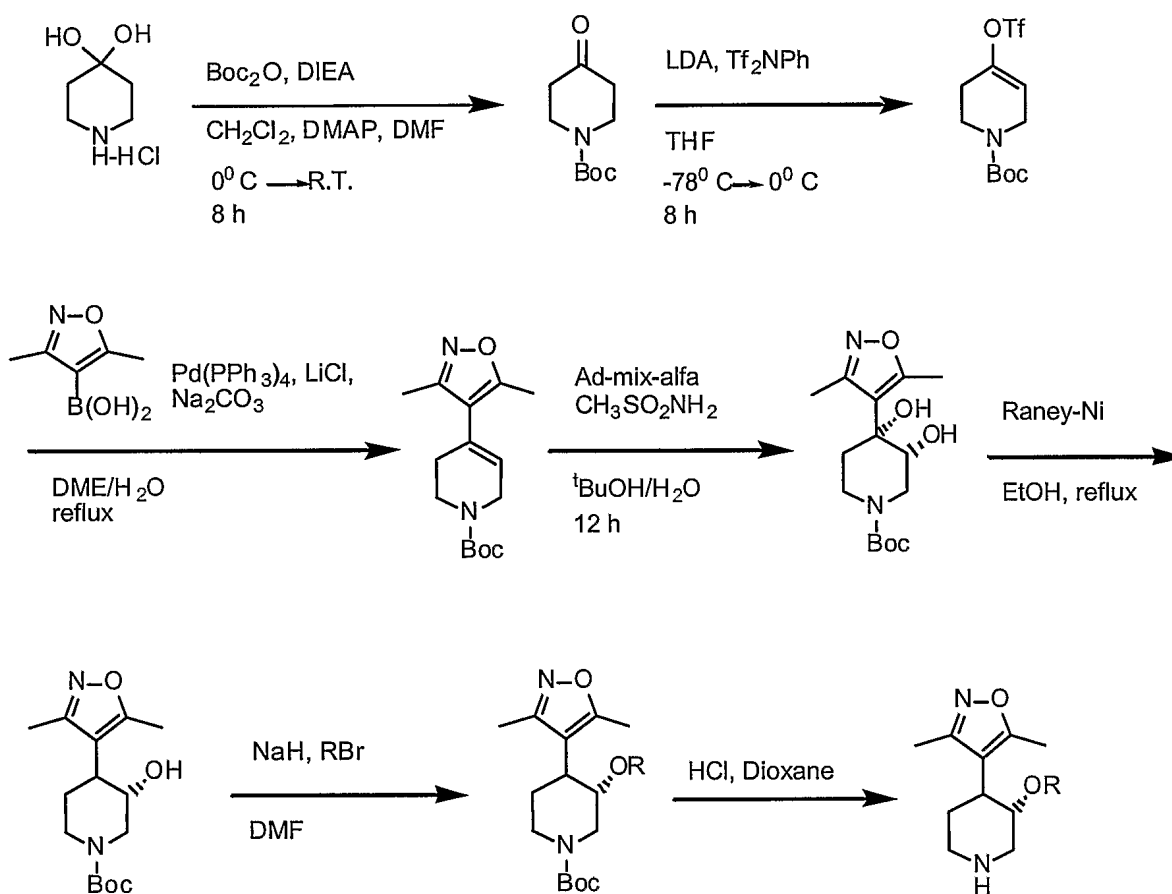
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3.

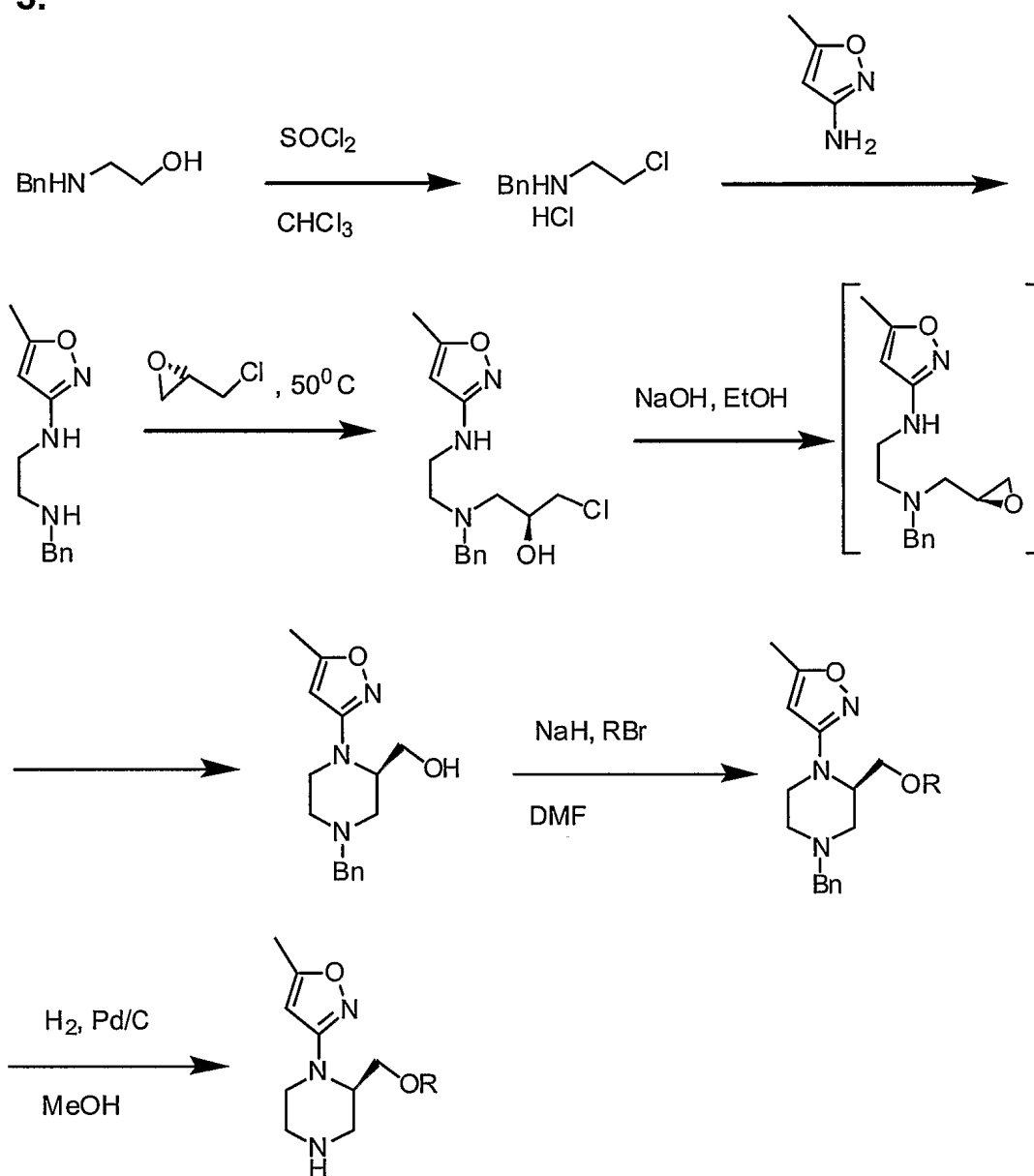
R = Bn, ^tBu Ref: *J. Am. Chem. Soc.* **2001**, 123, 1004-1005.

10

15

3-Alkyloxy-4-Isoxazolo-Piperidines**Synthetic Routes:****1.**R = Bn, Et, *i*Pr, *i*Bu, *t*BuRef: *Org. Lett.* **2001**, 3(15), 2317-2320.

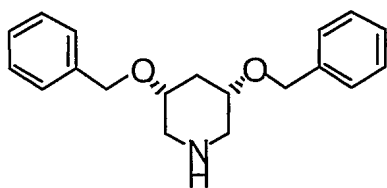
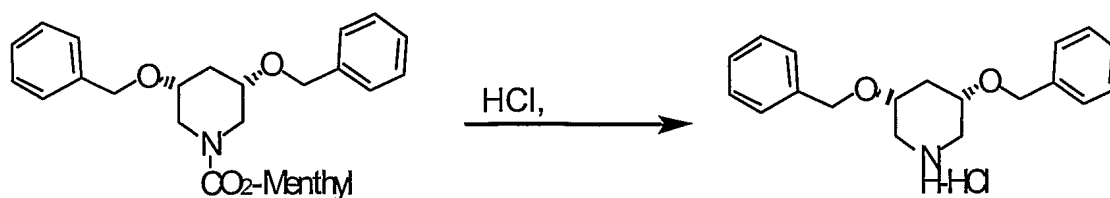
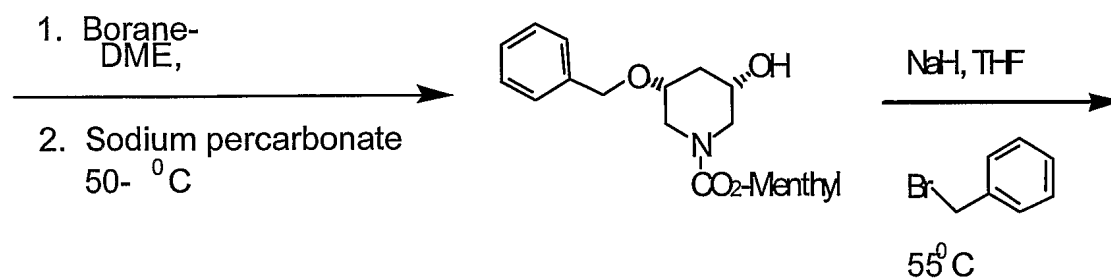
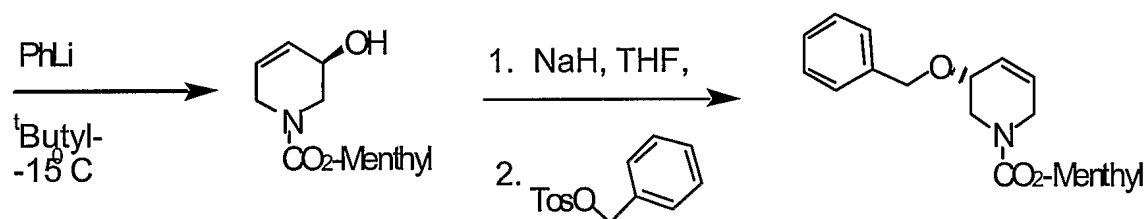
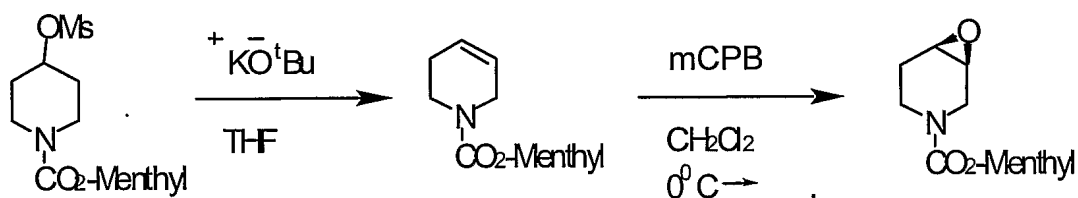
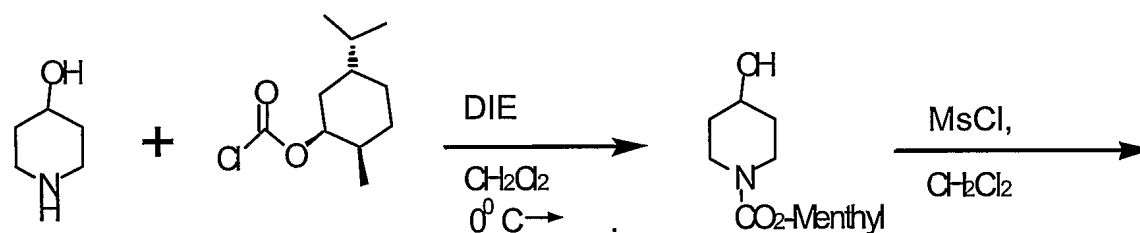
3.

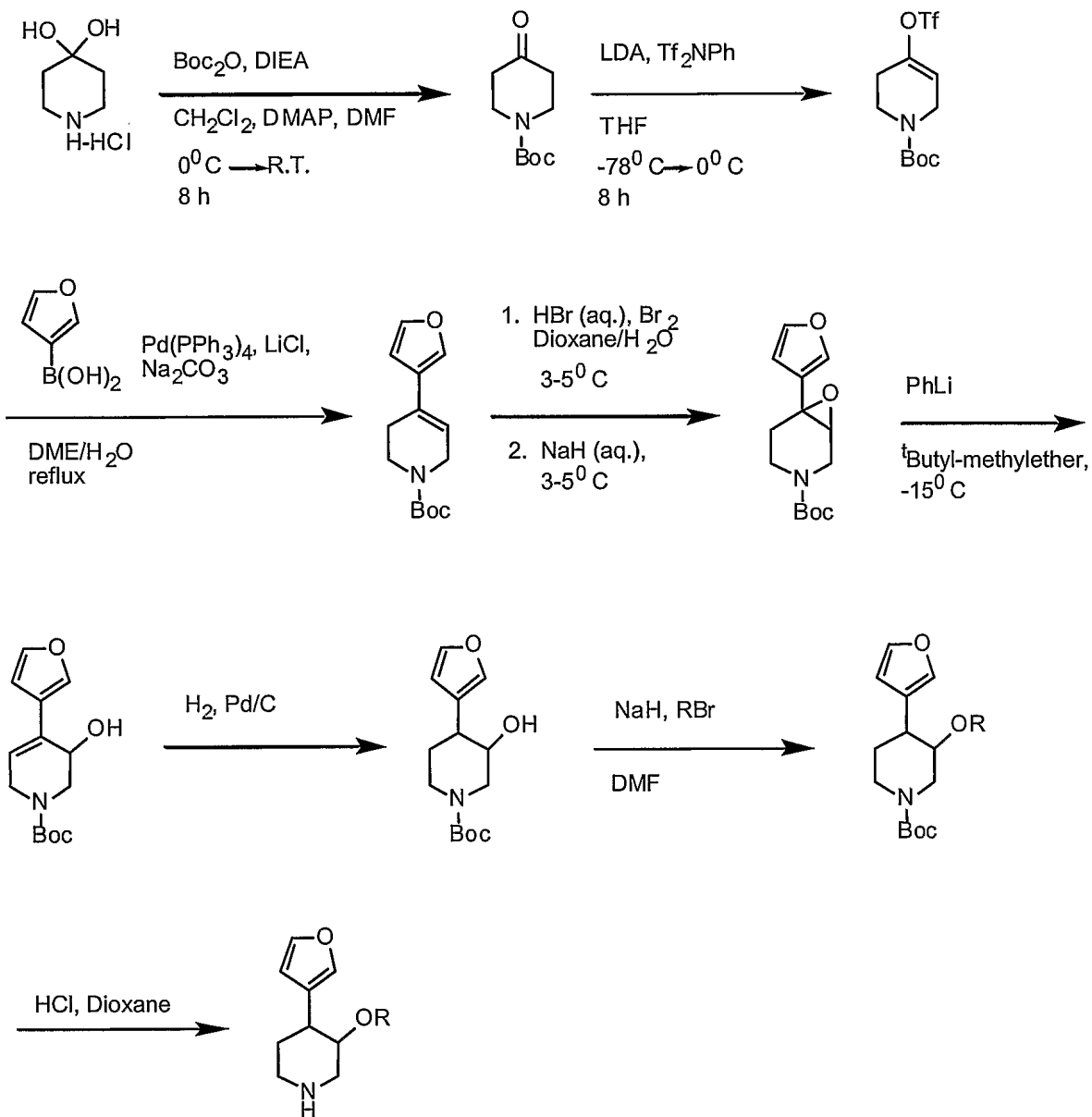
R = Bn, ^tBu

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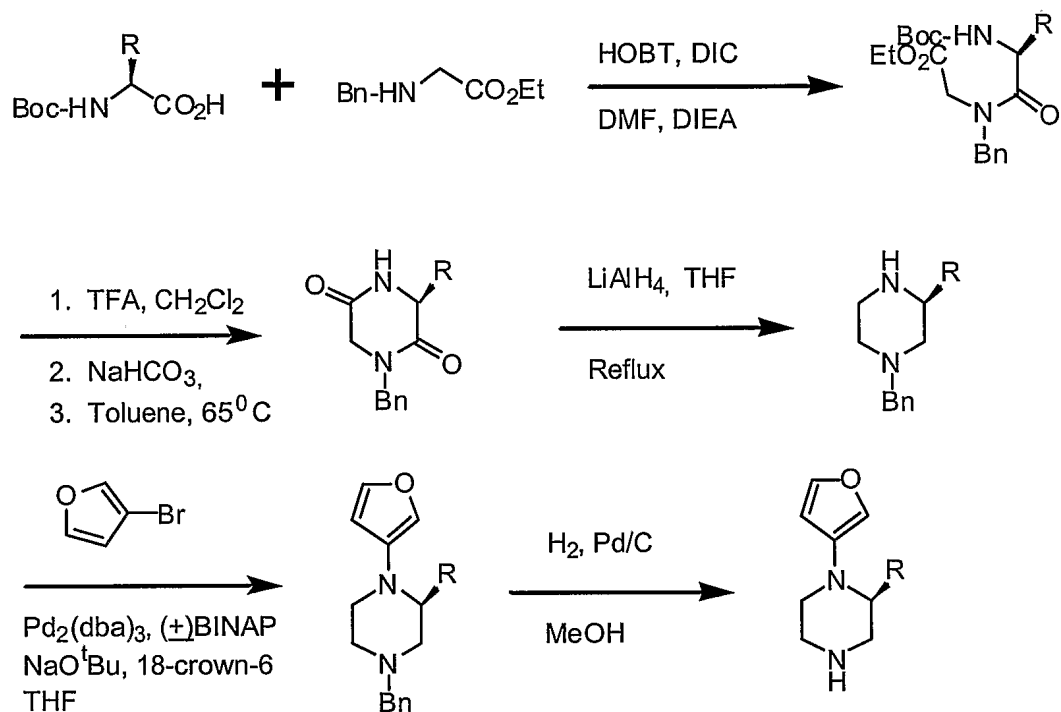
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3,5-Alkyloxy-Piperidines**Synthetic Route:**

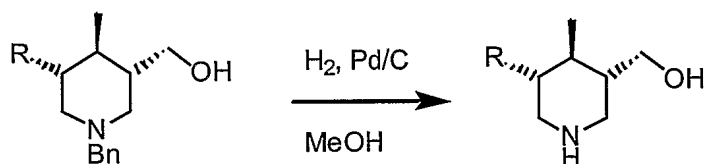
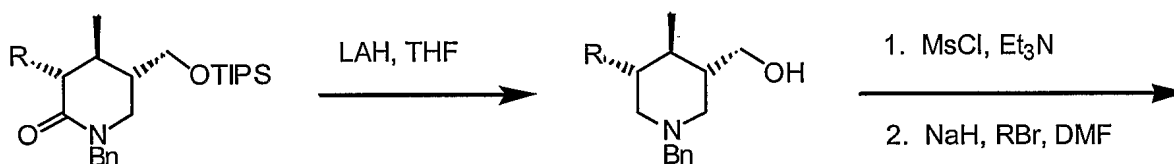
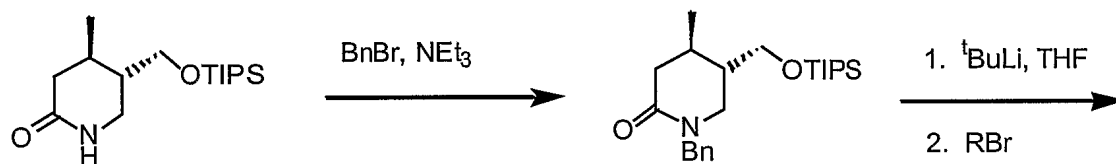
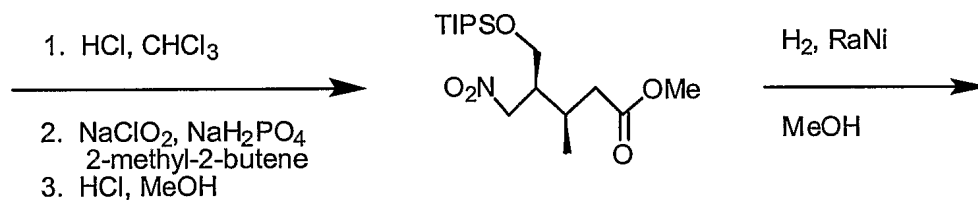
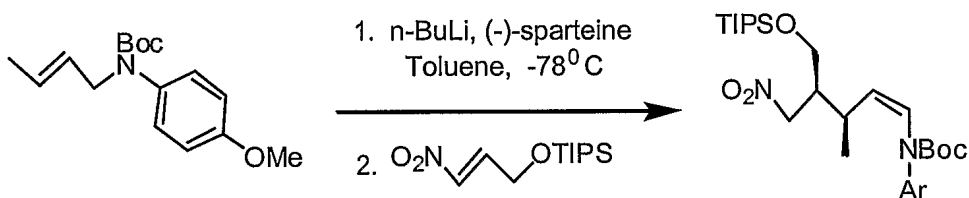
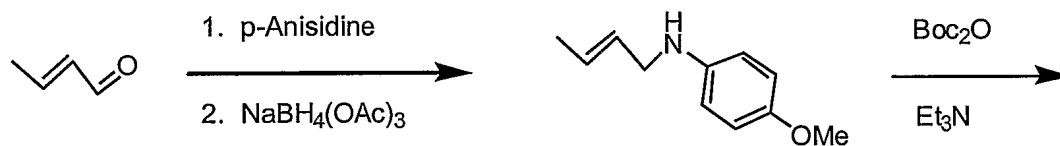
3-Alkyloxy-4-Furano-Piperidines:**1.**R = Bn, Et, *i*Pr, *i*Bu, *t*Bu

5

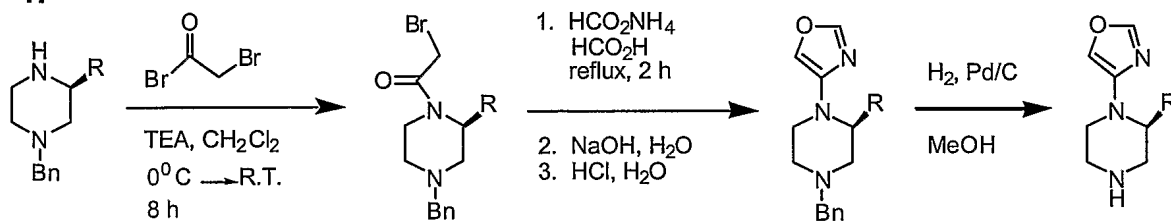
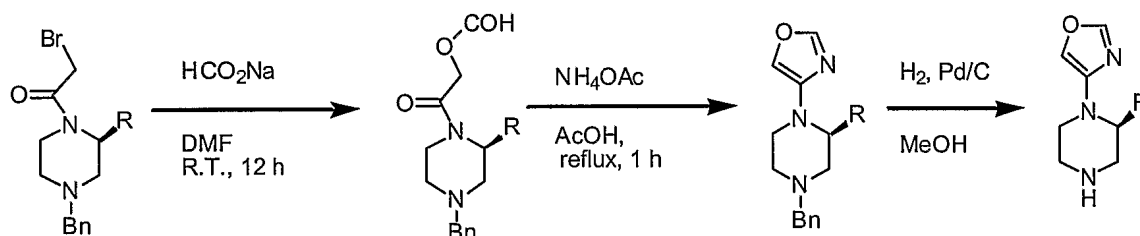
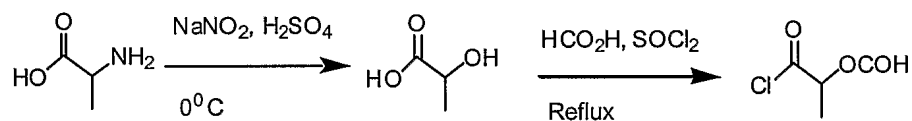
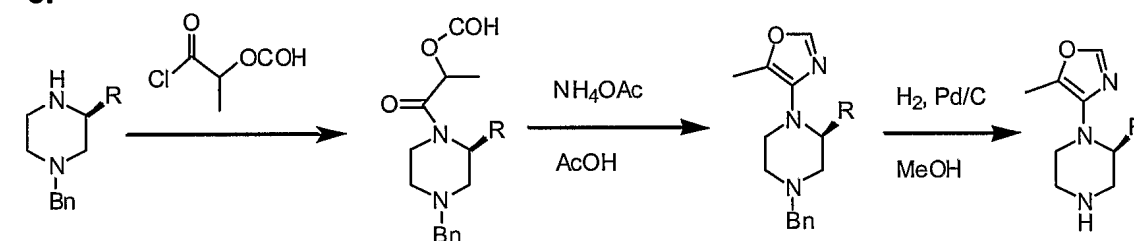
10

3-Alkyloxy- and 3-Alkyl-4-Furano-Piperazines

R = -CH₂OBn, -CH₂O^tBu, -CH₂CH(CH₃)₂, -Bn

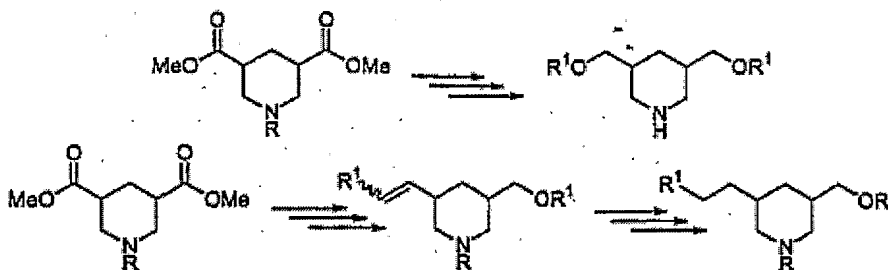
3,5-Alkyloxy-Piperidines

R = Bn, ^tBu

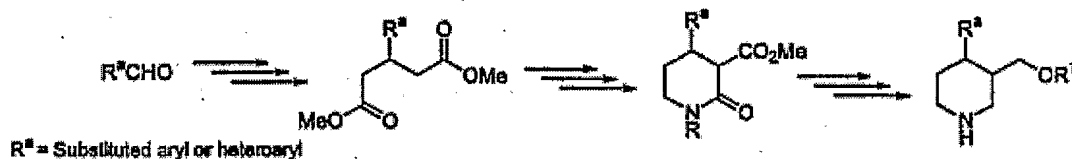
3-Alkyloxy- and 3-Alkyl-4-Oxazolo-Piperazines**1.****2.****3.**

$\text{R} = -\text{OBn}, -\text{O}^t\text{Bu}, -\text{CH}_2\text{CH}(\text{CH}_3)_2, -\text{Bn}$

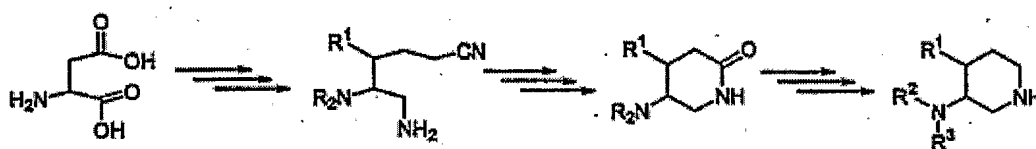
Exemplifications of this invention may be made as taught by Lesma *et al. J. Org. Chem.*, 1998, 63, 3492 (and references cited ther



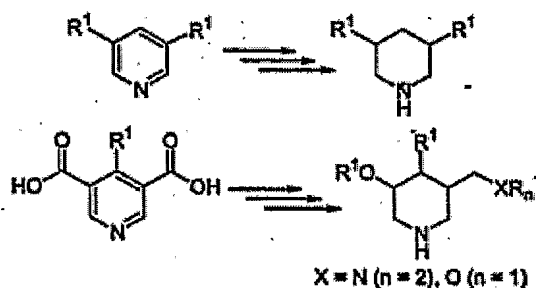
Exemplifications of this invention may be made as taught by Yu *et al. Tetrahedron Lett.*, 2000, 41, 5647 (and references cited ther



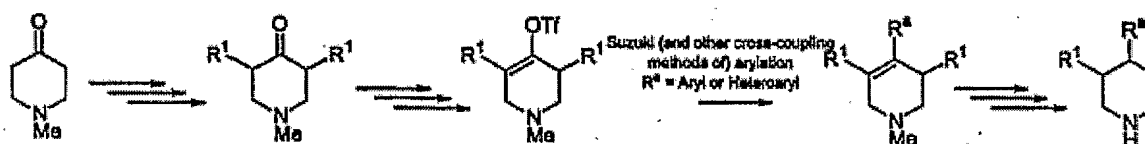
Exemplifications of this invention may be made as taught by Gmeiner *et al. J. Org. Chem.*, 2001, 66, 7406 (and references cited th



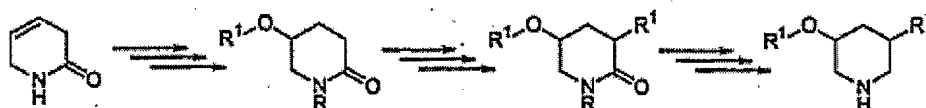
Exemplifications of this invention may be made as taught by Bols *et al. J. Org. Chem.*, 2000, 65, 7432 (and references cited therein):



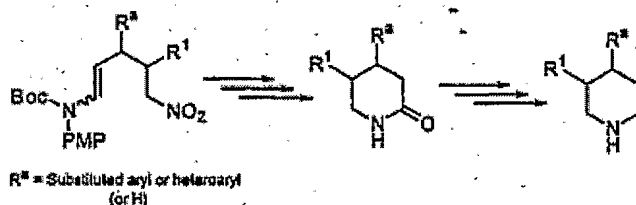
Exemplifications of this invention may be made as taught by Liras *et al. Org. Lett.*, 2001, 3, 3483 (and references cited therein):



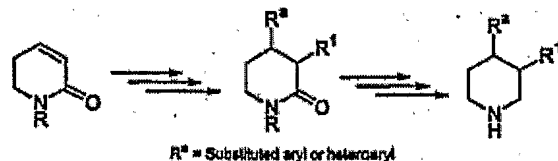
Exemplifications of this invention may be made as taught by Liebskind *et al. Org. Lett.*, 2001, 3, 3381 (and references cited there



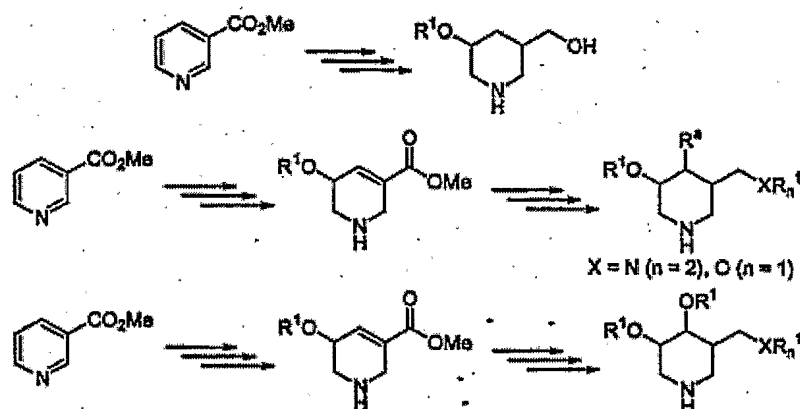
Exemplifications of this invention may be made as taught by Beak *et al.* *J. Am. Chem. Soc.*, 2001, 123, 1004 (and references cited therein):



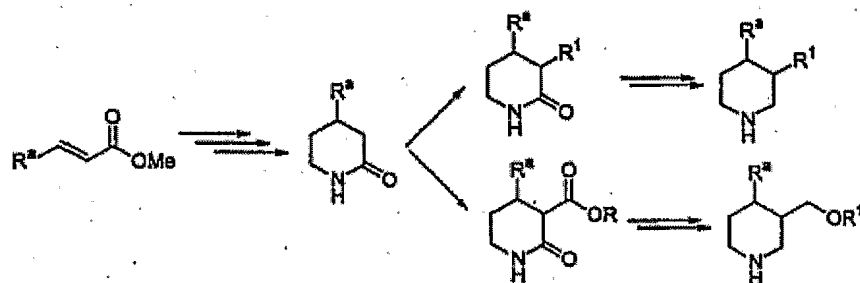
Exemplifications of this invention may be made as taught by Hayashi *et al.* *J. Org. Chem.*, 2001, 66, 6852 (and references cited therein):



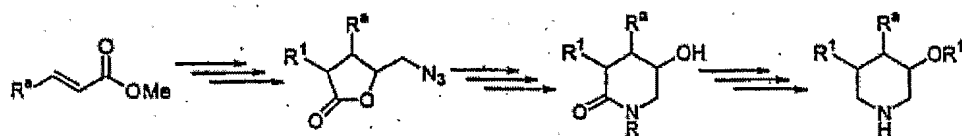
Exemplifications of this invention may be made as taught by Ganem *et al.* *Org. Lett.*, 2001, 3, 201 (and references cited therein):



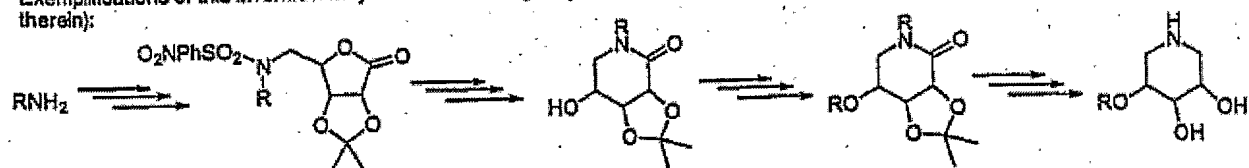
Exemplifications of this invention may be made as taught by Liu *et al.* *Tetrahedron: Asymmetry*, 2001, 12, 419 (and references cited therein):



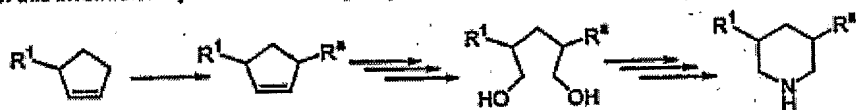
Exemplifications of this invention may be made as taught by Sabol *et al.* *Tetrahedron Lett.*, 2001, 42, 1631 (and references cited therein):



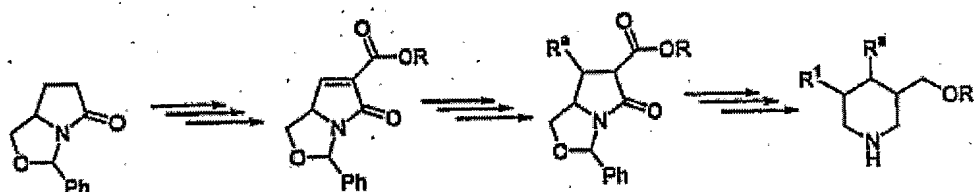
Exemplifications of this invention may be made as taught by Diez *et al. Tetrahedron Lett.*, 2001, 42, 871 (and references cited therein):



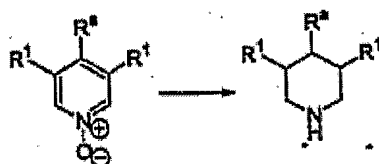
Exemplifications of this invention may be made as taught by Buchner & Metz *Tetrahedron Lett.*, 2001, 42, 5381 (and references cited therein):



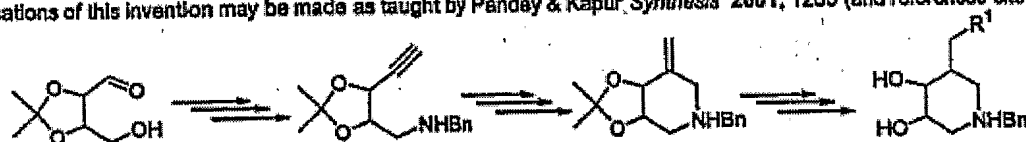
Exemplifications of this invention may be made as taught by Cossy *et al. Tetrahedron Lett.*, 2001, 42, 5705 (and references cited therein):



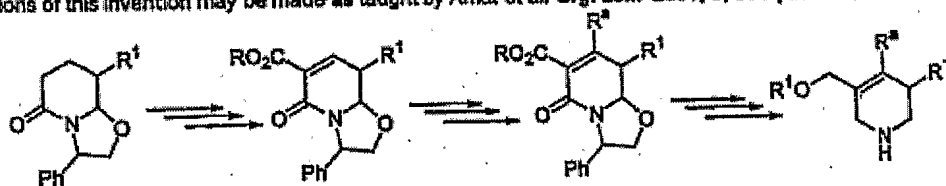
Exemplifications of this invention may be made as taught by Zacharie *et al. J. Org. Chem.*, 2001, 66, 5264 (and references cited therein):



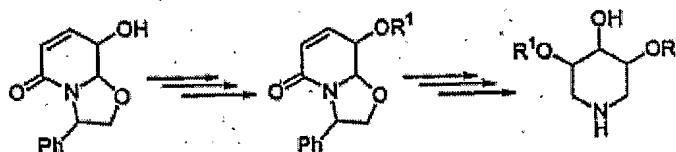
Exemplifications of this invention may be made as taught by Pandey & Kapur *Synthesis* 2001, 1263 (and references cited therein):



Exemplifications of this invention may be made as taught by Amat *et al. Org. Lett.* 2001, 3, 811 (and references cited therein):



Exemplifications of this invention may be made as taught by Amat *et al. Org. Lett.* 2001, 3, 3257 (and references cited therein):

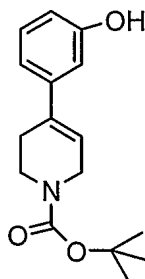


5 In accordance with the above preparative schemes, Example 1 was prepared as described below.

Example 1

(+/-) - (3R,4R) -4- (3-hydroxyphenyl)piperidin-3-yl 1,1'-biphenyl-4-carboxylate hydrochloride

10



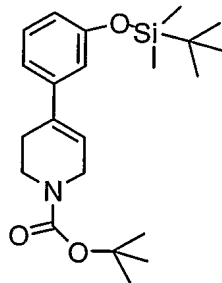
Step 1: Preparation of tert-Butyl 4-(3-hydroxyphenyl)-3,6-dihydropyridine-1(2H)-carboxylate

15

The tert-butyl 4-{[(trifluoromethyl)sulfonyl]oxy}-3,6-dihydropyridine-1(2H)-carboxylate (6.42 g, 9.23 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol 4.69 g, 21.3 mmol, and tetrakis(triphenylphosphine)palladium(0) (200 mg, 0.17 mmol) were mixed in dioxane (20 mL), ethanol (10 mL) and 2 M aqueous sodium carbonate (5.0 mL). The solution was refluxed for 4 hours, cooled to room temperature, and poured into ethyl acetate (150 mL). The solution was extracted with 1N aqueous hydrochloric acid (2 x 100 mL), filtered through celite, extracted with saturated aqueous sodium bicarbonate (2 x 100 mL), and extracted with saturated with saturated aqueous ammonium chloride (2 x 100 mL). The solution was dried over sodium sulfate, vacuum filtered through a bed of silica gel and solvent removed at reduced pressure to afford a red oil. The tert-butyl 4-(3-hydroxyphenyl)-3,6-dihydropyridine-1(2H)-carboxylate (5.3 g, 19.2 mmol) was obtained as a combination of two crystallization crops from dichloromethane/hexane

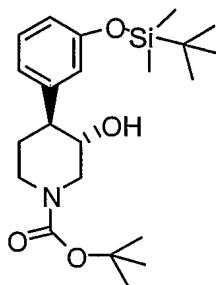
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5 crystallization solvents. HRMS m/z 276.1614 (calcd for M + H 276.1594)



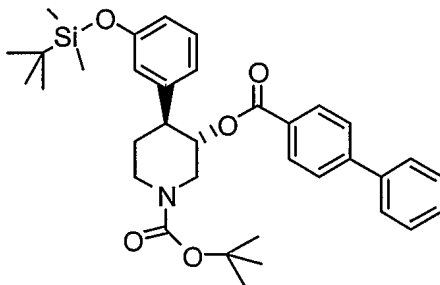
10 **Step 2: Preparation of *tert*-Butyl 4-(3-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-3,6-dihydropyridine-1(2H)-carboxylate**

The *tert*-butyl 4-(3-hydroxyphenyl)-3,6-dihydropyridine-
15 1(2H)-carboxylate (4.01 g, 14.58 mmol), *tert*-butyldimethylsilyl chloride (2.73 g, 18.22 mmol), triethylamine (4.01 g, 40.0 mmol) and a catalytic amount of dimethylaminopyridine (100 mg, 0.80 mmol) were mixed in dichloromethane (100 mL) at room temperature for 16 h. The solvent was removed at reduced pressure and the
20 resulting semisolid dissolved in diethylether (100 mL). The solution was extracted with 1N aqueous hydrochloric acid (2 x 50 mL), extracted with saturated aqueous sodium bicarbonate (2 x 50 mL), and extracted with saturated with saturated aqueous ammonium chloride (2 x 50 mL). The solution was dried over
25 sodium sulfate and solvent removed at reduced pressure. The *tert*-butyl 4-(3-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (4.8 g, 12.33 mmol) was isolated as a clear colorless oil by preparative silica chromatography (5% ethyl acetate/ 95% hexanes). HRMS m/z
30 388.2305 (calcd for M - H 388.2302)



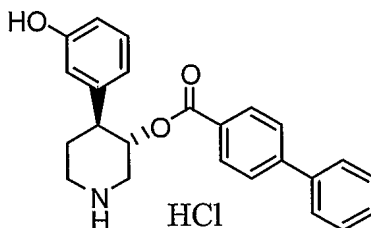
Step 3: Preparation of (+/-)-tert-Butyl (3S,4S)-4-(3-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-3-hydroxypiperidine-1-carboxylate

The *tert*-butyl 4-(3-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (4.61 g, 11.85 mmol) was dissolved in tetrahydrofuran (50 mL). The solution was cooled to 0°C and borane-methyl sulfide complex (1.79g, 23.7 mmol) was slowly added. The solution was heated to reflux for 2 H and cooled to room temperature. 1 M aqueous sodium hydroxide solution (30 mL) was added dropwise to control the gas evolution. 35% Aqueous hydrogen peroxide (45 mL) was added and solution refluxed for 2 H. The solution was cooled to room temperature and poured into diethylether (200 mL). The solution was extracted with 2.5 M aqueous sodium hydroxide (2 x 75 mL) and the organic layer checked for peroxides with starch iodide paper. The organic layer extracted with saturated ammonium chloride (1 x 50 mL) and dried over sodium sulfate. The (+/-)-*tert*-butyl (3S,4S)-4-(3-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-3-hydroxypiperidine-1-carboxylate (2.3 g, 5.65 mmol) as a semi solid by preparative silica chromatography (0-10% ethyl acetate/ hexanes). HRMS *m/z* 408.2564 (calcd for M + H 408.2565)



Step 4: Preparation of (+/-)-tert-Butyl (3R,4R)-3-[(1,1'-biphenyl-4-ylcarbonyl)oxy]-4-(3-{[tert-butyl(dimethyl)silyl]oxy}phenyl)piperidine-1-carboxylate

The (+/-)-tert-butyl (3S,4S)-4-(3-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-3-hydroxypiperidine-1-carboxylate (206 mg, 0.51 mmol), 1'-biphenyl-4-carbonyl chloride (540 mg, 2.50 mmol), triethylamine (400 mg, 4.00 mmol), and a catalytic amount of dimethylaminopyridine (10.0 mg, 0.08 mmol) was mixed together in acetonitrile (10.0 mL) at room temperature for 16 H. Ammonium hydroxide solution (5 mL) was added to the solution and it was stirred for 1 H. The heterogeneous solution was poured into ethyl acetate (50 mL) and hexanes (5 mL). The solution was extracted with 1N aqueous hydrochloric acid (2 x 10 mL), extracted with saturated aqueous sodium bicarbonate (2 x 10 mL), and extracted with saturated with saturated aqueous ammonium chloride (2 x 10 mL). The solution was dried over sodium sulfate and solvent removed at reduced pressure. The (+/-)-tert-butyl (3R,4R)-3-[(1,1'-biphenyl-4-ylcarbonyl)oxy]-4-(3-{[tert-butyl(dimethyl)silyl]oxy}phenyl)piperidine-1-carboxylate (164 mg, 0.28 mmol) was isolated as a semisolid by radial silica gel chromatography (25% ethyl acetate/hexanes). HRMS m/z 588.3150 (calcd for M + H 588.3140)



5

Step 5: Preparation of (+/-)-(3R,4R)-4-(3-Hydroxyphenyl)piperidin-3-yl 1,1'-biphenyl-4-carboxylate hydrochloride

10

The (+/-)-*tert*-butyl (3R,4R)-3-[(1,1'-biphenyl-4-ylcarbonyl)oxy]-4-(3-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)piperidine-1-carboxylate (91 mg, 0.16 mmol) was dissolved in 4 N Hydrogen chloride in dioxanes (3.0 mL). The solution was stirred for 4 H at room temperature and diethylether (10 mL) was added. The solution was kept at room temperature for 16 H and solids formed. The (+/-)-(3R,4R)-4-(3-hydroxyphenyl)piperidin-3-yl 1,1'-biphenyl-4-carboxylate hydrochloride (56 mg, 0.13 mmol) was obtained as a white solid.

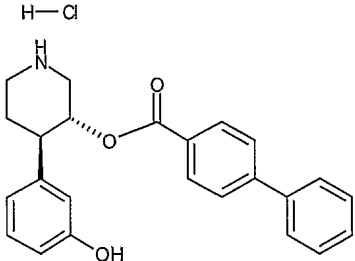
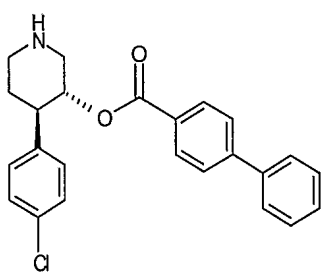
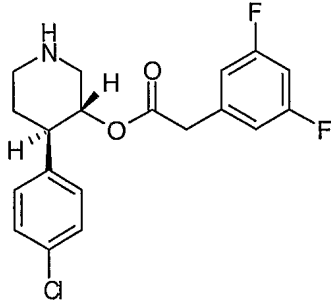
HRMS m/z 374.1753 (calcd for M + H 374.1751)

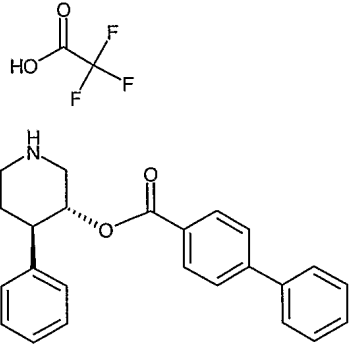
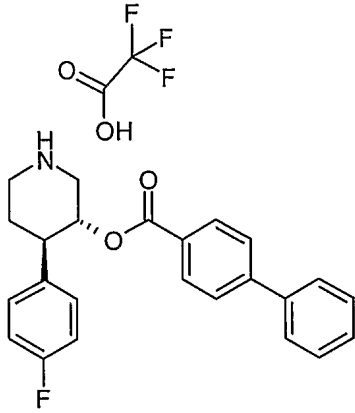
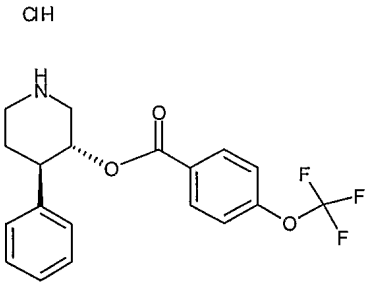
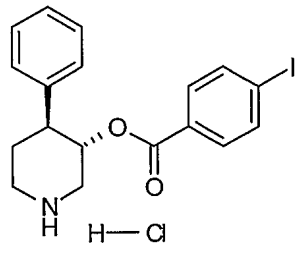
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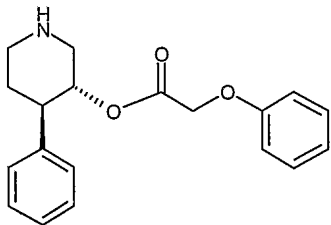
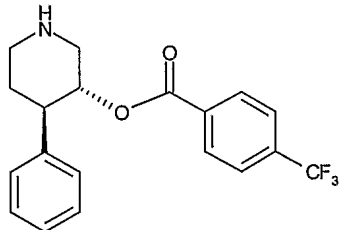
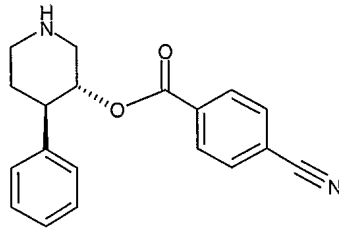
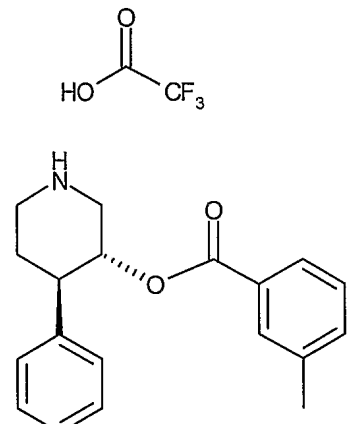
The invention is illustrated further by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them.

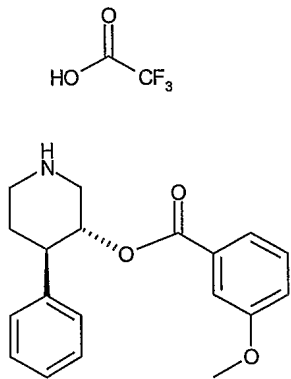
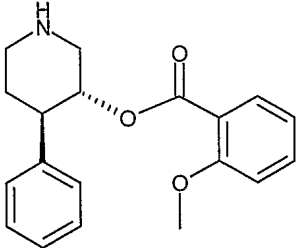
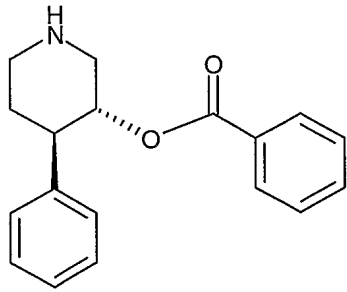
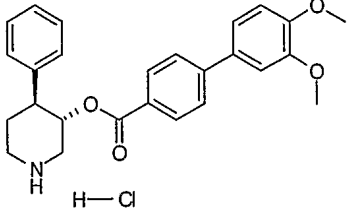
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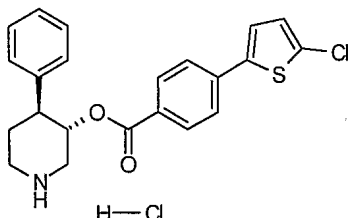
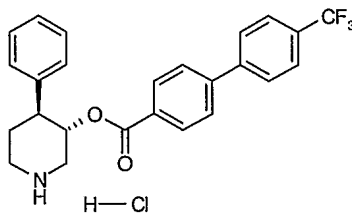
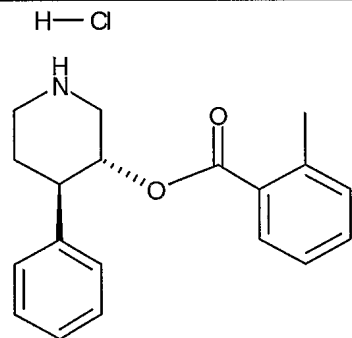
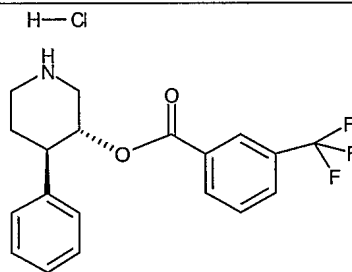
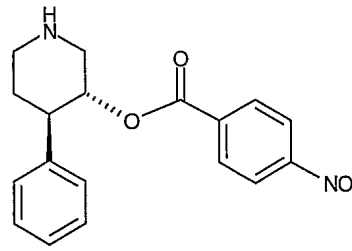
Examples 2 through 60, as represented by the structures shown below, were prepared using similar procedures as those described above. Example 1 and examples 2-60 are shown below:

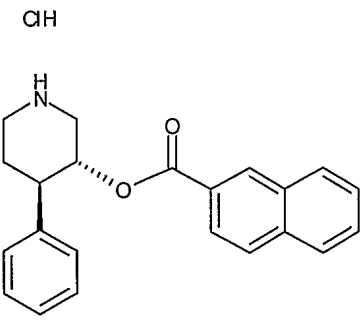
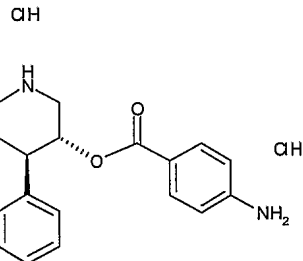
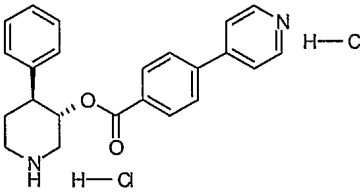
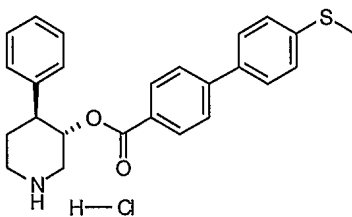
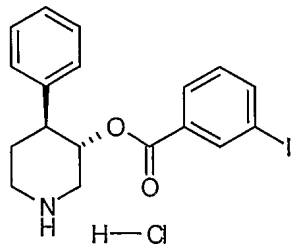
	Structure	Compound Name(s)	Exact Mass (m + H)	Calc. Exact Mass (M + H)
Example 1		(+/-)-(3R,4R)-4-(3-hydroxyphenyl)piperidin-3-yl 1,1'-biphenyl-4-carboxylate hydrochloride	374.1753	374.1784
Example 2		(+/-)-(3R,4R)-4-(4-chlorophenyl)piperidin-3-yl 1,1'-biphenyl-4-carboxylate trifluoroacetate	392.1417	392.1418
Example 3		(+/-)-(3R,4R)-4-(4-chlorophenyl)piperidin-3-yl (3,5-difluorophenyl)acetate	366.1072	366.1072

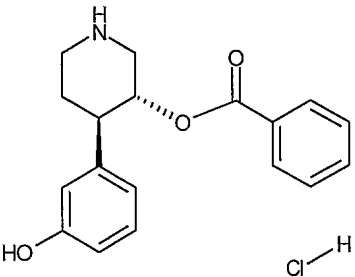
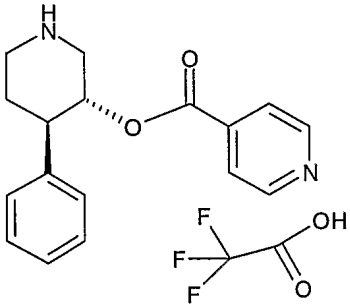
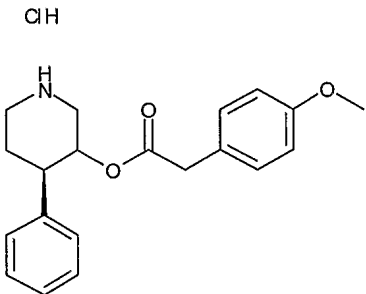
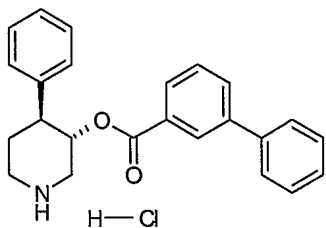
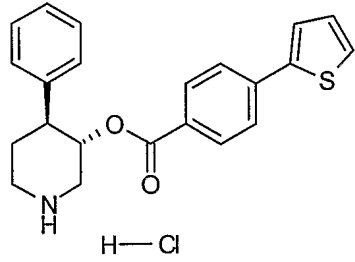
Example 4		(+/-)-(3R,4R)-4-phenylpiperidin-3-yl 1-naphthoate hydrochloride	358.1785	358.1802
Example 5		(+/-)-(3R,4R)-4-(4-fluorophenyl)piperidin-3-yl 1,1'-biphenyl-4-carboxylate trifluoroacetate	376.1713	376.1303
Example 6		(+/-)-(3R,4R)-4-phenylpiperidin-3-yl 4-(trifluoromethoxy)benzoate hydrochloride	366.1292	366.1317
Example 7		(+/-)-(3S,4S)-4-phenylpiperidin-3-yl 4-iodobenzoate hydrochloride	408.0429	408.0461

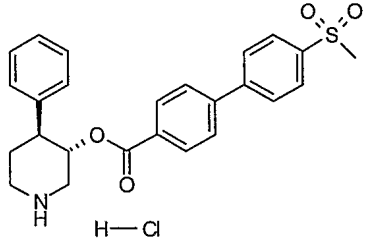
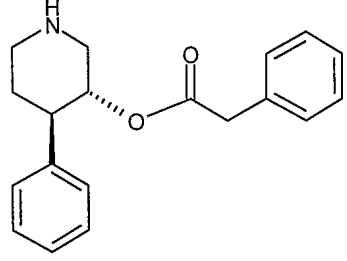
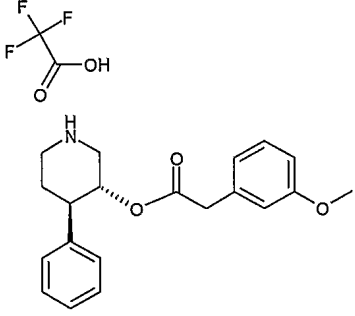
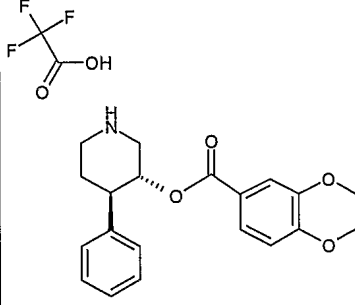
Example 9	CH 	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl phenoxycetate hydrochloride	312.1598	312.16
Example 10	CH 	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 4-(trifluoromethyl)benzoate hydrochloride	350.1381	350.1368
Example 11	CH 	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 4-cyanobenzoate hydrochloride	307.1413	307.1441
Example 12		(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 3-methylbenzoate trifluoroacetate	296.1644	296.1645

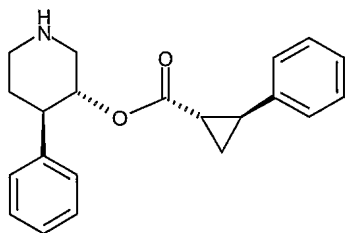
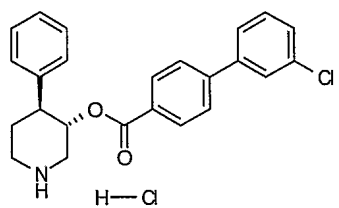
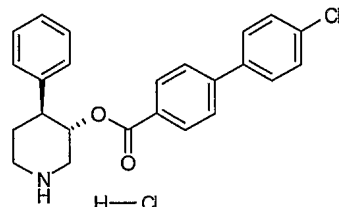
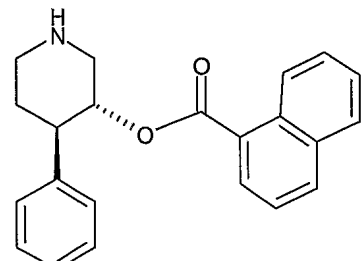
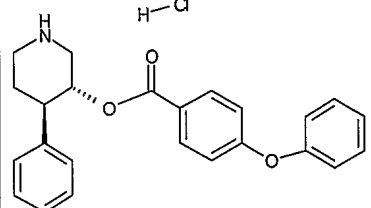
Example 13		(+/-)-(3R,4R)-4-phenylpiperidin-3-yl 3-methoxybenzoate trifluoroacetate	312.1623	312.1595
Example 14	CH 	(+/-)-(3R,4R)-4-phenylpiperidin-3-yl 2-methoxybenzoate hydrochloride	312.1610	312.1594
Example 15	CH 	(+/-)-(3R,4R)-4-phenylpiperidin-3-yl benzoate hydrochloride	282.1470	282.1489
Example 16		(+/-)-(3S,4S)-4-phenylpiperidin-3-yl 3',4'-dimethoxy-1,1'-biphenyl-4-carboxylate hydrochloride	418.2020	418.2013

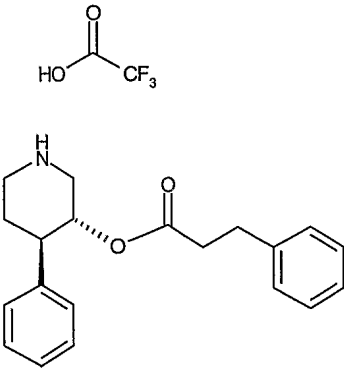
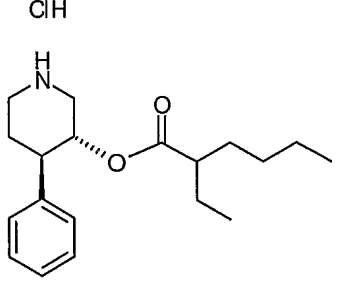
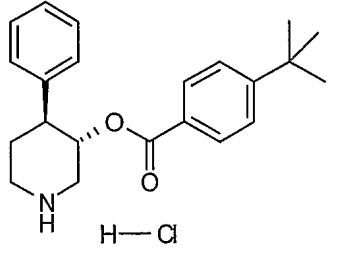
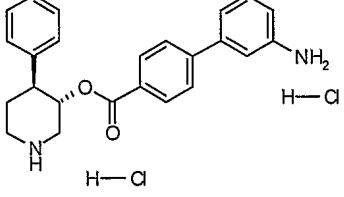
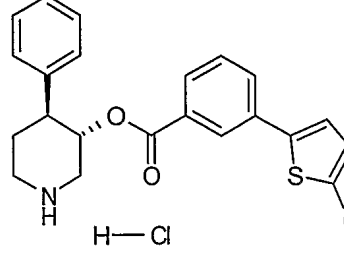
Example 17		(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4-(5-chlorothiophen-2-yl)benzoate hydrochloride	398.0959	398.0976
Example 18		(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4'-(trifluoromethyl)-1,1'-biphenyl-4-carboxylate hydrochloride	426.1671	426.1675
Example 19		(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 2-methylbenzoate hydrochloride	296.1622	296.1645
Example 20		(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 3-(trifluoromethyl)benzoate hydrochloride	350.1351	350.1362
Example 21		(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 4-nitrobenzoate hydrochloride	327.1330	327.1339

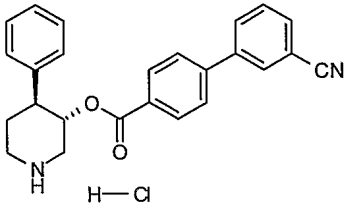
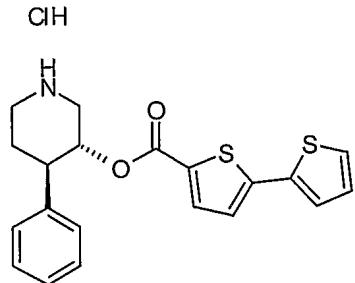
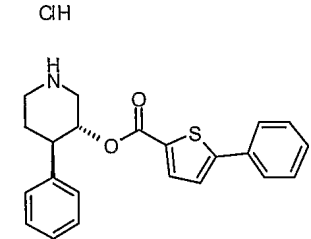
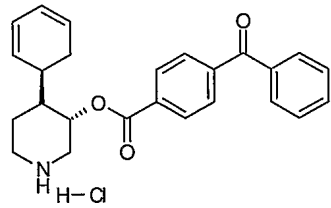
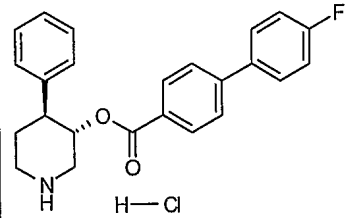
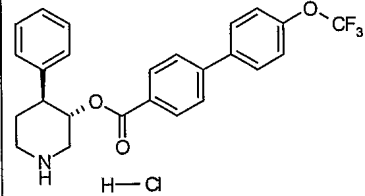
Example 22		(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 2-naphthoate hydrochloride	332.1631	332.1645
Example 23		(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 4-aminobenzoate dihydrochloride	297.1615	297.1598
Example 24		(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4-pyridin-4-ylbenzoate dihydrochloride	359.1733	359.1754
Example 25		(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4'-(methylthio)-1,1'-biphenyl-4-carboxylate hydrochloride	404.1684	404.0455
Example 26		(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 3-iodobenzoate hydrochloride	408.0455	407.0382

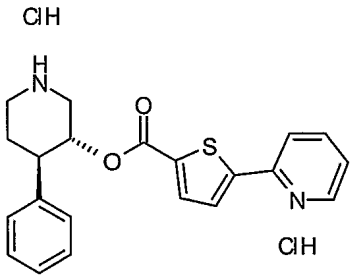
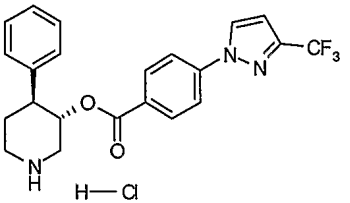
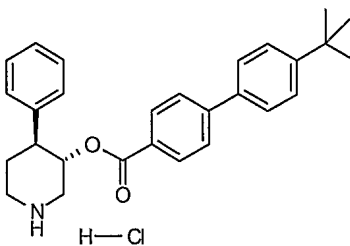
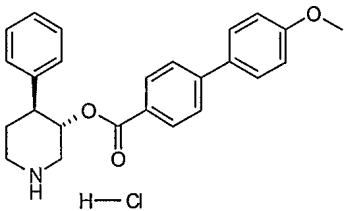
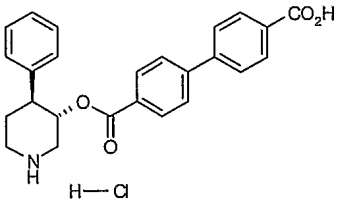
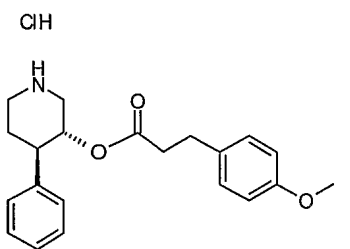
Example 27		(+/-)-(3R,4R)-4-(3-hydroxyphenyl)piperidin-3-yl benzoate hydrochloride	298.1463	298.1438
Example 28		(+/-)-(3R,4R)-4-(3-pyridyl)benzoate hydrochloride	283.1428	283.1441
Example 29		(3R,4R)-4-phenylpiperidin-3-yl 1,1'-biphenyl-4-carboxylate	326.1760	326.1751
Example 30		(+/-)-(3S,4S)-4-phenylpiperidin-3-yl 1,1'-biphenyl-3-carboxylate hydrochloride	358.1835	358.1802
Example 31		(+/-)-(3S,4S)-4-phenylpiperidin-3-yl 4-thien-2-ylbenzoate hydrochloride	364.1387	364.1366

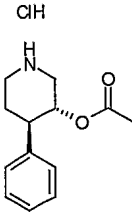
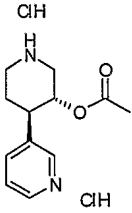
Example 32		(+/-)-(3S,4S)-4-phenylpiperidin-3-yl 4'-(methylsulfonyl)-1,1'-biphenyl-4-carboxylate hydrochloride	436.1559	436.1577
Example 33	ClH 	(+/-)-(3R,4R)-4-phenylpiperidin-3-yl phenylacetate hydrochloride	296.1621	296.1645
Example 34		(+/-)-(3R,4R)-4-phenylpiperidin-3-yl (3-methoxyphenyl)acetate trifluoroacetate	326.1733	326.1751
Example 35		(+/-)-(3R,4R)-4-phenylpiperidin-3-yl 3,4-dimethoxybenzoate trifluoroacetate	342.1697	342.1700

Example 36	CH 	(+/-)-(3R,4R)-4-phenylpiperidin-3-yl (1R,2S)-2-phenylcyclopropanecarboxylate hydrochloride	322.1806	322.1802
Example 37	 H—Cl	(+/-)-(3S,4S)-4-phenylpiperidin-3-yl 3'-chloro-1,1'-biphenyl-4-carboxylate hydrochloride	392.1420	392.1412
Example 38	 H—Cl	(+/-)-(3S,4S)-4-phenylpiperidin-3-yl 4'-chloro-1,1'-biphenyl-4-carboxylate hydrochloride	392.1420	392.1412
Example 39	CH 	(+/-)-(3R,4R)-4-phenylpiperidin-3-yl 1-naphthoate hydrochloride	332.1671	332.1645
Example 40	H—Cl 	(+/-)-(3R,4R)-4-phenylpiperidin-3-yl 4-phenoxybenzoate hydrochloride	374.1751	374.1751

Example 41		(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 3-phenylpropanoate trifluoroacetate	310.1795	310.1802
Example 42		(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 2-ethylhexanoate hydrochloride	304.2234	304.2271
Example 43		(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4-tert-butylbenzoate hydrochloride	338.2143	338.2120
Example 44		(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 3'-amino-1,1'-biphenyl-4-carboxylate dihydrochloride	373.1887	373.1916
Example 45		(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 3-(5-chlorothien-2-yl)benzoate hydrochloride	398.1016	398.0981

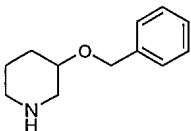
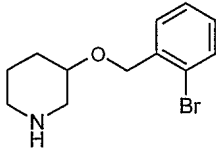
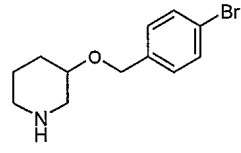
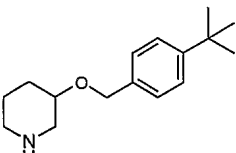
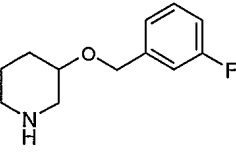
Example 46		(+/-)-(3S,4S)-4-phenylpiperidin-3-yl 3'-cyano-1,1'-biphenyl-4-carboxylate hydrochloride (Generated by ACD/Name software)	373.1767	383.1754
Example 47		(+/-)-(3R,4R)-4-phenylpiperidin-3-yl 2,2'-bithiophene-5-carboxylate hydrochloride	370.0908	370.0935
Example 48		(+/-)-(3R,4R)-4-phenylpiperidin-3-yl 5-phenylthiophene-2-carboxylate hydrochloride	364.1335	364.1371
Example 49		(+/-)-(3S,4R)-4-[(1R)-cyclohexa-2,4-dien-1-yl]piperidin-3-yl 4-benzoylbenzoate hydrochloride)	386.1778	386.1756
Example 50		(+/-)-(3S,4S)-4-phenylpiperidin-3-yl 4'-fluoro-1,1'-biphenyl-4-carboxylate hydrochloride	376.1679	376.1707
Example 51		(+/-)-(3S,4S)-4-phenylpiperidin-3-yl 4'-(trifluoromethoxy)-1,1'-biphenyl-4-carboxylate hydrochloride	442.1607	442.1625

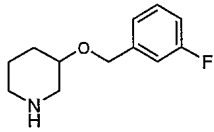
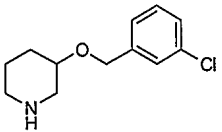
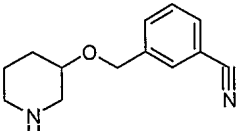
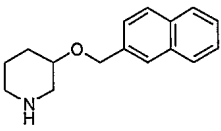
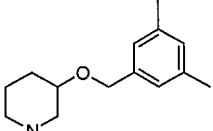
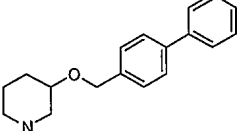
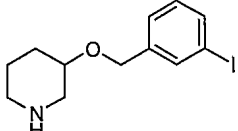
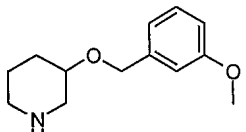
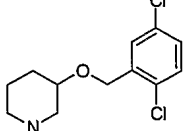
Example 52		(+/-)-(3R,4R)-4-phenylpiperidin-3-yl 5-pyridin-2-ylthiophene-2-carboxylate dihydrochloride	365.1336	365.1318
Example 53		(+/-)-(3S,4S)-4-phenylpiperidin-3-yl 4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]benzoate hydrochloride	416.1566	416.158
Example 54		(+/-)-(3S,4S)-4-phenylpiperidin-3-yl 4'-tert-butyl-1,1'-biphenyl-4-carboxylate hydrochloride	414.2417	414.2428
Example 55		(+/-)-(3S,4S)-4-phenylpiperidin-3-yl 4'-methoxy-1,1'-biphenyl-4-carboxylate hydrochloride	388.1936	388.1907
Example 56		(+/-)-4'-([[(3S,4S)-4-phenylpiperidin-3-yl]oxy]carbonyl)-1,1'-biphenyl-4-carboxylic acid hydrochloride	402.1706	402.1700
Example 57		(+/-)-(3R,4R)-4-phenylpiperidin-3-yl 3-(4-methoxyphenyl)propanoate hydrochloride	340.1888	340.1907

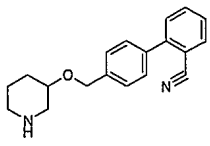
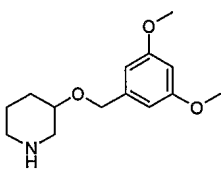
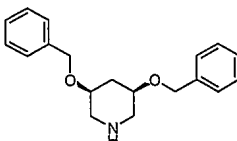
Example 59		(+/-)-(3R,4R)-4-phenylpiperidin-3-yl acetate hydrochloride	220.1332	220.1334
Example 60		(+/-)-(3R,4R)-4-pyridin-3-ylpiperidin-3-yl acetate dihydrochloride	460.1815	460.1788

5

Examples 61-79 were prepared in accordance with the above synthetic routes as shown below:

Example	Structure	FW	Ion Found (ES+)
61		191.28	192.1
62		270.17	272.1
63		270.17	270.1
64		247.38	248.3
65		209.27	210.1

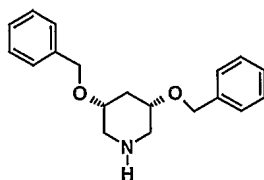
66		259.27	260.2
67		225.72	226.1
68		216.29	217.2
69		241.34	242.2
70		219.33	220.2
71		267.37	268.2
72		317.17	318.1
73		221.3	222.2
74		260.17	260.1

75		292.38	293.3
76		251.33	252.2
79		297.4	298.2

5

Examples 80 was also prepared in accordance with the above synthetic routes as described herein:

10

Example 80

OAMS supporting ions at: ESI+ 298.2

15

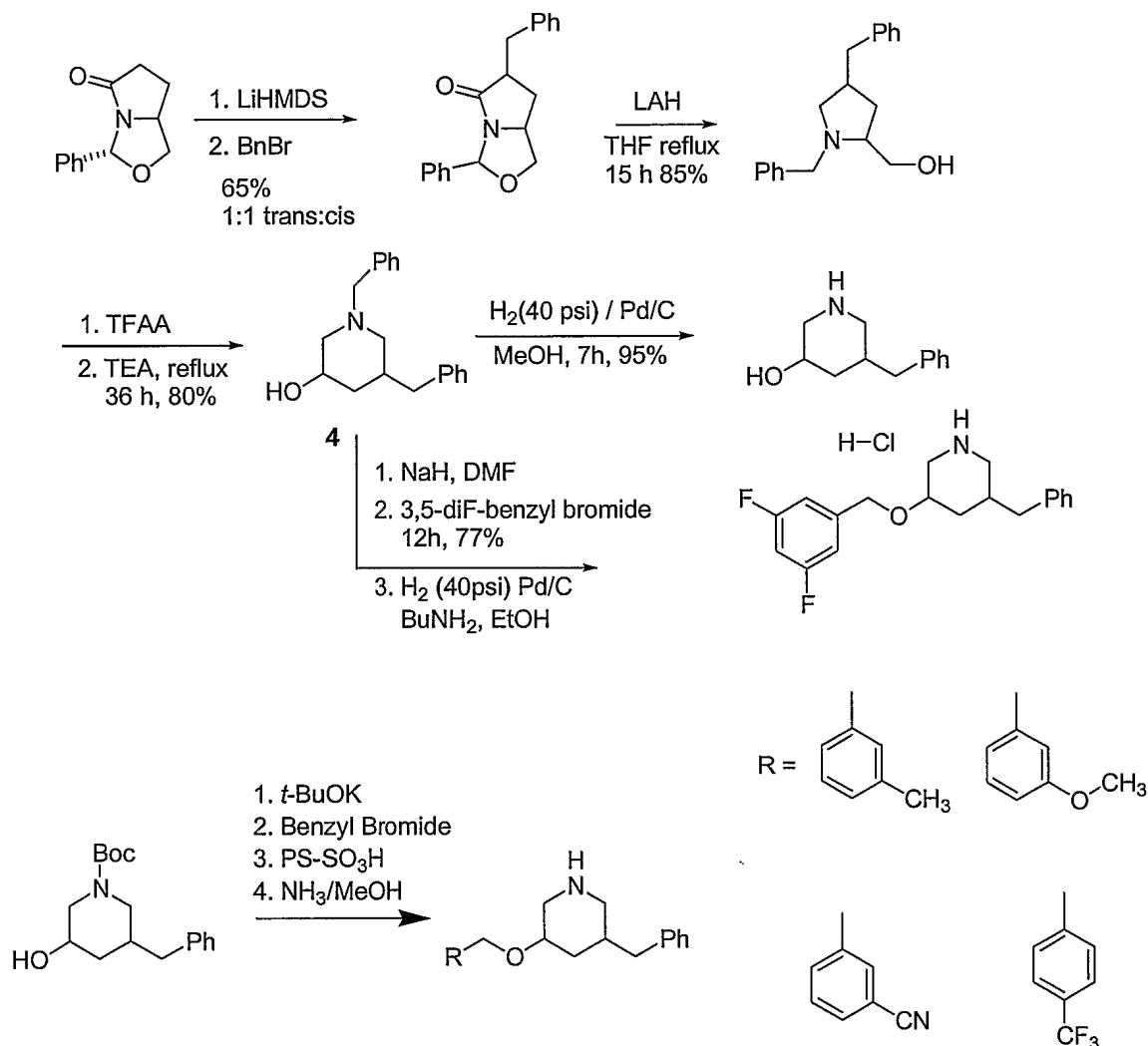
$[\alpha]_D^{25} = 0^\circ$ (c 0.72, chloroform).

Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71.

Found: C, 76.46; H, 7.76; N, 5.00.

20

In another embodiment, 3-alkoxy-5-alkyl piperidines of the invention may be prepared utilizing the routes shown below and as described:



5

Preparation of 3-alkyl-5-benzyloxy piperidines

To a THF (100 ml) solution of **1** (5.4 g, 26.6 mmol) (JOC, 1986, 51, 3140), at -78°C, was added LiHMDS (28 ml, 28 mmol, 1.0M in THF). The mixture was stirred for 1 hour followed by addition of benzyl bromide and allowed to warm to room temperature. After stirring overnight at r.t. the reaction was quenched with sat'd aq. NH₄Cl (75 ml) and extracted with EtOAc. The organic layer was washed NaHCO₃ (50 ml), brine (50 ml), and dried over MgSO₄ to give 4.9 g of **2** (64%) as a mixture of diastereomers. Flash chromatography 10% EtOAc/Heptane to 65% EtOAc/heptane yields 2.9 g of the *trans* isomer and 2.1 g of the *cis* isomer.

5 To a refluxing THF (8ml) suspension of LiAlH_4 (0.46 g, 12.3 mmol) was added a THF (8 ml) solution of **2** (2.4 g, 8.2 mmol) (*Biotech & Bioeng* 1998/99, 61, 143). The reaction was maintained at reflux for 12h followed by cooling to 0°C and the slow addition of sat's aq. NaSO_4 . The mixture was diluted with
10 EtOAc and filtered through Celite and the filtrate dried over MgSO_4 . Concentration *in vacuo* gave 2.2 g of **3** (85%) as a clear oil. To a THF (60 ml) solution of **3** (2.2 g, 7.8 mmol) was added TFAA (2.5 g, 11.7 mmol) dropwise followed by warming to r.t.. After 1.5 h at r.t. Et_3N (4.3 ml, 31.2 mmol) was added dropwise
15 followed by heating at reflux for 40h. After cooling to r.t. the mixture was treated with 10% NaOH and stirred for 1h. The mixture was diluted with EtOAc (75ml) and washed with NaHCO_3 (2 x 20 ml), brine (20 ml) and the organic layer dried over Na_2SO_4 . Flash chromatography 5% MeOH/ CHCl_3 gave 1.6 g of **4** (73%).

20 A parr apparatus was charged with Pd/C 0.470 mg and **4** (1.26 g, 4.5 mmol) in 40 ml of MeOH. The apparatus was charged with 40 psi. H_2 and shaken at r.t. for 6 h. The reaction mixture was filtered through Celite and conc. *in vacuo*. The resulting residue was dissolved in THF (30 ml) followed by the addition of
25 Boc_2O (1.2 g, 5.4 mmol). After stirring at r.t for 3h the reaction was diluted with EtOAc (70 ml) and washed with H_2O (3 x 20 ml). The organic layer was dried over MgSO_4 and concentrated *in vacuo* to yield **5** (0.74 g, 57%) as a white solid after flash chromatography 50% EtOAc/heptane.

30 Example 82:

3-benzyl-5-[(3,5-difluorobenzyl)oxy]piperidine hydrochloride.

Compound **5** (0.10 g , 0.34 mmol) in THF (1 ml) was treated with
35 0.7 ml of 1.0 M *t*-BuOK in THF and stirred for 15 min. at r.t.. The mixture was treated with 2.0 eq. of 3,5-difluorobenzyl bromide and stirred at 50°C for 18 h. The mixture was diluted

5 with 5 ml of MeOH followed by the addition of 1 g of DOWEX®
50X2-400 ion-exchange resin and stirred at 45°C for 5h. The
resin was collected by filtration and washed with MeOH and
CH₂Cl₂ (3 x 10 ml). The resin was then treated with 7N NH₃/MeOH
to elute the final compound. The desired salt was obtained by
10 treating the amine with either HCl or TFA in Et₂O.
HRMS $m+H = 318.1663$

The following were prepared according to the methods described
for example 82.

15

Example 83: 3-benzyl-5-[(3-methylbenzyl)oxy]piperidine
hydrochloride. HRMS $m+H = 296.2012$.

Example 84. 3-benzyl-5-{[4-
20 (trifluoromethyl)benzyl]oxy}piperidine hydrochloride. HRMS $m+H$
= 349.1653

Example 85. 3-({5-benzylpiperidin-3-
yl]oxy)methyl)benzonitrile. HRMS $m+H = 307.1807$.

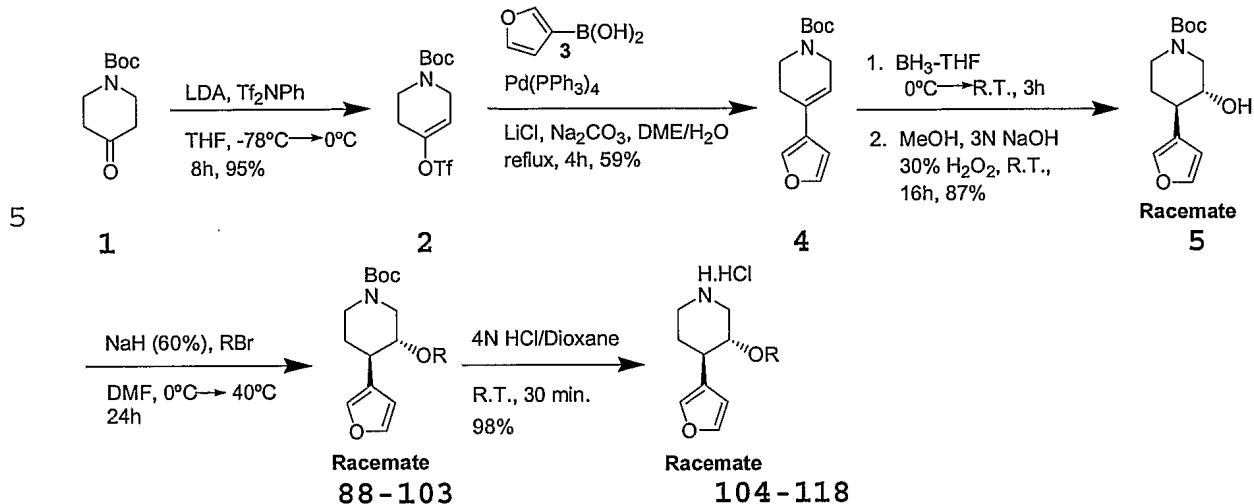
25

Example 86. 3-benzyl-5-[(3-methoxybenzyl)oxy]piperidine
hydrochloride. HRMS $m+H = 312.1965$.

Example 87. 5-benzylpiperidin-3-yl 1,1'-biphenyl-4-
30 carboxylate trifluoroacetate. HRMS $m+H = 372.1953$

35

Synthesis of Furyl Piperidine Analogs



4-Trifluoromethanesulfonyloxy-3,6-dihydro-2H-pyridine-1-
carboxylic acid tert-butyl ester (2).

A solution of *t*-butyl 4-oxopiperidine-1-carboxylate (6.50g, 32.6 mmol) in THF (50 mL) was added dropwise to a stirred solution of LDA (24 mL, 35.8 mmol, 1.1 eq., 1.5 M in hexanes) in THF (50 mL) at -78° C. After stirring for 30 min, a solution of *N*-phenyltrifluoromethanesulfonamide (12.48 g, 35.0 mmol, 1.07 eq.) in THF was added. The reaction mixture was stirred under inert atmosphere for 6 h at 0° C. The reaction was concentrated in vacuo and filtered over a pad of alumina (hexanes/EtOAc 9:1) to afford **2** as a pale yellow oil which was used without further purification (10.26 g, 95 %).

4-Furan-3-yl-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-
butyl ester (4).

A flask was charged with boronic acid **3** (6.22 g, 55.6 mmol), triflate **2** (55.27 g, 166.8 mmol, 3 eq.), lithium chloride (7.07 g, 166.8 mmol, 3 eq.), aqueous 2N Na₂CO₃ (56 mL), 1,2-dimethoxyethane (120 mL) and Pd(PPh₃)₄ (3.21 g, 2.8 mmol, 0.05 eq.). The reaction mixture was heated to reflux under inert atmosphere for 4 h. After cooling to room temperature the reaction mixture was concentrated under reduced pressure. The resulting residue was partitioned between dichloromethane (150 mL), aqueous 2N Na₂CO₃ (125 mL), and concentrated ammonium

5 hydroxide (9 mL). The layers were separated and the aqueous layer extracted again with dichloromethane (3 × 125 mL). The combined organics were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography (hexanes/CH₂Cl₂/EtOAc 9:1:1) to
10 yield **4** as a light yellow oil (8.13 g, 59 %). TLC R_f = 0.43; 400 MHz ¹H-NMR (CDCl₃) δ 1.48 (s, 9H), 2.37 (s, 2H), 3.60 (t, J = 3.6 Hz, 2H), 4.03 (s, 2H), 5.87 (s, 1H), 6.51 (s, 1H), 7.38 (d, J = 6.8 Hz, 2H); 125 MHz ¹³C-NMR (CDCl₃) δ 26.9, 39.5 (broad), 40.8 (broad), 43.6 (broad), 79.7, 107.2, 118.7 (broad), 126.8,
15 138.1, 143.5, 154.9. HRMS Calcd. for C₁₄H₁₉NO₃Na [M⁺+Na]: 272.1263. Found: 272.1271.

4-Furan-3-yl-3-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (5). To a solution of **4** (2.33 g, 9.358 mmol) in THF (10 mL) at 0° C borane-tetrahydrofuran, BH₃-THF (28.07 mL, 28.07
20 mmol, 3 eq., 1M sol. in THF) was added dropwise. After stirring the reaction mixture under inert atmosphere at room temperature for 3h, the unreacted borane was quenched by the addition of methyl alcohol (30 mL). After quenching, 3N NaOH (30 mL) was added slowly to the reaction mixture. This was followed by the
25 addition of 30 % H₂O₂ (15 mL). The reaction mixture was stirred under inert atmosphere at room temperature for 16h. Solvents were removed under reduced pressure and the crude mixture was dissolved in ethyl acetate (60 mL). The ethyl acetate solution was washed with water (40 mL), bicarbonate solution (40 mL),
30 water (40 mL), and brine (40 mL), dried over anhydrous magnesium sulfate and filtered. Removal of solvent at reduced pressure yielded the pure, white, crystalline solid **5** (2.18 g, 87 %). TLC R_f = 0.48 (95 % CH₂Cl₂-MeOH); 400 MHz ¹H-NMR (CDCl₃) δ 1.47 (s, 9H), 1.57-1.69 (m, 1H), 1.82-1.85 (m, 0.5H), 1.86-1.88 (m, 0.5H), 2.50 (ddd, J = 12.4, 10.0, 4.0 Hz, 1H), 2.62 (t, J = 10.8 Hz, 1H), 2.76 (m, 1H), 3.47 (m, 1H), 4.12 (m, 1H), 4.32 (m, 1H), 6.35 (s, 1H), 7.38 (d, J = 18.8 Hz, 2H); 125 MHz ¹³C-NMR (CDCl₃)
35

5 δ 14.4, 20.2, 28.6, 40.2, 60.1, 70.1, 80.1, 109.5, 126.0, 139.7,
143.6, 154.9. HRMS Calcd. for $C_{14}H_{21}NO_4Na$ [M^+Na]: 290.1368.
Found: 290.1368.

General procedure for alkylation reactions (88-103). To a
stirred suspension of sodium hydride (1.3 eq., 60 % suspension
10 in mineral oil) in dimethylformamide (8 mL) at 0° C was added
the alcohol 5 (usually 0.10 g, 0.4 mmol). Following stirring
under inert atmosphere at room temperature for 1h benzyl bromide
(3 eq.) was added. The reaction mixture was heated to 40° C and
stirred under inert atmosphere for 48h. To the reaction mixture
15 was added ethyl acetate (40 mL) and water (20 mL). The layers
were separated and the organic layer dried over anhydrous
magnesium sulfate, and concentrated *in vacuo*. Purification by
flash column chromatography (hexanes/EtOAc 5:1) yielded pure
products 88-103 (Table 1).

20

Table 1. Yields and product characterization for the alkylation reaction.

#	Name	% Yield	Calcd. HRMS	Found HRMS
88	3-Benzoyloxy-4-furan-3-yl-piperidine-1-carboxylic acid <i>tert</i> -butyl ester	41	380.1838 [M^+Na]	380.1840
89	3-(Biphenyl-4-ylmethoxy)-4-furan-3-yl-piperidine-1-carboxylic acid <i>tert</i> -butyl ester	43	456.2151 [M^+Na]	456.2146
90	4-Furan-3-yl-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylic acid <i>tert</i> -butyl ester	6	430.1994 [M^+Na]	430.2094
91	4-Furan-3-yl-3-(naphthalen-1-ylmethoxy)-piperidine-1-carboxylic acid <i>tert</i> -butyl ester	43	430.1994 [M^+Na]	430.1988
92	4-Furan-3-yl-3-(4-phenoxybenzyloxy)-piperidine-1-carboxylic acid <i>tert</i> -butyl ester	56	472.2100 [M^+Na]	472.2110
93	3-(4- <i>tert</i> -Butyl-benzyloxy)-	68	436.2464	436.2464

	4-furan-3-yl-piperidine-1-carboxylic acid tert-butyl ester		[M ⁺ +Na]	
94	3-(Anthracen-9-ylmethoxy)-4-furan-3-yl-piperidine-1-carboxylic acid tert-butyl ester	29	480.2151 [M ⁺ +Na]	480.2159
95	4-Furan-3-yl-3-(3-methyl-benzyloxy)-piperidine-1-carboxylic acid tert-butyl ester	74	394.1994 [M ⁺ +Na]	394.2002
96	3-(3,5-Dimethoxy-benzyloxy)-4-furan-3-yl-piperidine-1-carboxylic acid tert-butyl ester	59	440.2049 [M ⁺ +Na]	440.2053
97	3-(4-Bromo-benzyloxy)-4-furan-3-yl-piperidine-1-carboxylic acid tert-butyl ester	66	458.0943 [M ⁺ +Na]	458.0966
98	4-Furan-3-yl-3-(4-methanesulfonyl-benzyloxy)-piperidine-1-carboxylic acid tert-butyl ester	32	458.1613 [M ⁺ +Na]	458.1633
99	4-Furan-3-yl-3-(2-methyl-allyloxy)-piperidine-1-carboxylic acid tert-butyl ester	38	344.1838 [M ⁺ +Na]	344.1831
100	3-Cyclohexylmethoxy-4-furan-3-yl-piperidine-1-carboxylic acid tert-butyl ester	4	386.2307 [M ⁺ +Na]	386.2306
101	3-(2-Cyclohexyl-ethoxy)-4-furan-3-yl-piperidine-1-carboxylic acid tert-butyl ester	41	400.2461 [M ⁺ +Na]	400.2455
102	4-Furan-3-yl-3-isobutoxy-piperidine-1-carboxylic acid tert-butyl ester	9	346.1994 [M ⁺ +Na]	346.1981
103	3-(2-Ethyl-butoxy)-4-furan-3-yl-piperidine-1-carboxylic acid tert-butyl ester	4	374.2307 [M ⁺ +Na]	374.2304

5

General procedure for ^tBoc removal reaction (104-118). To 88-
10 103 (usually 0.05 g) was added 4N HCl-dioxane (3 mL). The

reaction mixture was stirred under inert atmosphere at room temperature for 30 min. Removal of solvent at reduced pressure followed by trituration with diethyl ether yielded pure products 104-118 (Table 2).

Table 2. Yields and product characterization for the ^tBoc deprotection reaction.

#	Name	% Yield	Calcd. HRMS	Found HRMS
104	3-Benzyloxy-4-furan-3-yl-piperidine	85	280.1313 [M ⁺ +Na]	280.1316
105	3-(Biphenyl-4-ylmethoxy)-4-furan-3-yl-piperidine	98	334.1807 [M ⁺ +H]	334.1806
106	4-Furan-3-yl-3-(naphthalen-2-ylmethoxy)-piperidine	99	330.1470 [M ⁺ +Na]	330.1463
107	4-Furan-3-yl-3-(naphthalen-1-ylmethoxy)-piperidine	99	308.1650 [M ⁺ +H]	308.1651
108	4-Furan-3-yl-3-(4-phenoxy-benzyloxy)-piperidine	99	350.1756 [M ⁺ +H]	350.1767
109	3-(4-tert-Butyl-benzyloxy)-4-furan-3-yl-piperidine	89	314.2120 [M ⁺ +H]	314.2125
110	3-(Anthracen-9-ylmethoxy)-4-furan-3-yl-piperidine	52	358.1807 [M ⁺ +H]	358.1815
111	4-Furan-3-yl-3-(3-methyl-benzyloxy)-piperidine	99	272.1650 [M ⁺ +H]	272.1639
112	3-(3,5-Dimethoxy-benzyloxy)-4-furan-3-yl-piperidine	99	318.1705 [M ⁺ +H]	318.1703
113	3-(4-Bromo-benzyloxy)-4-furan-3-yl-piperidine	99	336.0599 [M ⁺ +H]	336.0610
114	4-Furan-3-yl-3-(2-methyl-allyloxy)-piperidine	98	222.1494 [M ⁺ +H]	222.1498
115	3-Cyclohexylmethoxy-4-furan-3-yl-piperidine	99	264.1963 [M ⁺ +H]	264.1950
116	3-(2-Cyclohexyl-ethoxy)-4-furan-3-yl-piperidine	58	278.2120 [M ⁺ +H]	278.2126
117	4-Furan-3-yl-3-isobutoxy-piperidine	73	224.1650 [M ⁺ +H]	224.1658
118	3-(2-Ethyl-butoxy)-4-furan-3-yl-piperidine	93	252.1964 [M ⁺ +H]	

Examples for alkylation and ^tBoc deprotection reactions:

3-Benzyloxy-4-furan-3-yl-piperidine-1-carboxylic acid *tert*-butyl ester (**88**). To a stirred suspension of sodium hydride (0.02 g,

5 0.5 mmol, 1.3 eq., 60 % suspension in mineral oil) in dimethylformamide (8 mL) at 0° C was added the alcohol 5 (0.10 g, 0.4 mmol). Following stirring under inert atmosphere at room temperature for 1h benzyl bromide (0.13 mL, 1.1 mmol, 3 eq.) was added. The reaction mixture was heated to 40° C and stirred
10 under inert atmosphere for 48h. To the reaction mixture was added ethyl acetate (40 mL) and water (20 mL). The layers were separated and the organic layer dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Purification by flash column chromatography (hexanes/EtOAc 5:1) yielded clear viscous
15 liquid 6 (0.05 g, 41 %). TLC R_f = 0.22; 400 MHz ^1H -NMR (CDCl_3) δ 1.47 (s, 9H), 1.62 (ddd, J = 16.8, 12.4, 4.4 Hz, 1H), 1.89 (m, 1H), 2.66 (m, 2H), 2.79 (t, J = 12.4 Hz, 1H), 3.25 (s, 1H), 4.06 (m, 1H), 4.38 (d, J = 11.2 Hz, 2H), 4.53 (s, 1H), 6.33 (s, 1H), 7.19 (d, J = 7.2 Hz, 2H), 7.27 (m, 4H), 7.37 (s, 1H); 125 MHz
20 ^{13}C -NMR (CDCl_3) δ 28.6, 39.5, 72.1, 78.1, 78.0, 110.2, 126.5, 127.8, 128.0, 129.0, 138.3, 139.4, 142.8. HRMS Calcd. for $\text{C}_{21}\text{H}_{27}\text{NO}_4\text{Na}$ [$\text{M}^+ + \text{Na}$]: 380.1838. Found: 380.1840.

3-(Biphenyl-4-ylmethoxy)-4-furan-3-yl-piperidine-1-carboxylic
25 acid *tert*-butyl ester (89). Clear viscous liquid (43 %). TLC R_f = 0.21; 400 MHz ^1H -NMR (CDCl_3) δ 1.47 (s, 9H), 1.64 (m, 1H), 1.89 (m, 1H), 2.66 (m, 2H), 2.80 (t, J = 12.0 Hz, 1H), 3.29 (s, 1H), 4.06 (m, 1H), 4.42 (d, J = 11.2 Hz, 2H), 4.57 (s, 1H), 6.35 (s, 1H), 7.27 (m, 2H), 7.33 (m, 2H), 7.38 (m, 1H), 7.42 (m, 2H),
30 7.56 (m, 4H); 125 MHz ^{13}C -NMR (CDCl_3) δ 28.6, 39.5, 71.9, 78.2, 80.0, 110.3, 126.5, 127.2, 127.3, 127.4, 128.4, 128.9.4, 137.3, 139.4, 140.8, 141.0, 142.8, 154.8. HRMS Calcd. for $\text{C}_{27}\text{H}_{31}\text{NO}_4\text{Na}$ [$\text{M}^+ + \text{Na}$]: 456.2151. Found: 456.2146.

35 4-Furan-3-yl-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylic
acid *tert*-butyl ester (90). Clear viscous liquid (6 %). TLC R_f

5 = 0.27; 400 MHz ^1H -NMR (CDCl_3) δ 1.44 (s, 9H), 1.63 (m, 1H), 1.89 (m, 1H), 2.69 (m, 2H), 2.80 (m, 1H), 3.30 (s, 1H), 4.09 (m, 1H), 4.54 (d, J = 11.6 Hz, 2H), 4.68 (m, 1H), 6.33 (s, 1H), 7.25 (m, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.32 (m, 2H), 7.62 (s, 1H), 7.78 (m, 3H); 125 MHz ^{13}C -NMR (CDCl_3) δ 28.6, 39.6, 72.2, 78.2, 80.0, 10
110.3, 125.9, 126.0, 126.2, 126.5, 126.6, 127.8, 128.1, 128.3, 133.2, 133.4, 135.8, 139.5, 142.8. HRMS Calcd. for $\text{C}_{25}\text{H}_{29}\text{NO}_4\text{Na}$ $[\text{M}^+ + \text{Na}]$: 430.1994. Found: 430.2094.

4-Furan-3-yl-3-(naphthalen-1-ylmethoxy)-piperidine-1-carboxylic
15 acid tert-butyl ester (91). Clear viscous liquid (43 %). TLC R_f = 0.12; 400 MHz ^1H -NMR (CDCl_3) δ 1.46 (s, 9H), 1.63 (m, 1H), 1.86 (m, 1H), 2.65 (m, 2H), 2.77 (m, 1H), 3.36 (s, 1H), 4.06 (m, 1H), 4.51-5.12 (m, 3H), 6.26 (s, 1H), 7.27 (d, J = 27.2 Hz, 2H), 7.40 (m, 3H), 7.78 (m, 4H); 125 MHz ^{13}C -NMR (CDCl_3) δ 28.6, 39.5, 20
70.7, 78.1, 80.0, 109.9, 124.3, 125.3, 125.9, 126.2, 126.4, 126.9, 128.5, 129.0, 131.9, 133.6, 133.9, 139.5, 142.8. HRMS Calcd. for $\text{C}_{25}\text{H}_{29}\text{NO}_4\text{Na}$ $[\text{M}^+ + \text{Na}]$: 430.1994. Found: 430.1988.

4-Furan-3-yl-3-(4-phenoxy-benzyloxy)-piperidine-1-carboxylic
25 acid tert-butyl ester (92). Clear viscous liquid (56 %). TLC R_f = 0.16; 400 MHz ^1H -NMR (CDCl_3) δ 1.46 (s, 9H), 1.61 (m, 1H), 1.85 (m, 1H), 2.62 (m, 2H), 2.78 (t, J = 12 Hz, 1H), 3.23 (m, 1H), 4.04 (m, 1H), 4.33 (d, J = 11.6 Hz, 2H), 4.51 (m, 1H), 6.28 (s, 1H), 6.89 (m, 3H), 6.99 (m, 2H), 7.09 (t, J = 7.2 Hz, 1H), 7.28
30 (m, 5H); 125 MHz ^{13}C -NMR (CDCl_3) δ 28.6, 39.4, 71.6, 78.4, 80.0, 110.2, 118.1, 119.0, 122.5, 123.4, 126.4, 129.7, 129.9, 139.3, 140.4, 142.8, 154.7, 157.3, 157.5. HRMS Calcd. for $\text{C}_{27}\text{H}_{31}\text{NO}_5\text{Na}$ $[\text{M}^+ + \text{Na}]$: 472.2100. Found: 472.2110.

35 3-(4-tert-Butyl-benzyloxy)-4-furan-3-yl-piperidine-1-carboxylic
acid tert-butyl ester (93). Clear viscous liquid (68 %). TLC R_f

5 = 0.21; 400 MHz ^1H -NMR (CDCl_3) δ 1.32 (s, 9H), 1.49 (s, 9H), 1.64 (ddd, J = 16.8, 12.4, 4.4 Hz, 1H), 1.90 (m, 1H), 2.66 (m, 2H), 2.80 (t, J = 12.4 Hz, 1H), 3.27 (s, 1H), 4.09 (m, 1H), 4.36 (d, J = 10.8 Hz, 2H), 4.52 (m, 1H), 6.36 (s, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.33 (m, 3H), 7.38 (t, J = 1.6 Hz, 1H); 125 MHz ^{13}C -NMR
10 (CDCl_3) δ 14.3, 22.8, 28.6, 31.5, 34.7, 39.5, 72.0, 78.1, 80.0, 110.2, 125.4, 126.5, 127.8, 135.2, 139.4, 142.7, 150.763, 154.8. HRMS Calcd. for $\text{C}_{25}\text{H}_{35}\text{NO}_4\text{Na}$ [$\text{M}^+ + \text{Na}$]: 436.2464. Found: 436.2464.

3-Benzoyloxy-4-furan-3-yl-piperidine (104). To **6** (0.07 g, 0.2 mmol) was added 4N HCl-dioxane (4 mL). The reaction mixture was stirred under inert atmosphere for 30 min. Removal of solvent at reduced pressure followed by trituration with diethyl ether yielded pure, crystalline **22** (0.05 g, 85 %); 400 MHz ^1H -NMR (CD_3OD) δ 2.02 (m, 1H), 2.22 (m, 1H), 2.99 (m, 2H), 3.12 (m, 1H), 3.60 (m, 0.5H), 3.68 (m, 1H), 3.75 (m, 0.5H), 3.82 (td, J = 8.4, 3.6 Hz, 1H), 4.60 (d, J = 11.2 Hz, 1H), 4.51 (d, J = 11.2 Hz, 1H), 6.46 (s, 1H), 7.30 (m, 5H), 7.49 (m, 2H); 125 MHz ^{13}C -NMR (CD_3OD) δ 27.4, 37.2, 43.8, 46.8, 73.9, 75.8, 104.2, 110.9, 129.1, 129.2, 129.5, 139.2, 141.2, 144.6. HRMS Calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_2\text{Na}$ [$\text{M}^+ + \text{Na}$]: 280.1313. Found: 280.1316.
25

3-(Biphenyl-4-ylmethoxy)-4-furan-3-yl-piperidine (105). Solid (98 %); 400 MHz ^1H -NMR (CD_3OD) δ 2.02 (m, 1H), 2.22 (m, 1H), 2.99 (m, 2H), 3.11 (m, 1H), 3.59 (m, 0.5H), 3.66 (m, 1H), 3.74 (m, 0.5H), 3.82 (td, J = 8.0, 3.2 Hz, 1H), 4.54 (d, J = 11.6 Hz, 1H), 4.62 (d, J = 11.6 Hz, 1H), 6.46 (s, 1H), 7.34 (m, 2H), 7.43 (m, 3H); 7.49 (m, 2H), 7.58 (m, 4H); 125 MHz ^{13}C -NMR (CD_3OD) δ 27.4, 37.2, 43.8, 46.8, 73.1, 75.8, 110.9, 128.0, 128.1, 128.6, 129.8, 130.0, 141.2, 144.7. HRMS Calcd. for $\text{C}_{22}\text{H}_{24}\text{NO}_2$ [$\text{M}^+ + \text{H}$]:
35 334.1807. Found: 334.1806.

5 4-Furan-3-yl-3-(naphthalen-2-ylmethoxy)-piperidine(106). Solid
(99 %); 400 MHz ^1H -NMR (CD_3OD) δ 1.99 (m, 1H), 2.24 (m, 1H), 3.03
(m, 2H), 3.11 (m, 1H), 3.59 (m, 0.5H), 3.67 (m, 1H), 3.75 (m,
0.5H), 3.83 (td, J = 8.0, 3.2 Hz, 1H), 4.69 (d, J = 11.6 Hz,
1H), 4.76 (d, J = 11.6 Hz, 1H), 6.44 (s, 1H), 7.38 (d, J = 8.4
10 Hz, 2H), 7.49 (m, 4H); 7.74 (s, 1H), 7.83 (m, 3H); 125 MHz ^{13}C -
NMR (CD_3OD) δ 27.3, 37.1, 43.8, 46.9, 68.2, 73.4, 110.8, 127.0,
127.2, 127.9, 128.7, 129.0, 129.2, 134.7, 141.2, 144.6. HRMS
Calcd. for $\text{C}_{20}\text{H}_{21}\text{NO}_2$ [$\text{M}^+ + \text{Na}$]: 330.1470. Found: 330.1463.

15 4-Furan-3-yl-3-(naphthalen-1-ylmethoxy)-piperidine(107). Solid
(99 %); 400 MHz ^1H -NMR (CD_3OD) δ 1.98 (m, 1H), 2.12 (m, 1H), 2.91
(m, 2H), 3.03 (m, 1H), 3.46 (m, 1H), 3.63 (s, 1H), 3.86 (m, 1H),
4.91 (d, J = 11.6 Hz, 1H), 4.96 (d, J = 11.6 Hz, 1H), 6.36 (s,
1H), 7.42 (m, 5H), 7.84 (m, 3H); 125 MHz ^{13}C -NMR (CD_3OD) δ 27.8,
20 37.4, 43.9, 47.0, 68.2, 71.9, 75.7, 110.6, 125.3, 126.3, 127.0,
127.3, 128.4, 130.0, 130.2, 134.4, 135.3, 141.3, 144.6. HRMS
Calcd. for $\text{C}_{20}\text{H}_{21}\text{NO}_2$ [$\text{M}^+ + \text{H}$]: 308.1650. Found: 308.1651.

4-Furan-3-yl-3-(4-phenoxy-benzyloxy)-piperidine(108). Solid (99
25 %); 400 MHz ^1H -NMR (CD_3OD) δ 1.99 (m, 1H), 2.17 (m, 1H), 2.96 (m,
2H), 3.08 (m, 1H), 3.49 (m, 1H), 3.65 (s, 1H), 3.78 (m, 1H),
4.45 (d, J = 11.6 Hz, 1H), 4.57 (d, J = 11.6 Hz, 1H), 6.39 (s,
1H), 6.95 (m, 5H), 7.10 (t, J = 7.2 Hz, 1H), 7.32 (m, 4H), 7.42
(s, 1H); 125 MHz ^{13}C -NMR (CD_3OD) δ 27.4, 37.2, 43.9, 46.8, 72.9,
30 76.0, 110.8, 119.2, 119.3, 120.0, 123.8, 124.6, 125.9, 130.7,
131.0, 141.2, 141.3, 144.6, 158.6, 159.0. HRMS Calcd. for
 $\text{C}_{22}\text{H}_{24}\text{NO}_3$ [$\text{M}^+ + \text{H}$]: 350.1756. Found: 350.1767.

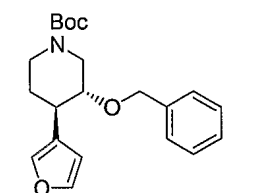
3-(4-tert-Butyl-benzyloxy)-4-furan-3-yl-piperidine(109). Solid
35 (89 %); 400 MHz ^1H -NMR (CD_3OD) δ 1.99 (m, 1H), 2.23 (m, 1H), 2.98
(m, 2H), 3.10 (m, 1H), 3.45 (m, 1H), 3.67 (s, 1H), 3.78 (m, 1H),

5 4.49 (d, $J = 11.6$ Hz, 1H), 4.55 (d, $J = 11.6$ Hz, 1H), 6.43 (s, 1H), 7.20 (d, $J = 8.0$ Hz, 2H), 7.37 (d, $J = 8$ Hz, 4H), 7.47 (d, $J = 15.6$ Hz, 1H); 125 MHz ^{13}C -NMR (CD_3OD) δ 27.3, 31.9, 35.5, 37.1, 43.8, 46.9, 68.3, 73.2, 75.5, 110.9, 126.0, 126.4, 129.2, 136.1, 141.2, 144.7, 152.3. HRMS Calcd. for $\text{C}_{20}\text{H}_{28}\text{NO}_2$ [$\text{M}^+ + \text{H}$]:
10 314.2120. Found: 314.2125.

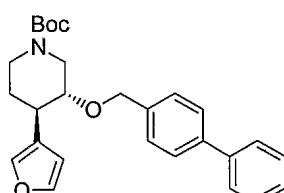
Table of compounds

Products of alkylation reactions (88-103)

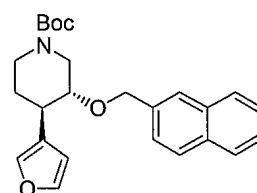
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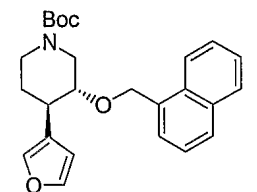
3-Benzyloxy-4-furan-3-yl-piperidine-1-carboxylic acid *tert*-butyl ester, **88**,
Exact Mass: 357.1940



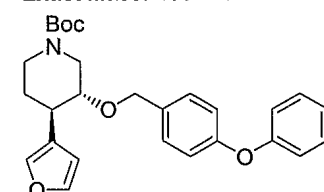
3-(Biphenyl-4-ylmethoxy)-4-furan-3-yl-piperidine-1-carboxylic acid *tert*-butyl ester, **89**,
Exact Mass: 433.2253



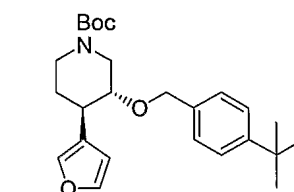
4-Furan-3-yl-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylic acid *tert*-butyl ester, **90**,
Exact Mass: 407.2097



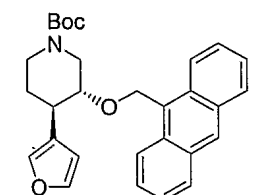
4-Furan-3-yl-3-(naphthalen-1-ylmethoxy)-piperidine-1-carboxylic acid *tert*-butyl ester, **91**,
Exact Mass: 407.2097



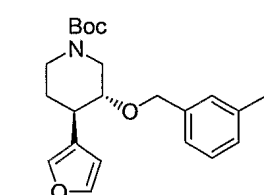
4-Furan-3-yl-3-(4-phenoxybenzyloxy)-piperidine-1-carboxylic acid *tert*-butyl ester, **92**,
Exact Mass: 449.2202



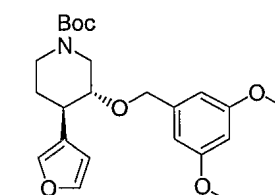
3-(4-*tert*-Butylbenzyloxy)-4-furan-3-yl-piperidine-1-carboxylic acid *tert*-butyl ester, **93**,
Exact Mass: 313.2042



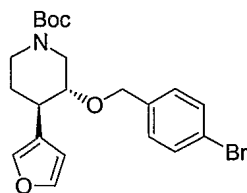
3-(Anthracen-9-ylmethoxy)-4-furan-3-yl-piperidine-1-carboxylic acid *tert*-butyl ester, **94**,
Exact Mass: 457.2253



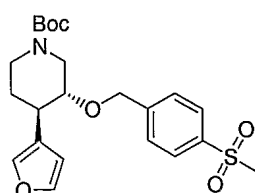
4-Furan-3-yl-3-(3-methylbenzyloxy)-piperidine-1-carboxylic acid *tert*-butyl ester, **95**,
Exact Mass: 371.2097



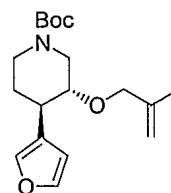
3-(3,5-Dimethoxybenzyloxy)-4-furan-3-yl-piperidine-1-carboxylic acid *tert*-butyl ester, **96**,
Exact Mass: 417.2151



3-(4-Bromo-benzyloxy)-4-furan-3-yl-piperidine-1-carboxylic acid *tert*-butyl ester, **97**,
Exact Mass: 435.1045

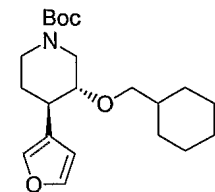


4-Furan-3-yl-3-(4-methanesulfonyl-benzyloxy)-piperidine-1-carboxylic acid *tert*-butyl ester, **98**,
Exact Mass: 435.1716

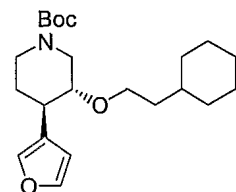


4-Furan-3-yl-3-(2-methyl-allyloxy)-piperidine-1-carboxylic acid *tert*-butyl ester, **99**,
Exact Mass: 321.1940

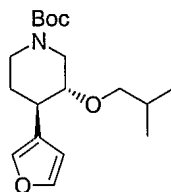
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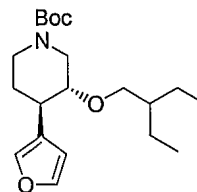
3-Cyclohexylmethoxy-4-furan-3-yl-piperidine-1-carboxylic acid *tert*-butyl ester, **100**,
Exact Mass: 363.2410



3-(2-Cyclohexyl-ethoxy)-4-furan-3-yl-piperidine-1-carboxylic acid *tert*-butyl ester, **101**,
Exact Mass: 377.2566



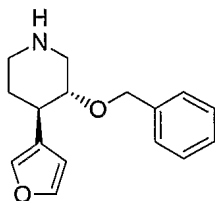
4-Furan-3-yl-3-isobutoxy-piperidine-1-carboxylic acid *tert*-butyl ester, **102**,
Exact Mass: 323.2097



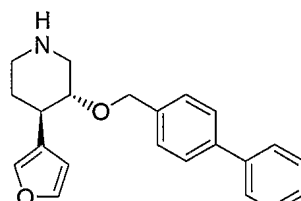
3-(2-Ethyl-butoxy)-4-furan-3-yl-piperidine-1-carboxylic acid *tert*-butyl ester, **103**,
Exact Mass: 351.4804

Products of ^tBoc deprotection reactions (104-118)

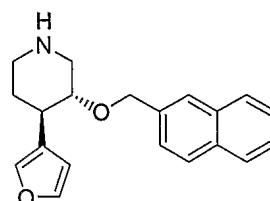
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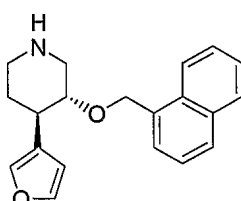
3-Benzyloxy-4-furan-3-yl-piperidine, **104**,
Exact Mass: 257.1416



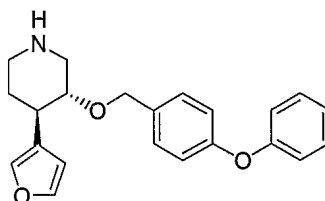
3-(Biphenyl-4-ylmethoxy)-4-furan-3-yl-piperidine, **105**,
Exact Mass: 333.1729



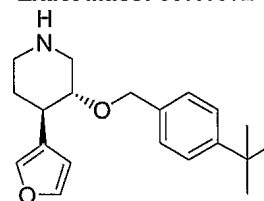
4-Furan-3-yl-3-(naphthalen-2-ylmethoxy)-piperidine, **106**,
Exact Mass: 307.1572



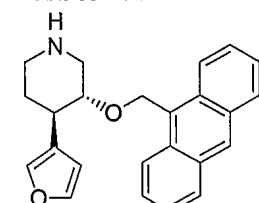
4-Furan-3-yl-3-(naphthalen-1-ylmethoxy)-piperidine, **107**,
Exact Mass: 307.1572



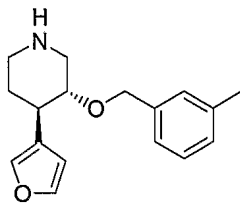
4-Furan-3-yl-3-(4-phenoxybenzyloxy)-piperidine, **108**,
Exact Mass: 349.1678



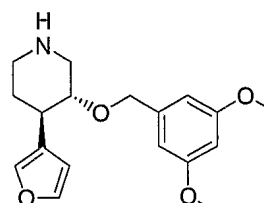
3-(4-*tert*-Butyl-benzyloxy)-4-furan-3-yl-piperidine, **109**,
Exact Mass: 313.2042



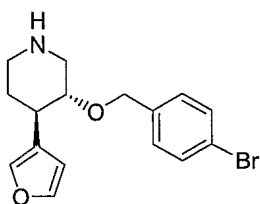
3-(Anthracen-9-ylmethoxy)-4-furan-3-yl-piperidine, **110**,
Exact Mass: 357.1729



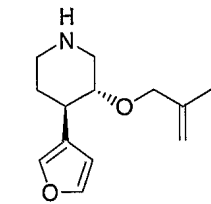
4-Furan-3-yl-3-(3-methylbenzyloxy)-piperidine, **111**,
Exact Mass: 271.1572



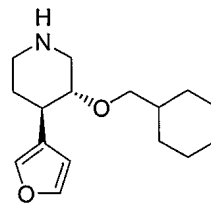
3-(3,5-Dimethoxy-benzyloxy)-4-furan-3-yl-piperidine, **112**,
Exact Mass: 317.1627



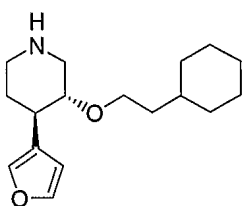
3-(4-Bromo-benzyloxy)-4-furan-3-yl-piperidine, **113**,
Exact Mass: 335.0521



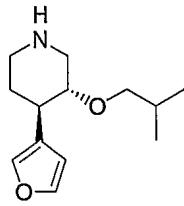
4-Furan-3-yl-3-(2-methylallyloxy)-piperidine, **114**,
Exact Mass: 221.1416



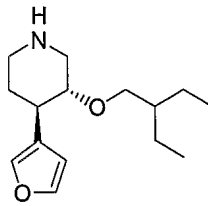
3-Cyclohexylmethoxy-4-furan-3-yl-piperidine, **115**,
Exact Mass: 263.1885



3-(2-Cyclohexyl-ethoxy)-4-furan-3-yl-piperidine, **116**,
Exact Mass: 277.2042



4-Furan-3-yl-3-isobutoxy-piperidine, **117**,
Exact Mass: 223.1572



3-(2-Ethyl-butoxy)-4-furan-3-yl-piperidine, **118**,
Exact Mass: 251.1885

Biology Examples

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the invention to its fullest extent. The invention, however, may be better understood with reference to the following examples. These examples are intended to be representative of specific embodiments of the invention, and are not intended as limiting the scope of the invention.

Example A

Enzyme Inhibition Assay

The compounds of the invention are analyzed for inhibitory activity by use of the MBP-C125 assay. This assay determines the relative inhibition of beta-secretase cleavage of a model APP substrate, MBP-C125SW, by the compounds assayed as compared with an untreated control. A detailed description of the assay parameters can be found, for example, in U.S. Patent No. 5,942,400. Briefly, the substrate is a fusion peptide formed of maltose binding protein (MBP) and the carboxy terminal 125 amino

5 acids of APP-SW, the Swedish mutation. The beta-secretase enzyme is derived from human brain tissue as described in Sinha et al, 1999, *Nature* 40:537-540) or recombinantly produced as the full-length enzyme (amino acids 1-501), and can be prepared, for example, from 293 cells expressing the recombinant cDNA, as
10 described in WO00/47618.

Inhibition of the enzyme is analyzed, for example, by immunoassay of the enzyme's cleavage products. One exemplary ELISA uses an anti-MBP capture antibody that is deposited on precoated and blocked 96-well high binding plates, followed by
15 incubation with diluted enzyme reaction supernatant, incubation with a specific reporter antibody, for example, biotinylated anti-SW192 reporter antibody, and further incubation with streptavidin/alkaline phosphatase. In the assay, cleavage of the intact MBP-C125SW fusion protein results in the generation
20 of a truncated amino-terminal fragment, exposing a new SW-192 antibody-positive epitope at the carboxy terminus. Detection is effected by a fluorescent substrate signal on cleavage by the phosphatase. ELISA only detects cleavage following Leu 596 at the substrate's APP-SW 751 mutation site.

25 Specific Assay Procedure

Compounds are diluted in a 1:1 dilution series to a six-point concentration curve (two wells per concentration) in one 96-plate row per compound tested. Each of the test compounds is prepared in DMSO to make up a 10 millimolar stock solution. The
30 stock solution is serially diluted in DMSO to obtain a final compound concentration of 200 micromolar at the high point of a 6-point dilution curve. Ten (10) microliters of each dilution is added to each of two wells on row C of a corresponding V-bottom plate to which 190 microliters of 52 millimolar NaOAc,
35 7.9% DMSO, pH 4.5 are pre-added. The NaOAc diluted compound plate is spun down to pellet precipitant and 20 microliters/well is transferred to a corresponding flat-bottom plate to which 30

5 microliters of ice-cold enzyme-substrate mixture (2.5
microliters MBP-C125SW substrate, 0.03 microliters enzyme and
24.5 microliters ice cold 0.09% TX100 per 30 microliters) is
added. The final reaction mixture of 200 micromolar compound at
the highest curve point is in 5% DMSO, 20 millimolar NaOAc,
10 0.06% TX100, at pH 4.5.

Warming the plates to 37 degrees C starts the enzyme
reaction. After 90 minutes at 37 degrees C, 200
microliters/well cold specimen diluent is added to stop the
reaction and 20 microliters/well was transferred to a
15 corresponding anti-MBP antibody coated ELISA plate for capture,
containing 80 microliters/well specimen diluent. This reaction
is incubated overnight at 4 degrees C and the ELISA is developed
the next day after a 2 hour incubation with anti-192SW antibody,
followed by Streptavidin-AP conjugate and fluorescent substrate.
20 The signal is read on a fluorescent plate reader.

Relative compound inhibition potency is determined by
calculating the concentration of compound that showed a fifty
percent reduction in detected signal (IC_{50}) compared to the
enzyme reaction signal in the control wells with no added
25 compound. In this assay, the compounds of the invention
exhibited an IC_{50} of less than 50 micromolar.

Example B

Cell Free Inhibition Assay Utilizing a Synthetic APP Substrate

A synthetic APP substrate that can be cleaved by beta-
30 secretase and having N-terminal biotin and made fluorescent by
the covalent attachment of Oregon green at the Cys residue is
used to assay beta-secretase activity in the presence or absence
of the inhibitory compounds of the invention. Useful substrates
include the following:

35

Biotin-SEVNL-DAEFR[Oregon green]KK
Biotin-SEVKM-DAEFR[Oregon green]KK
Biotin-GLNIKTEEISEISY-EVEFRC

[SEQ ID NO: 1]

[SEQ ID NO: 2]

5 [Oregon green]KK [SEQ ID NO: 3]
Biotin-ADRGLTTRPGSGLTNIKTEEISEVNL-DAEF
Oregon green]KK [SEQ ID NO: 4]
Biotin-FVNQHLCoxGSHLVEALY-LVCoXGERGFFYTPKA
[Oregon green]KK [SEQ ID NO: 5]

10

The enzyme (0.1 nanomolar) and test compounds (0.001 - 100 micromolar) are incubated in pre-blocked, low affinity, black plates (384 well) at 37 degrees for 30 minutes. The reaction is initiated by addition of 150 millimolar substrate to a final
15 volume of 30 microliter per well. The final assay conditions are: 0.001 - 100 micromolar compound inhibitor; 0.1 molar sodium acetate (pH 4.5); 150 nanomolar substrate; 0.1 nanomolar soluble beta-secretase; 0.001% Tween 20, and 2% DMSO. The assay mixture is incubated for 3 hours at 37 degrees C, and the
20 reaction is terminated by the addition of a saturating concentration of immunopure streptavidin. After incubation with streptavidin at room temperature for 15 minutes, fluorescence polarization is measured, for example, using a LJL Acquest (Ex485 nm/ Em530 nm). The activity of the beta-secretase enzyme
25 is detected by changes in the fluorescence polarization that occur when the substrate is cleaved by the enzyme. Incubation in the presence or absence of compound inhibitor demonstrates specific inhibition of beta-secretase enzymatic cleavage of its synthetic APP substrate. In this assay, compounds of the
30 invention exhibited an IC₅₀ of less than 50 micromolar.

Example C

Beta-Secretase Inhibition: P26-P4'SW Assay

Synthetic substrates containing the beta-secretase cleavage site of APP are used to assay beta-secretase activity, using the
35 methods described, for example, in published PCT application WO00/47618. The P26-P4'SW substrate is a peptide of the sequence:

(biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNLDAEF [SEQ ID NO: 6]

5

The P26-P1 standard has the sequence:

(biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNL [SEQ ID NO: 7].

Briefly, the biotin-coupled synthetic substrates are
10 incubated at a concentration of from about 0 to about 200
micromolar in this assay. When testing inhibitory compounds, a
substrate concentration of about 1.0 micromolar is preferred.
Test compounds diluted in DMSO are added to the reaction
mixture, with a final DMSO concentration of 5%. Controls also
15 contain a final DMSO concentration of 5%. The concentration of
beta secretase enzyme in the reaction is varied, to give product
concentrations with the linear range of the ELISA assay, about
125 to 2000 picomolar, after dilution.

The reaction mixture also includes 20 millimolar sodium
20 acetate, pH 4.5, 0.06% Triton X100, and is incubated at 37
degrees C for about 1 to 3 hours. Samples are then diluted in
assay buffer (for example, 145.4 nanomolar sodium chloride, 9.51
millimolar sodium phosphate, 7.7 millimolar sodium azide, 0.05%
Triton X405, 6g/liter bovine serum albumin, pH 7.4) to quench
25 the reaction, then diluted further for immunoassay of the
cleavage products.

Cleavage products can be assayed by ELISA. Diluted samples
and standards are incubated in assay plates coated with capture
antibody, for example, SW192, for about 24 hours at 4 degrees C.
30 After washing in TTBS buffer (150 millimolar sodium chloride, 25
millimolar Tris, 0.05% Tween 20, pH 7.5), the samples are
incubated with streptavidin-AP according to the manufacturer's
instructions. After a one hour incubation at room temperature,
the samples are washed in TTBS and incubated with fluorescent
35 substrate solution A (31.2 g/liter 2-amino-2-methyl-1-propanol,
30 mg/liter, pH 9.5). Reaction with streptavidin-alkaline
phosphate permits detection by fluorescence. Compounds that are

5 effective inhibitors of beta-secretase activity demonstrate reduced cleavage of the substrate as compared to a control.

Example D

Assays using Synthetic Oligopeptide-Substrates

Synthetic oligopeptides are prepared that incorporate the
10 known cleavage site of beta-secretase, and optionally detectable tags, such as fluorescent or chromogenic moieties. Examples of such peptides, as well as their production and detection methods are described in U.S. Patent No: 5,942,400, herein incorporated by reference. Cleavage products can be detected using high
15 performance liquid chromatography, or fluorescent or chromogenic detection methods appropriate to the peptide to be detected, according to methods well known in the art.

By way of example, one such peptide has the sequence SEVNLD-
DAEF [SEQ ID NO: 8], and the cleavage site is between residues
20 5 and 6. Another preferred substrate has the sequence ADRGLTTRPGSGLTNIKTEEISEVNLD-DAEF [SEQ ID NO: 9], and the cleavage site is between residues 26 and 27.

These synthetic APP substrates are incubated in the presence of beta-secretase under conditions sufficient to result
25 in beta-secretase mediated cleavage of the substrate. Comparison of the cleavage results in the presence of the compound inhibitor to control results provides a measure of the compound's inhibitory activity.

Example E

30 Inhibition of Beta-Secretase Activity - Cellular Assay

An exemplary assay for the analysis of inhibition of beta-secretase activity utilizes the human embryonic kidney cell line HEKp293 (ATCC Accession No. CRL-1573) transfected with APP751 containing the naturally occurring double mutation Lys651Met52
35 to Asn651Leu652 (numbered for APP751), commonly called the Swedish mutation and shown to overproduce A beta (Citron et al.,

5 1992, *Nature* 360:672-674), as described in U.S. Patent No. 5,604,102.

The cells are incubated in the presence/absence of the inhibitory compound (diluted in DMSO) at the desired concentration, generally up to 10 micrograms/ml. At the end of
10 the treatment period, conditioned media is analyzed for beta-secretase activity, for example, by analysis of cleavage fragments. A beta can be analyzed by immunoassay, using specific detection antibodies. The enzymatic activity is measured in the presence and absence of the compound inhibitors
15 to demonstrate specific inhibition of beta-secretase mediated cleavage of APP substrate.

Example F

Inhibition of Beta-Secretase in Animal Models of AD

Various animal models can be used to screen for inhibition
20 of beta-secretase activity. Examples of animal models useful in the invention include, but are not limited to, mouse, guinea pig, dog, and the like. The animals used can be wild type, transgenic, or knockout models. In addition, mammalian models can express mutations in APP, such as APP695-SW and the like
25 described herein. Examples of transgenic non-human mammalian models are described in U.S. Patent Nos. 5,604,102, 5,912,410 and 5,811,633.

PDAPP mice, prepared as described in Games et al., 1995, *Nature* 373:523-527 are useful to analyze *in vivo* suppression of
30 A beta release in the presence of putative inhibitory compounds. As described in U.S. Patent No. 6,191,166, 4 month old PDAPP mice are administered compound formulated in vehicle, such as corn oil. The mice are dosed with compound (1-30 mg/ml; preferably 1-10 mg/ml). After time, e.g., 3-10 hours, the
35 animals are sacrificed, and brains removed for analysis.

Transgenic animals are administered an amount of the compound inhibitor formulated in a carrier suitable for the

5 chosen mode of administration. Control animals are untreated,
treated with vehicle, or treated with an inactive compound.
Administration can be acute, i.e., single dose or multiple doses
in one day, or can be chronic, i.e., dosing is repeated daily
for a period of days. Beginning at time 0, brain tissue or
10 cerebral fluid is obtained from selected animals and analyzed
for the presence of APP cleavage peptides, including A beta, for
example, by immunoassay using specific antibodies for A beta
detection. At the end of the test period, animals are
sacrificed and brain tissue or cerebral fluid is analyzed for
15 the presence of A beta and/or beta-amyloid plaques. The tissue
is also analyzed for necrosis.

Animals administered the compound inhibitors of the
invention are expected to demonstrate reduced A beta in brain
tissues or cerebral fluids and reduced beta amyloid plaques in
20 brain tissue, as compared with non-treated controls.

Example G

Inhibition of A Beta Production in Human Patients

Patients suffering from Alzheimer's Disease (AD)
demonstrate an increased amount of A beta in the brain. AD
25 patients are administered an amount of the compound inhibitor
formulated in a carrier suitable for the chosen mode of
administration. Administration is repeated daily for the
duration of the test period. Beginning on day 0, cognitive and
memory tests are performed, for example, once per month.
30 Patients administered the compound inhibitors are expected
to demonstrate slowing or stabilization of disease progression
as analyzed by changes in one or more of the following disease
parameters: A beta present in CSF or plasma; brain or
hippocampal volume; A beta deposits in the brain; amyloid
35 plaque in the brain; and scores for cognitive and memory
function, as compared with control, non-treated patients.

5 Example H

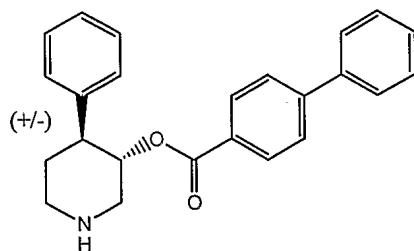
Prevention of A Beta Production in Patients at Risk for AD

Patients predisposed or at risk for developing AD are identified either by recognition of a familial inheritance pattern, for example, presence of the Swedish Mutation, and/or
10 by monitoring diagnostic parameters. Patients identified as predisposed or at risk for developing AD are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Administration is repeated daily for the duration of the test period.
15 Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

Patients administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease
20 parameters: A beta present in CSF or plasma; brain or hippocampal volume; amyloid plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated patients.

Example H: Biological Inhibition Activity

25 The biological activity of the compound prepared according to Example 29 was measured in accordance with the above described procedures



IC₅₀ of 11 uM against Bace in an enzyme assay.

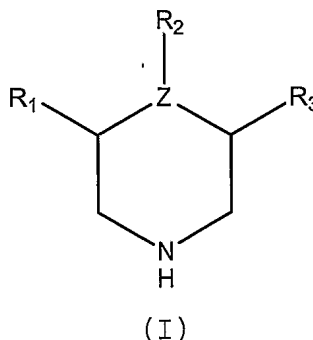
Bace IC₅₀ = 11,000 nM
Cat D IC₅₀ >20,000 nM

5 The invention has been described with reference to various
specific and preferred embodiments and techniques. However, it
should be understood that many variations and modifications may
be made while remaining within the spirit and scope of the
invention.

10

5 WHAT IS CLAIMED IS:

1. A compound of the formula I:



or a pharmaceutically acceptable salt or ester thereof,

wherein Z is CH or N;

wherein R₁ and R₃ are independently:

15 (I) C₁-C₁₀ alkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -O-phenyl, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are independently -H or C₁-C₆ alkyl, -OC(=O)NR_{1-a}R_{1-b}, -S(=O)₀₋₂R_{1-a}, -NR_{1-a}C(=O)NR_{1-a}R_{1-b}, -C(=O)NR_{1-a}R_{1-b}, and -S(=O)₂NR_{1-a}R_{1-b}, -
20 (CH₂)₀₋₃-(C₃-C₈) cycloalkyl where cycloalkyl can be optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, -CO-OH, -CO-O-(C₁-C₄ alkyl), -NR_{1-a}R_{1-b}; C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),
25

(II) -(CH₂)_{n1}-(R_{1-aryl}) where n₁ is zero or one and where R_{1-aryl} is phenyl, 1-naphthyl, 2-naphthyl and indanyl, indenyl, dihydronaphthyl, tetralinyl optionally substituted with one, two, three or four of the following independently selected
30 substituents on the aryl ring:

(1) C₁-C₆ alkyl optionally substituted with one, two or three substituents independently selected from the group

5 consisting of C_1 - C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -S(C_{1-6} alkyl), -S(aryl- C_{1-6} alkyl), -S(heteroaryl- C_{1-6} alkyl), -S=O(C_{1-6} alkyl), -S=O(aryl- C_{1-6} alkyl), -S=O(heteroaryl- C_{1-6} alkyl), -
 10 SO_2 (C_{1-6} alkyl), - SO_2 (aryl- C_{1-6} alkyl), - SO_2 (heteroaryl- C_{1-6} alkyl), -
 $NR_{1-a}R_{1-b}$, -C $\equiv$ N, -CF $_3$, C_1 - C_3 alkoxy, C_1 - C_3 alkoxy-(R_{1-aryl}), C_1 - C_3
 alkoxy-($R_{1-heteroaryl}$),

(2) C_2 - C_6 alkenyl with one or two double bonds, optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -S(C_{1-6} alkyl), -S(aryl- C_{1-6} alkyl), -
 15 S(heteroaryl- C_{1-6} alkyl), -S=O(C_{1-6} alkyl), -S=O(aryl- C_{1-6} alkyl), -S=O(heteroaryl- C_{1-6} alkyl), - SO_2 (C_{1-6} alkyl), - SO_2 (aryl- C_{1-6} alkyl), - SO_2 (heteroaryl- C_{1-6} alkyl), -C $\equiv$ N, -CF $_3$, C_1 - C_3 alkoxy, -
 $NR_{1-a}R_{1-b}$, C_1 - C_3 alkoxy-(R_{1-aryl}), C_1 - C_3 alkoxy-($R_{1-heteroaryl}$),

(3) C_2 - C_6 alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -S(C_{1-6} alkyl), -S(aryl- C_{1-6} alkyl), -
 20 S(heteroaryl- C_{1-6} alkyl), -S=O(C_{1-6} alkyl), -S=O(aryl- C_{1-6} alkyl), -S=O(heteroaryl- C_{1-6} alkyl), - SO_2 (C_{1-6} alkyl), - SO_2 (aryl- C_{1-6} alkyl), - SO_2 (heteroaryl- C_{1-6} alkyl), -C $\equiv$ N, -CF $_3$, C_1 - C_3 alkoxy, -
 25 $NR_{1-a}R_{1-b}$, C_1 - C_3 alkoxy-(R_{1-aryl}), C_1 - C_3 alkoxy-($R_{1-heteroaryl}$),

(4) -F, Cl, -Br and -I,

(5) - C_1 - C_6 alkoxy optionally substituted with one, two or three -F,

30 (6) - $NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are as defined below,

(7) -OH,

(8) -C $\equiv$ N,

(9) C_3 - C_7 cycloalkyl, optionally substituted with
 35 one, two or three substituents selected from the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -S(C_{1-6} alkyl), -

5 S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -
S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆
alkyl), -SO₂(aryl-C₁₋₆ alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N,
-CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-
(R_{1-heteroaryl}),

10 (10) -CO-(C₁-C₄ alkyl),
(11) -SO₂-NR_{1-a}R_{1-b},
(12) -CO-NR_{1-a}R_{1-b},
(13) -SO₂-(C₁-C₄ alkyl),

(III) -(CH₂)_{n₁}-(R_{1-heteroaryl}) where n₁ is as defined above

15 and where R_{1-heteroaryl} is selected from the group consisting of:

pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl,
indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl,
quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl,
isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl,
20 indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl,
furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl,
triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl,
isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-
carbolinyl, isochromanyl, chromanyl,
25 tetrahydroisoquinolinyl, isoindolinyl,
isobenzotetrahydrofuranlyl, isobenzotetrahydrothienyl,
isobenzothienyl, benzoxazolyl, pyridopyridinyl,
benzotetrahydrofuranlyl, benzotetrahydrothienyl, purinyl,
benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl,
30 pteridinyl, benzothiazolyl, imidazopyridinyl,
imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl,
benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl,
benzothiopyranyl, coumarinyl, isocoumarinyl, chromonyl,
chromanonyl, pyridinyl-N-oxide, tetrahydroquinolinyl,
35 dihydroquinolinyl, dihydroquinolinonyl,
dihydroisoquinolinonyl, dihydrocoumarinyl,
dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl,

5 benzoxazolinonyl, pyrrolyl N-oxide, pyrimidinyl N-oxide,
pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide,
indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide,
quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-
oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-
10 oxide, thiazolyl N-oxide, indolizinyll N-oxide, indazolyl N-
oxide, benzothiazolyl N-oxide, benzimidazolyl N-oxide,
pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-
oxide, triazolyl N-oxide, tetrazolyl N-oxide,
benzothiopyranyl S-oxide, benzothiopyranyl S,S-dioxide,

15 where the R_1 -heteroaryl group is bonded to $-(CH_2)_{n1}-$
by any ring atom of the parent R_1 -heteroaryl group substituted by
hydrogen such that the new bond to the R_1 -heteroaryl group replaces
the hydrogen atom and its bond, where heteroaryl is optionally
substituted with one, two, three or four of:

20 (1) C_1 - C_6 alkyl optionally substituted with one,
two or three substituents independently selected from the group
consisting of C_1 - C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -S(C_{1-6}
alkyl), -S(aryl- C_{1-6} alkyl), -S(heteroaryl- C_{1-6} alkyl), -S=O(C_{1-6}
alkyl), -S=O(aryl- C_{1-6} alkyl), -S=O(heteroaryl- C_{1-6} alkyl), -
25 SO₂(C_{1-6} alkyl), -SO₂(aryl- C_{1-6} alkyl), -SO₂(heteroaryl- C_{1-6} alkyl),
-NR_{1-a}R_{1-b}, -C≡N, -CF₃, C_1 - C_3 alkoxy, C_1 - C_3 alkoxy-(R_1 -aryl), C_1 - C_3
alkoxy-(R_1 -heteroaryl),

30 (2) C_2 - C_6 alkenyl with one or two double bonds,
optionally substituted with one, two or three substituents
independently selected from the group consisting of -F, -Cl,
-Br, -I, -OH, -SH, -S(C_{1-6} alkyl), -S(aryl- C_{1-6} alkyl), -
S(heteroaryl- C_{1-6} alkyl), -S=O(C_{1-6} alkyl), -S=O(aryl- C_{1-6} alkyl),
-S=O(heteroaryl- C_{1-6} alkyl), -SO₂(C_{1-6} alkyl), -SO₂(aryl- C_{1-6}
alkyl), -SO₂(heteroaryl- C_{1-6} alkyl), -C≡N, -CF₃, C_1 - C_3 alkoxy, -
35 NR_{1-a}R_{1-b}, C_1 - C_3 alkoxy-(R_1 -aryl), C_1 - C_3 alkoxy-(R_1 -heteroaryl),

(3) C_2 - C_6 alkynyl with one or two triple bonds,
optionally substituted with one, two or three substituents

5 independently selected from the group consisting of -F, -Cl,
-Br, -I, -OH, -SH, -S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -
S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl),
-S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆
10 NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(4) -F, -Cl, -Br and -I,

(5) -C₁-C₆ alkoxy optionally substituted with
one, two, or three -F,

(6) -NR_{N-2}R_{N-3},

15 (7) -OH,

(8) -C≡N,

(9) C₃-C₇ cycloalkyl, optionally substituted with
one, two or three substituents independently selected from the
group consisting of -F, -Cl, -Br, -I, -OH, -SH, -S(C₁₋₆ alkyl), -
20 S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -
S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆
alkyl), -SO₂(aryl-C₁₋₆ alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N,
-CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-
(R_{1-heteroaryl}),

25 (10) -CO-(C₁-C₄ alkyl),

(11) -SO₂-NR_{1-a}R_{1-b},

(12) -CO-NR_{1-a}R_{1-b},

(13) -SO₂-(C₁-C₄ alkyl), with the proviso that
when n₁ is zero, R_{1-heteroaryl} is not bonded to the carbon chain by
30 nitrogen,

(IV) -(CH₂)_{n1}-(R_{1-heterocycle}) where n₁ is as defined above
and R_{1-heterocycle} is selected from the group consisting of:

morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide,
thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl,
35 pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl,
tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl,
homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl

5 S,S-dioxide, oxazolidinonyl, dihydropyrazolyl,
dihydropyrrolyl dihydropyrazinyl dihydropyridinyl
dihydropyrimidinyl, dihydrofuryl, dihydropyranyl,
tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide,
homothiomorpholinyl S-oxide,

10 where the R₁-heterocycle group is bonded by any atom of
the parent R₁-heterocycle group substituted by hydrogen such that
the new bond to the R₁-heterocycle group replaces the hydrogen atom
and its bond, where heterocycle is optionally substituted with
one, two, three or four:

15 (1) C₁-C₆ alkyl optionally substituted with
one, two or three substituents independently selected from the
group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -
S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆ alkyl), -
S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-C₁₋₆
20 alkyl), -SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆ alkyl), -SO₂(heteroaryl-
C₁₋₆ alkyl), -NR_{1-a}R_{1-b}, -C≡N, -CF₃, C₁-C₃ alkoxy, C₁-C₃ alkoxy-(R₁-
aryl), C₁-C₃ alkoxy-(R₁-heteroaryl),

(2) C₂-C₆ alkenyl with one or two double
bonds, optionally substituted with one, two or three
25 substituents independently selected from the group consisting of
-F, -Cl, -Br, -I, -OH, -SH, -S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -
S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl),
-S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆
alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N, -CF₃, C₁-C₃ alkoxy, -
30 NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R₁-aryl), C₁-C₃ alkoxy-(R₁-heteroaryl),

(3) C₂-C₆ alkynyl with one or two triple
bonds, optionally substituted with one, two or three
substituents independently selected from the group consisting of
-F, -Cl, -Br, -I, -OH-SH, -S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -
35 S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl),
-S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆

- 5 alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R₁-aryl), C₁-C₃ alkoxy-(R₁-heteroaryl),
- (4) -F, -Cl, -Br and -I,
- (5) -C₁-C₆ alkoxy optionally substituted with one, two, or three -F,
- 10 (6) -NR_{N-2}R_{N-3},
- (7) -OH,
- (8) -C≡N,
- (9) C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from
- 15 the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆ alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R₁-aryl), C₁-C₃
- 20 alkoxy-(R₁-heteroaryl),
- (10) -CO-(C₁-C₄ alkyl),
- (11) -SO₂-NR_{1-a}R_{1-b},
- (12) -CO-NR_{1-a}R_{1-b},
- (13) -SO₂-(C₁-C₄ alkyl),
- 25 (14) =O, with the proviso that when n₁ is zero R₁-heterocycle is not bonded to the carbon chain by nitrogen;
- (V) -H;
- (VI) R_{N-1}-X_N- where X_N is selected from the group consisting of:
- 30 (A) -CO-,
- (B) -SO₂-
- where R_{N-1} is selected from the group consisting of:
- (A) R_{N-aryl} where R_{N-aryl} is phenyl, 1-naphthyl, 2-naphthyl, tetralinyl, indanyl, dihydronaphthyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl, optionally substituted with
- 35 one, two or three of the following substituents which can be the same or different and are:

- 5 (1) C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-C₁₋₆ alkyl), -
- 10 SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆ alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),
- (2) -OH,
- (3) -NO₂,
- 15 (4) -F, -Cl, -Br, -I,
- (5) -CO-OH,
- (6) -C≡N,
- (7) -(CH₂)₀₋₄-CO-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} are the same or different and are selected from the group
- 20 consisting of:
- (a) -H,
- (b) -C₁-C₆ alkyl optionally substituted with one substituent selected from the group consisting of:
- 25 (i) -OH,
- (ii) -NH₂,
- (c) -C₁-C₆ alkyl optionally substituted with one to three groups independently selected from -F, -Cl, -Br, and -I,
- 30 (d) -C₃-C₇ cycloalkyl,
- (e) -(C₁-C₂ alkyl)-(C₃-C₇ cycloalkyl),
- (f) -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl),
- (g) -C₂-C₆ alkenyl with one or two double bonds,
- 35 (h) -C₂-C₆ alkynyl with one or two triple bonds,

- 5 (i) $-C_1-C_6$ hydrocarbyl chain with one double bond and one triple bond,
- (j) $-R_1\text{-aryl}$,
- (k) $-R_1\text{-heteroaryl}$,
- (8) $-(CH_2)_{0-4}\text{-CO-}(C_1-C_{12} \text{ alkyl})$,
- 10 (9) $-(CH_2)_{0-4}\text{-CO-}(C_2-C_{12} \text{ alkenyl with one, two or three double bonds})$,
- (10) $-(CH_2)_{0-4}\text{-CO-}(C_2-C_{12} \text{ alkynyl with one, two or three triple bonds})$,
- (11) $-(CH_2)_{0-4}\text{-CO-}(C_3-C_7 \text{ cycloalkyl})$,
- 15 (12) $-(CH_2)_{0-4}\text{-CO-}R_1\text{-aryl}$,
- (13) $-(CH_2)_{0-4}\text{-CO-}R_1\text{-heteroaryl}$,
- (14) $-(CH_2)_{0-4}\text{-CO-}R_1\text{-heterocycle}$,
- (15) $-(CH_2)_{0-4}\text{-CO-}R_{N-4}$ where R_{N-4} is selected from the group consisting of morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl where each group is optionally substituted with one, two, three, or four of C_1-C_6 alkyl,
- 20 (16) $-(CH_2)_{0-4}\text{-CO-O-}R_{N-5}$ where R_{N-5} is selected from the group consisting of:
- (a) C_1-C_6 alkyl,
- (b) $-(CH_2)_{0-2}\text{-(}R_1\text{-aryl)}$,
- (c) C_2-C_6 alkenyl containing one or two double bonds,
- 30 (d) C_2-C_6 alkynyl containing one or two triple bonds,
- (e) C_3-C_7 cycloalkyl,
- (f) $-(CH_2)_{0-2}\text{-(}R_1\text{-heteroaryl)}$,
- (17) $-(CH_2)_{0-4}\text{-SO}_2\text{-NR}_{N-2}R_{N-3}$,
- 35 (18) $-(CH_2)_{0-4}\text{-SO-}(C_1-C_8 \text{ alkyl})$,
- (19) $-(CH_2)_{0-4}\text{-SO}_2\text{-(}C_1-C_{12} \text{ alkyl)}$,
- (20) $-(CH_2)_{0-4}\text{-SO}_2\text{-(}C_3-C_7 \text{ cycloalkyl)}$,

(21) - $(\text{CH}_2)_{0-4}$ -N(H or $\text{R}_{\text{N}-5}$)-CO-O- $\text{R}_{\text{N}-5}$ where $\text{R}_{\text{N}-5}$
5 can be the same or different,

(22) - $(\text{CH}_2)_{0-4}$ -N(H or $\text{R}_{\text{N}-5}$)-CO-N($\text{R}_{\text{N}-5}$)₂, where
each $\text{R}_{\text{N}-5}$ is independently defined herein,

(23) - $(\text{CH}_2)_{0-4}$ -N-CS-N($\text{R}_{\text{N}-5}$)₂, where each $\text{R}_{\text{N}-5}$ is
10 independently defined herein,

(24) - $(\text{CH}_2)_{0-4}$ -N(-H or $\text{R}_{\text{N}-5}$)-CO- $\text{R}_{\text{N}-2}$,

(25) - $(\text{CH}_2)_{0-4}$ -NR_{N-2}R_{N-3},

(26) - $(\text{CH}_2)_{0-4}$ -R_{N-4},

(27) - $(\text{CH}_2)_{0-4}$ -O-CO-(C₁-C₆ alkyl),

15 (28) - $(\text{CH}_2)_{0-4}$ -O-P(O)-(OR_{N-1})₂ where R_{N-1} is -H
or C₁-C₄ alkyl,

(29) - $(\text{CH}_2)_{0-4}$ -O-CO-N($\text{R}_{\text{N}-5}$)₂,

(30) - $(\text{CH}_2)_{0-4}$ -O-CS-N($\text{R}_{\text{N}-5}$)₂,

(31) - $(\text{CH}_2)_{0-4}$ -O-($\text{R}_{\text{N}-5}$)₂,

20 (32) - $(\text{CH}_2)_{0-4}$ -O-($\text{R}_{\text{N}-5}$)₂-COOH,

(33) - $(\text{CH}_2)_{0-4}$ -S-($\text{R}_{\text{N}-5}$)₂,

(34) - $(\text{CH}_2)_{0-4}$ -O-(C₁-C₆ alkyl optionally
substituted with one, two, three, four, or five of -F),

(35) C₃-C₇ cycloalkyl,

25 (36) C₂-C₆ alkenyl having one or two double
bonds and which is optionally substituted with C₁-C₃ alkyl, -F,
-Cl, -Br, -I, -OH, -SH, -S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -
S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl),
-S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆
30 alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N, -CF₃, C₁-C₃ alkoxy, -
NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R₁-aryl), C₁-C₃ alkoxy-(R₁-heteroaryl),

(37) C₂-C₆ alkynyl with one or two triple
bonds optionally substituted with C₁-C₃ alkyl, -F, -Cl, -Br, -I,
-OH, -SH, -S(C₁₋₆ alkyl), -S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆
35 alkyl), -S=O(C₁₋₆ alkyl), -S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-
C₁₋₆ alkyl), -SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆ alkyl),

5 SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b},
C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(38) -(CH₂)₀₋₄-N(-H or R_{N-5})-SO₂-R_{N-2}, or

(39) -(CH₂)₀₋₄-C₃-C₇ cycloalkyl,

(B) -R_{N-heteroaryl} where R_{N-heteroaryl} carries the same
10 definition as R_{1-heteroaryl}, where the R_{N-heteroaryl} group is bonded by
any atom of the parent R_{N-heteroaryl} group substituted by hydrogen
such that the new bond to the R_{N-heteroaryl} group replaces the
hydrogen atom and its bond, where heteroaryl is optionally
substituted with one, two, three, or four groups independently
15 selected from:

(1) C₁-C₆ alkyl, optionally substituted with
one, two or three substituents selected from the group
consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -S(C₁₋₆
alkyl), -S(aryl-C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆
20 alkyl), -S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-C₁₋₆ alkyl), -
SO₂(C₁₋₆ alkyl), -SO₂(aryl-C₁₋₆ alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl),
-C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-
C₃ alkoxy-(R_{1-heteroaryl}),

(2) -OH,

25 (3) -NO₂,

(4) -F, -Cl, -Br, -I,

(5) -CO-OH,

(6) -C≡N,

(7) -(CH₂)₀₋₄-CO-NR_{N-2}R_{N-3},

30 (C) R_{N-aryl}-W-R_{N-aryl},

(D) R_{N-aryl}-W-R_{N-heteroaryl},

(E) R_{N-aryl}-W-R_{N-heterocycle}, where R_{N-heterocycle} is the
same as R_{1-heterocycle}

(F) R_{N-heteroaryl}-W-R_{N-aryl},

35 (G) R_{N-heteroaryl}-W-R_{N-heteroaryl},

(H) R_{N-heteroaryl}-W-R_{N-heterocycle},

(I) R_{N-heterocycle}-W-R_{N-aryl},

5 (J) $R_{N\text{-heterocycle}}\text{-W-}R_{N\text{-heteroaryl}}$,
 (K) $R_{N\text{-heterocycle}}\text{-W-}R_{N\text{-heterocycle}}$, and
 where W is

- (1) $\text{-(CH}_2\text{)}_{0-4}\text{-}$,
 (2) -O- ,
 10 (3) $\text{-S(O)}_{0-2}\text{-}$,
 (4) $\text{-N(R}_{N-5}\text{)-}$, or
 (5) -CO- ;
 (VII) $\text{-(CR}_{C-x}\text{R}_{C-y}\text{)}_{0-4}\text{-R}_{C\text{-aryl}}$ where R_{C-x} and R_{C-y} are
 -H ,
 15 $C_1\text{-C}_4$ alkyl optionally substituted with one or
 two -OH ,
 $C_1\text{-C}_4$ alkoxy optionally substituted with one,
 two, or three of
 -F ,
 20 $\text{-(CH}_2\text{)}_{0-4}\text{-C}_3\text{-C}_7$ cycloalkyl,
 $C_2\text{-C}_6$ alkenyl containing one or two double bonds,
 $C_2\text{-C}_6$ alkynyl containing one or two triple bonds,
 phenyl,

and where R_{C-x} and R_{C-y} are taken together with the carbon to
 25 which they are attached to form a carbocycle of three, four,
 five, six and seven carbon atoms, optionally where one carbon
 atom is replaced by a heteroatom selected from the group
 consisting of -O- , -S- , $\text{-SO}_2\text{-}$, $\text{-NR}_{N-2}\text{-}$ and $R_{C\text{-aryl}}$ is the same as
 $R_{N\text{-aryl}}$;

- 30 (VIII) $\text{-(CR}_{C-x}\text{R}_{C-y}\text{)}_{0-4}\text{-R}_{C\text{-aryl}}\text{-R}_{C\text{-aryl}}$,
 (IX) $\text{-(CR}_{C-x}\text{R}_{C-y}\text{)}_{0-4}\text{-R}_{C\text{-aryl}}\text{-R}_{C\text{-heteroaryl}}$,
 (X) $\text{-(CR}_{C-x}\text{R}_{C-y}\text{)}_{0-4}\text{-R}_{C\text{-heteroaryl}}\text{-R}_{C\text{-aryl}}$
 (XI) $\text{-(CR}_{C-x}\text{R}_{C-y}\text{)}_{0-4}\text{-R}_{C\text{-heteroaryl}}\text{-R}_{C\text{-heteroaryl}}$,
 (XII) $\text{-(CR}_{C-x}\text{R}_{C-y}\text{)}_{0-4}\text{-R}_{C\text{-aryl}}\text{-R}_{C\text{-heterocycle}}$ and $R_{C\text{-heterocycle}}$ is
 35 the same as $R_{N\text{-heterocycle}}$,
 (XIII) $\text{-(CR}_{C-x}\text{R}_{C-y}\text{)}_{0-4}\text{-R}_{C\text{-heteroaryl}}\text{-R}_{C\text{-heterocycle}}$,
 (XIV) $\text{-(CR}_{C-x}\text{R}_{C-y}\text{)}_{0-4}\text{-R}_{C\text{-heterocycle}}\text{-R}_{C\text{-aryl}}$,

5 (XV) - $(\text{CR}_{\text{C}-\text{x}}\text{R}_{\text{C}-\text{y}})_{0-4}-\text{R}_{\text{C}}\text{-heterocycle}-\text{R}_{\text{C}}\text{-heteroaryl}$,
 (XVI) - $(\text{CR}_{\text{C}-\text{x}}\text{R}_{\text{C}-\text{y}})_{0-4}-\text{R}_{\text{C}}\text{-heterocycle}-\text{R}_{\text{C}}\text{-heterocycle}$,
 (XVII) - $[\text{C}(\text{R}_{\text{C}-1})(\text{R}_{\text{C}-2})]_{1-3}-\text{CO}-\text{N}-(\text{R}_{\text{C}-3})_2$ where $\text{R}_{\text{C}-1}$ and $\text{R}_{\text{C}-2}$
 are the same or different and are selected from the group
 consisting of:

10 (A) -H,
 (B) - $\text{C}_1\text{-C}_6$ alkyl, optionally substituted with
 one, two or three substituents selected from the group
 consisting of $\text{C}_1\text{-C}_3$ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -S(C_{1-6}
 alkyl), -S(aryl- C_{1-6} alkyl), -S(heteroaryl- C_{1-6} alkyl), -S=O(C_{1-6}
 15 alkyl), -S=O(aryl- C_{1-6} alkyl), -S=O(heteroaryl- C_{1-6} alkyl), -
 $\text{SO}_2(\text{C}_{1-6}$ alkyl), - $\text{SO}_2(\text{aryl-}\text{C}_{1-6}$ alkyl), - $\text{SO}_2(\text{heteroaryl-}\text{C}_{1-6}$ alkyl),
 -C $\equiv$ N, -CF $_3$, $\text{C}_1\text{-C}_6$ alkoxy, -O-phenyl, -NR $_{1-a}$ R $_{1-b}$, $\text{C}_1\text{-C}_3$ alkoxy-(R $_1$ -
 aryl), $\text{C}_1\text{-C}_3$ alkoxy-(R $_1$ -heteroaryl),

(C) $\text{C}_2\text{-C}_6$ alkenyl with one or two double bonds,
 20 optionally substituted with one, two or three substituents
 selected from the group consisting of $\text{C}_1\text{-C}_3$ alkyl, -F, -Cl, -Br,
 -I, -OH, -SH, -S(C_{1-6} alkyl), -S(aryl- C_{1-6} alkyl), -S(heteroaryl-
 C_{1-6} alkyl), -S=O(C_{1-6} alkyl), -S=O(aryl- C_{1-6} alkyl), -
 S=O(heteroaryl- C_{1-6} alkyl), - $\text{SO}_2(\text{C}_{1-6}$ alkyl), - $\text{SO}_2(\text{aryl-}\text{C}_{1-6}$
 25 alkyl), - $\text{SO}_2(\text{heteroaryl-}\text{C}_{1-6}$ alkyl), -C $\equiv$ N, -CF $_3$, $\text{C}_1\text{-C}_6$ alkoxy, -O-
 phenyl, -NR $_{1-a}$ R $_{1-b}$, $\text{C}_1\text{-C}_3$ alkoxy-(R $_1$ -aryl), $\text{C}_1\text{-C}_3$ alkoxy-(R $_1$ -heteroaryl),

(D) - $(\text{CH}_2)_{0-4}-\text{C}_3\text{-C}_7$ cycloalkyl, optionally
 substituted with one, two or three substituents selected from
 the group consisting of $\text{C}_1\text{-C}_3$ alkyl, -F, -Cl, -Br, -I, -OH, -SH,
 30 -S(C_{1-6} alkyl), -S(aryl- C_{1-6} alkyl), -S(heteroaryl- C_{1-6} alkyl), -
 S=O(C_{1-6} alkyl), -S=O(aryl- C_{1-6} alkyl), -S=O(heteroaryl- C_{1-6}
 alkyl), - $\text{SO}_2(\text{C}_{1-6}$ alkyl), - $\text{SO}_2(\text{aryl-}\text{C}_{1-6}$ alkyl), - $\text{SO}_2(\text{heteroaryl-}\text{C}_{1-6}$
 C_{1-6} alkyl), -C $\equiv$ N, -CF $_3$, $\text{C}_1\text{-C}_6$ alkoxy, -O-phenyl, -NR $_{1-a}$ R $_{1-b}$, $\text{C}_1\text{-C}_3$
 alkoxy-(R $_1$ -aryl), $\text{C}_1\text{-C}_3$ alkoxy-(R $_1$ -heteroaryl),

35 (E) - $(\text{C}_1\text{-C}_4$ alkyl)-R $_{\text{C}'\text{-aryl}}$ where R $_{\text{C}'\text{-aryl}}$ is as
 defined for R $_1$ -aryl,

(F) - $(\text{C}_1\text{-C}_4$ alkyl)-R $_{\text{C}}\text{-heteroaryl}$,

- 5 (G) - (C₁-C₄ alkyl) -R_C-heterocycle,
 (H) -R_C-heteroaryl,
 (I) -R_C-heterocycle, and
 (J) -R_{C'}-aryl,

and where R_{C-3} is the same or different and is:

- 10 (A) -H,
 (B) -C₁-C₆ alkyl optionally substituted with one,
 two or three substituents selected from the group consisting of
 C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -S(C₁₋₆ alkyl), -S(aryl-
 C₁₋₆ alkyl), -S(heteroaryl-C₁₋₆ alkyl), -S=O(C₁₋₆ alkyl), -
 15 S=O(aryl-C₁₋₆ alkyl), -S=O(heteroaryl-C₁₋₆ alkyl), -SO₂(C₁₋₆
 alkyl), -SO₂(aryl-C₁₋₆ alkyl), -SO₂(heteroaryl-C₁₋₆ alkyl), -C≡N,
 -CF₃, C₁-C₆ alkoxy, -O-phenyl, and -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R₁-
 aryl), C₁-C₃ alkoxy-(R₁-heteroaryl),
 (C) -(CH₂)₀₋₄-C₃-C₇ cycloalkyl,
 20 (D) -(C₁-C₄ alkyl)-R_{C'}-aryl,
 (E) -(C₁-C₄ alkyl)-R_C-heteroaryl, or
 (F) -(C₁-C₄ alkyl)-R_C-heterocycle;
 (XVIII) -(CH₂)_o-Q-(CH₂)_p-B, where o and p are
 independently integers of 1-4, Q is O, S, SO, SO₂, NR₁, and B is
 25 C₁₋₆ alkyl, aryl, heteroaryl, or heterocycle;
 (XIX) -O-R₉, -S-R₉, -NH-R₉, or N(R₉)₂;
 (XXVII) -OC(=O)-R₉
 (XXVIII) -C(=O)O-R₉
 (XXIX) -N(R₈)C(=O)-R₉
 30 (XXX) -C(=O)N(R₈)-R₉
 (XXXI) -SO₂N(R₈)C(=O)-R₉
 (XXXII) -C(=O)N(R₈)SO₂-R₉
 (XXXIII) -SO₂-R₉;

wherein R₈ is defined as H or C₁-C₆ alkyl optionally substituted
 35 with one to three groups independently selected from -OH, -NH₂,
 -F, -Cl, -Br, and -I;

wherein R₉ is defined as (I)-(XVIII) above

5 and wherein R_2 is C_1 to C_6 alkyl, cyclohexyl, cyclopentyl, pyridinyl, phenyl, isoxazole, pyrazole, furan, thiophene, and other five and six membered heterocycles containing carbon, nitrogen, oxygen and sulfur, said C_1 to C_6 alkyl, cyclohexyl, cyclopentyl, pyridinyl, phenyl, furan, thiophene may be
10 optionally substituted with one, two or three radicals selected from CF_3 , OCF_3 , hydroxyl, halo, C_{1-2} -alkyl, C_{1-2} -haloalkyl, cyano, carboxyl, C_{1-2} -alkoxycarbonyl, C_{1-2} -hydroxyalkyl, thioalkyl, aminosulfonyl, C_{1-2} -alkylaminosulfonyl, methyl C_{1-2} -haloalkoxy, amino, C_{1-2} -alkylamino, phenylamino, nitro, C_{1-2} -alkoxy- C_{1-2} -alkyl,
15 C_{1-2} -alkylsulfinyl, C_{1-2} -alkoxy and C_{1-3} -alkylthio.

2. A compound according to claim 1, wherein at least one of R_1 , R_2 or R_3 is H.

20 3. A compound according to claim 1, wherein at least two of R_1 , R_2 or R_3 is H.

4. A compound according to claim 1, wherein R_1 and R_3 are independently:

25 (I) $-(CH_2)_{n_1}-(R_{1-aryl})$, where n_1 is zero or one and where R_{1-aryl} is phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthalyl, or tetralinyl optionally substituted with one, two, three, or four of the following substituents on the aryl ring:

30 (A) C_1 - C_6 alkyl optionally substituted with one, two or three substituents selected from the group consisting of C_1 - C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF $_3$, C_1 - C_3 alkoxy, and -NR $_{1-a}$ R $_{1-b}$, C_1 - C_3 alkoxy-(R_{1-aryl}), C_1 - C_3 alkoxy-($R_{1-heteroaryl}$),

35 (B) C_2 - C_6 alkenyl with one or two double bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -Br, -I, -OH, -

5 SH, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1-a}R_{1-b}$, C_1-C_3 alkoxy- (R_{1-aryl}) ,
 C_1-C_3 alkoxy- $(R_{1-heteroaryl})$,

(C) C_2-C_6 alkynyl with one or two triple bonds,
optionally substituted with one, two or three substituents
selected from the group consisting of $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-$

10 SH, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1-a}R_{1-b}$, C_1-C_3 alkoxy- (R_{1-aryl}) ,
 C_1-C_3 alkoxy- $(R_{1-heteroaryl})$,

(D) $-F$, Cl , $-Br$, or $-I$,

(E) $-C_1-C_6$ alkoxy optionally substituted with
one, two, or three $-F$,

15 (F) $-NR_{N-2}R_{N-3}$, where R_{N-2} and R_{N-3} are independently
selected from the group consisting of:

(1) $-H$,

(2) $-C_1-C_6$ alkyl optionally substituted with
one substituent selected from the group consisting of:

20 (a) $-OH$, and

(b) $-NH_2$,

(3) $-C_1-C_6$ alkyl optionally substituted with
one to three $-F$, $-Cl$, $-Br$, or $-I$,

(4) $-C_3-C_7$ cycloalkyl,

25 (5) $-(C_1-C_2 \text{ alkyl})-(C_3-C_7 \text{ cycloalkyl})$,

(6) $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_3 \text{ alkyl})$,

(7) $-C_2-C_6$ alkenyl with one or two double
bonds,

(8) $-C_2-C_6$ alkynyl with one or two triple

30 bonds,

(9) $-C_1-C_6$ alkyl chain with one double bond
and one triple bond,

(10) $-R_{1-aryl}$, where R_{1-aryl} is as defined
above, and

35 (11) $-R_{1-heteroaryl}$,

(G) $-OH$,

(H) $-C\equiv N$,

5 (I) C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(K) -CO-(C₁-C₄ alkyl),

10 (L) -SO₂-NR_{1-a}R_{1-b},

(M) -CO-NR_{1-a}R_{1-b}, or

(N) -SO₂-(C₁-C₄ alkyl), or

(II) -(CH₂)_{n1}-(R_{1-heteroaryl}), where n₁ is zero or one and where R_{1-heteroaryl} is selected from the group consisting of:

15 pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indoliziny, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, 20 furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl,

where the R_{1-heteroaryl} group is bonded to -(CH₂)_{n1}- by any ring atom of the parent R_{1-heteroaryl} group substituted by hydrogen such that the new bond to the R_{1-heteroaryl} group replaces 25 the hydrogen atom and its bond, where heteroaryl is optionally substituted with one, two, three, or four of:

(1) C₁-C₆ alkyl optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ 30 alkoxy, and -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(2) C₂-C₆ alkenyl with one or two double bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -Br, -I, -OH, - 35 SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl, C₁-C₃ alkoxy, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

- 5 (3) C₂-C₆ alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl, C₁-C₃ alkoxy, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),
- 10 (4) -F, Cl, -Br, or -I,
- (5) -C₁-C₆ alkoxy optionally substituted with one, two, or three -F,
- (6) -NR_{N-2}R_{N-3},
- 15 (7) -OH,
- (8) -C≡N,
- (9) C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl, C₁-C₃ alkoxy, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),
- 20 (10) -CO-(C₁-C₄ alkyl),
- (11) -SO₂-NR_{1-a}R_{1-b},
- (12) -CO-NR_{1-a}R_{1-b}, or
- 25 (13) -SO₂-(C₁-C₄ alkyl), with the proviso that when n₁ is zero R_{1-heteroaryl} is not bonded to the carbon chain by nitrogen.

5. A compound according to claim 1, wherein R₁ and R₃ are independently:

30

phenyl, 1-naphthyl, 2-naphthyl, tetralinyl, indanyl, dihydronaphthyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl, each of which is optionally substituted with one, two or three of the following substituents which can be the same or different and are:

35

(1) C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group

- 5 consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -
CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃
alkoxy-(R_{1-heteroaryl}),
- (2) -OH,
- (3) -NO₂,
- 10 (4) -F, -Cl, -Br, or -I,
- (5) -CO-OH,
- (6) -C≡N,
- (7) -(CH₂)₀₋₄-CO-NR_{N-2}R_{N-3},
- (8) -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl),
- 15 (9) -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl with one, two
or three double bonds),
- (10) -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl with one,
two or three triple bonds),
- (11) -(CH₂)₀₋₄-CO-(C₃-C₇ cycloalkyl),
- 20 (12) -(CH₂)₀₋₄-CO-R_{1-aryl},
- (13) -(CH₂)₀₋₄-CO-R_{1-heteroaryl},
- (14) -(CH₂)₀₋₄-CO-R_{1-heterocycle},
- (15) -(CH₂)₀₋₄-CO-R_{N-4} where R_{N-4} is selected
from the group consisting of morpholinyl, thiomorpholinyl,
25 piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl,
homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide,
pyrrolinyl and pyrrolidinyl where each group is optionally
substituted with one, two, three, or four of: C₁-C₆ alkyl,
- (16) -(CH₂)₀₋₄-CO-O-R_{N-5} where R_{N-5} is selected
30 from the group consisting of:
- (a) C₁-C₆ alkyl,
- (b) -(CH₂)₀₋₂-(R_{1-aryl}),
- (c) C₂-C₆ alkenyl containing one or two
double bonds,
- 35 (d) C₂-C₆ alkynyl containing one or two
triple bonds,
- (e) C₃-C₇ cycloalkyl, and

- 5 (f) - (CH₂)₀₋₂ - (R₁-heteroaryl),
- (17) - (CH₂)₀₋₄ - SO₂ - NR_{N-2}R_{N-3},
- (18) - (CH₂)₀₋₄ - SO - (C₁-C₈ alkyl),
- (19) - (CH₂)₀₋₄ - SO₂ - (C₁-C₁₂ alkyl),
- (20) - (CH₂)₀₋₄ - SO₂ - (C₃-C₇ cycloalkyl),
- 10 (21) - (CH₂)₀₋₄ - N(H or R_{N-5}) - CO - O - R_{N-5} where R_{N-5} can be the same or different,
- (22) - (CH₂)₀₋₄ - N(H or R_{N-5}) - CO - N(R_{N-5})₂, where R_{N-5} can be the same or different,
- (23) - (CH₂)₀₋₄ - N - CS - N(R_{N-5})₂, where R_{N-5} can be
- 15 the same or different,
- (24) - (CH₂)₀₋₄ - N(-H or R_{N-5}) - CO - R_{N-2} where R_{N-5} and R_{N-2} can be the same or different,
- (25) - (CH₂)₀₋₄ - NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} can be the same or different,
- 20 (26) - (CH₂)₀₋₄ - R_{N-4},
- (27) - (CH₂)₀₋₄ - O - CO - (C₁-C₆ alkyl),
- (28) - (CH₂)₀₋₄ - O - P(O) - (OR_{N-aryl-1})₂ where R_{N-aryl-1} is -H or C₁-C₄ alkyl,
- (29) - (CH₂)₀₋₄ - O - CO - N(R_{N-5})₂,
- 25 (30) - (CH₂)₀₋₄ - O - CS - N(R_{N-5})₂,
- (31) - (CH₂)₀₋₄ - O - (R_{N-5})₂,
- (32) - (CH₂)₀₋₄ - O - (R_{N-5})₂ - COOH,
- (33) - (CH₂)₀₋₄ - S - (R_{N-5})₂,
- (34) - (CH₂)₀₋₄ - O - (C₁-C₆ alkyl optionally
- 30 substituted with one, two, three, four, or five -F),
- (35) C₃-C₇ cycloalkyl,
- (36) C₂-C₆ alkenyl with one or two double bonds optionally substituted with C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, or -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R₁-
- 35 aryl), C₁-C₃ alkoxy-(R₁-heteroaryl),
- (37) C₂-C₆ alkynyl with one or two triple bonds optionally substituted with C₁-C₃ alkyl, -F, -Cl, -Br, -I,

5 -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, or -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R₁-aryl), C₁-C₃ alkoxy-(R₁-heteroaryl),

(38) -(CH₂)₀₋₄-N(-H or R_{N-5})-SO₂-R_{N-2} where R_{N-5} and R_{N-2} can be the same or different, or

(39) -(CH₂)₀₋₄- C₃-C₇ cycloalkyl.

10

6. A compound according to claim 1, wherein R₁ and R₃ are independently R_{N-1}C(O)-; and

R_{N-1} is R_{N-heteroaryl} where R_{N-heteroaryl} is selected from the group consisting of:

15 pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, 20 benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, 25 isoindolinyl, isobenzotetrahydrofuranlyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benztetrahydrofuranlyl, benztetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, 30 pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, coumarinyl,

where the R_{N-heteroaryl} group is bonded by any 35 atom of the parent R_{N-heteroaryl} group substituted by hydrogen such that the new bond to the R_{N-heteroaryl} group replaces the hydrogen

5 atom and its bond, where heteroaryl is optionally substituted with one, two, three, or four of:

(1) C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -
10 CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(2) -OH,

(3) -NO₂,

(4) -F, -Cl, -Br, or -I

15 (5) -CO-OH,

(6) -C≡N,

(7) -(CH₂)₀₋₄-CO-NR_{N-2}R_{N-3},

(8) -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl),

(9) -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl with one, two
20 or three double bonds),

(10) -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl with one,
two or three triple bonds),

(11) -(CH₂)₀₋₄-CO-(C₃-C₇ cycloalkyl),

(12) -(CH₂)₀₋₄-CO-R_{1-aryl},

25 (13) -(CH₂)₀₋₄-CO-R_{1-heteroaryl},

(14) -(CH₂)₀₋₄-CO-R_{1-heterocycle},

(15) -(CH₂)₀₋₄-CO-R_{N-4},

(16) -(CH₂)₀₋₄-CO-O-R_{N-5},

(17) -(CH₂)₀₋₄-SO₂-NR_{N-2}R_{N-3},

30 (18) -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl),

(19) -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl),

(20) -(CH₂)₀₋₄-SO₂-(C₃-C₇ cycloalkyl),

(21) -(CH₂)₀₋₄-N(H or R_{N-5})-CO-O-R_{N-5} where R_{N-5}
5 can be the same or different,

35 (22) -(CH₂)₀₋₄-N(H or R_{N-5})-CO-N(R_{N-5})₂, where
R_{N-5} can be the same or different,

- 5 (23) - $(\text{CH}_2)_{0-4}-\text{N}-\text{CS}-\text{N}(\text{R}_{\text{N}-5})_2$, where $\text{R}_{\text{N}-5}$ can be the same or different,
- (24) - $(\text{CH}_2)_{0-4}-\text{N}(-\text{H} \text{ or } \text{R}_{\text{N}-5})-\text{CO}-\text{R}_{\text{N}-2}$ where $\text{R}_{\text{N}-5}$ and $\text{R}_{\text{N}-2}$ can be the same or different,
- (25) - $(\text{CH}_2)_{0-4}-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$ where $\text{R}_{\text{N}-2}$ and $\text{R}_{\text{N}-3}$ can
10 be the same or different,
- (26) - $(\text{CH}_2)_{0-4}-\text{R}_{\text{N}-4}$,
- (27) - $(\text{CH}_2)_{0-4}-\text{O}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$,
- (28) - $(\text{CH}_2)_{0-4}-\text{O}-\text{P}(\text{O})-(\text{OR}_{\text{N-aryl-1}})_2$ where $\text{R}_{\text{N-aryl-1}}$
is -H or C_1-C_4 alkyl,
- 15 (29) - $(\text{CH}_2)_{0-4}-\text{O}-\text{CO}-\text{N}(\text{R}_{\text{N}-5})_2$,
- (30) - $(\text{CH}_2)_{0-4}-\text{O}-\text{CS}-\text{N}(\text{R}_{\text{N}-5})_2$,
- (31) - $(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{\text{N}-5})_2$,
- (32) - $(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{\text{N}-5})_2-\text{COOH}$,
- (33) - $(\text{CH}_2)_{0-4}-\text{S}-(\text{R}_{\text{N}-5})_2$,
- 20 (34) - $(\text{CH}_2)_{0-4}-\text{O}-(\text{C}_1-\text{C}_6 \text{ alkyl optionally substituted with one, two, three, four, or five -F})$,
- (35) C_3-C_7 cycloalkyl,
- (36) C_2-C_6 alkenyl with one or two double bonds optionally substituted with C_1-C_3 alkyl, -F, -Cl, -Br, -I,
25 -OH, -SH, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_3 alkoxy, or $-\text{NR}_{1-a}\text{R}_{1-b}$, C_1-C_3 alkoxy- $(\text{R}_{1-\text{aryl}})$, C_1-C_3 alkoxy- $(\text{R}_{1-\text{heteroaryl}})$,
- (37) C_2-C_6 alkynyl with one or two triple bonds optionally substituted with C_1-C_3 alkyl, -F, -Cl, -Br, -I,
-OH, -SH, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_3 alkoxy, or $-\text{NR}_{1-a}\text{R}_{1-b}$, C_1-C_3 alkoxy- $(\text{R}_{1-\text{aryl}})$, C_1-C_3 alkoxy- $(\text{R}_{1-\text{heteroaryl}})$,
30 (38) - $(\text{CH}_2)_{0-4}-\text{N}(-\text{H} \text{ or } \text{R}_{\text{N}-5})-\text{SO}_2-\text{R}_{\text{N}-2}$ where $\text{R}_{\text{N}-5}$ and $\text{R}_{\text{N}-2}$ can be the same or different, or
- (39) - $(\text{CH}_2)_{0-4}-\text{C}_3-\text{C}_7$ cycloalkyl.

35 7. A compound according to claim 1, wherein R_1 and R_3 are independently $\text{R}_{\text{N}-1}\text{C}(\text{O})-$; and $\text{R}_{\text{N}-1}$ is phenyl, 1-naphthyl, or 2-naphthyl, each of which is optionally substituted with one, two

5 or three of the following substituents which can be the same or different and are:

(1) C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -
10 CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),

(2) -OH,

(3) -NO₂,

(4) -F, -Cl, -Br, or -I,

15 (5) -CO-OH,

(6) -C≡N,

(7) -(CH₂)₀₋₄-CO-NR_{N-2}R_{N-3},

(8) -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl),

(9) -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl with one, two
20 or three double bonds),

(10) -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl with one,
two or three triple bonds),

(11) -(CH₂)₀₋₄-CO-(C₃-C₇ cycloalkyl),

(12) -(CH₂)₀₋₄-CO-R_{1-aryl},

25 (13) -(CH₂)₀₋₄-CO-R_{1-heteroaryl},

(14) -(CH₂)₀₋₄-CO-R_{1-heterocycle},

(15) -(CH₂)₀₋₄-CO-R_{N-4} where R_{N-4} is selected from the group consisting of morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl,
30 homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl where each group is optionally substituted with one, two, three, or four of: C₁-C₆ alkyl,

(16) -(CH₂)₀₋₄-CO-O-R_{N-5} where R_{N-5} is selected from the group consisting of:

35 (a) C₁-C₆ alkyl,

(b) -(CH₂)₀₋₂-(R_{1-aryl}),

- 5 (c) C₂-C₆ alkenyl containing one or two
double bonds,
- (d) C₂-C₆ alkynyl containing one or two
triple bonds,
- (e) C₃-C₇ cycloalkyl, and
- 10 (f) - (CH₂)₀₋₂ - (R₁-heteroaryl),
- (17) - (CH₂)₀₋₄ - SO₂ - NR_{N-2}R_{N-3},
- (18) - (CH₂)₀₋₄ - SO - (C₁-C₈ alkyl),
- (19) - (CH₂)₀₋₄ - SO₂ - (C₁-C₁₂ alkyl),
- (20) - (CH₂)₀₋₄ - SO₂ - (C₃-C₇ cycloalkyl),
- 15 (21) - (CH₂)₀₋₄ - N(H or R_{N-5}) - CO - O - R_{N-5} where R_{N-5}
can be the same or different,
- (22) - (CH₂)₀₋₄ - N(H or R_{N-5}) - CO - N(R_{N-5})₂, where
R_{N-5} can be the same or different,
- (23) - (CH₂)₀₋₄ - N - CS - N(R_{N-5})₂, where R_{N-5} can be
20 the same or different,
- (24) - (CH₂)₀₋₄ - N(-H or R_{N-5}) - CO - R_{N-2} where R_{N-5}
and R_{N-2} can be the same or different,
- (25) - (CH₂)₀₋₄ - NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} can
be the same or different,
- 25 (26) - (CH₂)₀₋₄ - R_{N-4},
- (27) - (CH₂)₀₋₄ - O - CO - (C₁-C₆ alkyl),
- (28) - (CH₂)₀₋₄ - O - P(O) - (OR_{N-aryl-1})₂ where R_{N-aryl-1}
is -H or C₁-C₄ alkyl,
- (29) - (CH₂)₀₋₄ - O - CO - N(R_{N-5})₂,
- 30 (30) - (CH₂)₀₋₄ - O - CS - N(R_{N-5})₂,
- (31) - (CH₂)₀₋₄ - O - (R_{N-5})₂,
- (32) - (CH₂)₀₋₄ - O - (R_{N-5})₂ - COOH,
- (33) - (CH₂)₀₋₄ - S - (R_{N-5})₂,
- (34) - (CH₂)₀₋₄ - O - (C₁-C₆ alkyl optionally
35 substituted with one, two, three, four, or five -F),
- (35) C₃-C₇ cycloalkyl,

- 5 (36) C₂-C₆ alkenyl with one or two double bonds optionally substituted with C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, or -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R₁-aryl), C₁-C₃ alkoxy-(R₁-heteroaryl),
- 10 (37) C₂-C₆ alkynyl with one or two triple bonds optionally substituted with C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, or -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R₁-aryl), C₁-C₃ alkoxy-(R₁-heteroaryl),
- (38) -(CH₂)₀₋₄-N(-H or R_{N-5})-SO₂-R_{N-2} where R_{N-5} and R_{N-2} can be the same or different, or
- 15 (39) -(CH₂)₀₋₄- C₃-C₇ cycloalkyl.

8. A compound according to claim 1, wherein R₁ and R₃ are independently R_{N-1}C(O)-; and R_{N-1} is phenyl optionally substituted with one, two or three of the following substituents which can be the same or different and are:

20

- (1) C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R₁-aryl), C₁-C₃ alkoxy-(R₁-heteroaryl),
- 25 (2) -OH,
- (3) -NO₂,
- (4) -F, -Cl, -Br, or -I,
- 30 (5) -CO-OH,
- (6) -C≡N,
- (7) -(CH₂)₀₋₄-CO-NR_{N-2}R_{N-3},
- (8) -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl),
- (9) -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl with one, two or three double bonds),
- 35

- 5 (10) - (CH₂)₀₋₄-CO- (C₂-C₁₂ alkynyl with one,
two or three triple bonds),
- (11) - (CH₂)₀₋₄-CO- (C₃-C₇ cycloalkyl),
- (12) - (CH₂)₀₋₄-CO-R₁-aryl,
- (13) - (CH₂)₀₋₄-CO-R₁-heteroaryl,
- 10 (14) - (CH₂)₀₋₄-CO-R₁-heterocycle,
- (15) - (CH₂)₀₋₄-CO-R_{N-4} where R_{N-4} is selected
from the group consisting of morpholinyl, thiomorpholinyl,
piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl,
homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide,
- 15 pyrrolinyl and pyrrolidinyl where each group is optionally
substituted with one, two, three, or four of: C₁-C₆ alkyl,
- (16) - (CH₂)₀₋₄-CO-O-R_{N-5} where R_{N-5} is selected
from the group consisting of:
- (a) C₁-C₆ alkyl,
- 20 (b) - (CH₂)₀₋₂- (R₁-aryl),
- (c) C₂-C₆ alkenyl containing one or two
double bonds,
- (d) C₂-C₆ alkynyl containing one or two
triple bonds,
- 25 (e) C₃-C₇ cycloalkyl, and
- (f) - (CH₂)₀₋₂- (R₁-heteroaryl),
- (17) - (CH₂)₀₋₄-SO₂-NR_{N-2}R_{N-3},
- (18) - (CH₂)₀₋₄-SO- (C₁-C₈ alkyl),
- (19) - (CH₂)₀₋₄-SO₂- (C₁-C₁₂ alkyl),
- 30 (20) - (CH₂)₀₋₄-SO₂- (C₃-C₇ cycloalkyl),
- (21) - (CH₂)₀₋₄-N(H or R_{N-5})-CO-O-R_{N-5} where R_{N-5}
can be the same or different,
- (22) - (CH₂)₀₋₄-N(H or R_{N-5})-CO-N(R_{N-5})₂, where
R_{N-5} can be the same or different,
- 35 (23) - (CH₂)₀₋₄-N-CS-N(R_{N-5})₂, where R_{N-5} can be
the same or different,

- 5 (24) $-(CH_2)_{0-4}-N(-H \text{ or } R_{N-5})-CO-R_{N-2}$ where R_{N-5}
and R_{N-2} can be the same or different,
- (25) $-(CH_2)_{0-4}-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} can
be the same or different,
- (26) $-(CH_2)_{0-4}-R_{N-4}$,
- 10 (27) $-(CH_2)_{0-4}-O-CO-(C_1-C_6 \text{ alkyl})$,
- (28) $-(CH_2)_{0-4}-O-P(O)-(OR_{N-aryl-1})_2$ where $R_{N-aryl-1}$
is $-H$ or C_1-C_4 alkyl,
- (29) $-(CH_2)_{0-4}-O-CO-N(R_{N-5})_2$,
- (30) $-(CH_2)_{0-4}-O-CS-N(R_{N-5})_2$,
- 15 (31) $-(CH_2)_{0-4}-O-(R_{N-5})_2$,
- (32) $-(CH_2)_{0-4}-O-(R_{N-5})_2-COOH$,
- (33) $-(CH_2)_{0-4}-S-(R_{N-5})_2$,
- (34) $-(CH_2)_{0-4}-O-(C_1-C_6 \text{ alkyl optionally}$
substituted with one, two, three, four, or five $-F$),
- 20 (35) C_3-C_7 cycloalkyl,
- (36) C_2-C_6 alkenyl with one or two double
bonds optionally substituted with C_1-C_3 alkyl, $-F$, $-Cl$, $-Br$, $-I$,
 $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, or $-NR_{1-a}R_{1-b}$, C_1-C_3 alkoxy- $(R_{1-}$
 $aryl)$, C_1-C_3 alkoxy- $(R_{1-heteroaryl})$,
- 25 (37) C_2-C_6 alkynyl with one or two triple
bonds optionally substituted with C_1-C_3 alkyl, $-F$, $-Cl$, $-Br$, $-I$,
 $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, or $-NR_{1-a}R_{1-b}$, C_1-C_3 alkoxy- $(R_{1-}$
 $aryl)$, C_1-C_3 alkoxy- $(R_{1-heteroaryl})$,
- (38) $-(CH_2)_{0-4}-N(-H \text{ or } R_{N-5})-SO_2-R_{N-2}$ where R_{N-5}
30 and R_{N-2} can be the same or different, or
- (39) $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl.

9. A compound according to claim 1, wherein R_1 and R_3 are
independently $R_{N-1}C(O)-$; and

35 R_{N-1} is phenyl of which is optionally substituted with one, two
or three of the following substituents which can be the same or
different and are:

- 5 (1) C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R_{1-heteroaryl}),
- 10 (2) -OH,
(3) -NO₂,
(4) -F, -Cl, -Br, or -I,
(5) -CO-OH,
(6) -C≡N,
- 15 (7) -(CH₂)₀₋₄-CO-NR_{N-2}R_{N-3},
(8) -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl),
(9) -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl with one, two or three double bonds),
(10) -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl with one, two or three triple bonds),
- 20 (11) -(CH₂)₀₋₄-CO-(C₃-C₇ cycloalkyl),
(12) -(CH₂)₀₋₄-CO-R_{1-aryl},
(13) -(CH₂)₀₋₄-CO-R_{1-heteroaryl},
(14) -(CH₂)₀₋₄-CO-R_{1-heterocycle},
- 25 (15) -(CH₂)₀₋₄-CO-R_{N-4} where R_{N-4} is selected from the group consisting of morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl where each group is optionally
- 30 substituted with one, two, three, or four of: C₁-C₆ alkyl,
(16) -(CH₂)₀₋₄-CO-O-R_{N-5} where R_{N-5} is selected from the group consisting of:
(a) C₁-C₆ alkyl,
(b) -(CH₂)₀₋₂-(R_{1-aryl}),
- 35 (c) C₂-C₆ alkenyl containing one or two double bonds,

5 (d) C₂-C₆ alkynyl containing one or two
triple bonds, and

(e) C₃-C₇ cycloalkyl,

(17) - (CH₂)₀₋₄-N(H or R_{N-5}) -CO-O-R_{N-5} where R_{N-5}
5 can be the same or different,

10 (18) - (CH₂)₀₋₄-N(H or R_{N-5}) -CO-N(R_{N-5})₂, where
R_{N-5} can be the same or different,

(19) - (CH₂)₀₋₄-N-CS-N(R_{N-5})₂, where R_{N-5} can be
the same or different,

(20) - (CH₂)₀₋₄-N(-H or R_{N-5}) -CO-R_{N-2} where R_{N-5}
15 and R_{N-2} can be the same or different,

(21) - (CH₂)₀₋₄-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} can
be the same or different,

(22) - (CH₂)₀₋₄-R_{N-4},

(23) - (CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl),

20 (24) - (CH₂)₀₋₄-O-CO-N(R_{N-5})₂,

(25) - (CH₂)₀₋₄-O-CS-N(R_{N-5})₂,

(26) - (CH₂)₀₋₄-O-(R_{N-5})₂,

(27) - (CH₂)₀₋₄-O-(R_{N-5})₂-COOH,

(28) - (CH₂)₀₋₄-O-(C₁-C₆ alkyl optionally
25 substituted with one, two, three, four, or five -F),

(29) - (CH₂)₀₋₄-N(-H or R_{N-5}) -SO₂-R_{N-2} where R_{N-5}
and R_{N-2} can be the same or different, or

(30) - (CH₂)₀₋₄- C₃-C₇ cycloalkyl.

30 10. A compound according to claim 1, wherein R₁ and R₃ are
independently R_{N-1}C(O)-; and

R₁ represents -(CH₂)_{n1}-phenyl where n₁ is zero or one and where
phenyl is optionally substituted with one, two, or three of the
following substituents which are the same or different:

35 (A) C₁-C₆ alkyl optionally substituted with one,
two or three substituents selected from the group consisting of
C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃

5 alkoxy, and $-NR_{1-a}R_{1-b}$, C_1-C_3 alkoxy- (R_{1-aryl}) , C_1-C_3 alkoxy- $(R_{1-heteroaryl})$,

(B) C_2-C_6 alkenyl with one or two double bonds, optionally substituted with one, two or three substituents selected from the group consisting of $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1-a}R_{1-b}$, C_1-C_3 alkoxy- (R_{1-aryl}) , C_1-C_3 alkoxy- $(R_{1-heteroaryl})$,

(C) C_2-C_6 alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1-a}R_{1-b}$, C_1-C_3 alkoxy- (R_{1-aryl}) , C_1-C_3 alkoxy- $(R_{1-heteroaryl})$,

(D) $-F$, Cl , $-Br$, or $-I$,

(E) $-C_1-C_6$ alkoxy optionally substituted with one, two, or three $-F$,

20 (F) $-NR_{N-2}R_{N-3}$, where R_{N-2} and R_{N-3} are independently selected from the group consisting of:

(1) $-H$,

(2) $-C_1-C_6$ alkyl optionally substituted with one substituent selected from the group consisting of:

25 (a) $-OH$, and

(b) $-NH_2$,

(3) $-C_1-C_6$ alkyl optionally substituted with one to three $-F$, $-Cl$, $-Br$, or $-I$,

(4) $-C_3-C_7$ cycloalkyl,

30 (5) $-(C_1-C_2 \text{ alkyl})-(C_3-C_7 \text{ cycloalkyl})$,

(6) $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_3 \text{ alkyl})$,

(7) $-C_2-C_6$ alkenyl with one or two double bonds,

(8) $-C_2-C_6$ alkynyl with one or two triple

35 bonds,

(9) $-C_1-C_6$ alkyl chain with one double bond and one triple bond,

- 5 (10) $-R_1\text{-aryl}$, , and
 (11) $-R_1\text{-heteroaryl}$, ,
 (G) $-\text{OH}$,
 (H) $-\text{C}\equiv\text{N}$,
 (I) $\text{C}_3\text{-C}_7$ cycloalkyl, optionally substituted with
 10 one, two or three substituents selected from the group
 consisting of $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1\text{-C}_3$
 alkoxy, and $-\text{NR}_{1-a}\text{R}_{1-b}$, $\text{C}_1\text{-C}_3$ alkoxy- $(R_1\text{-aryl})$, $\text{C}_1\text{-C}_3$ alkoxy- $(R_1\text{-}$
 $\text{heteroaryl})$,
 (J) $-\text{CO}-(\text{C}_1\text{-C}_4 \text{ alkyl})$,
 15 (K) $-\text{SO}_2\text{-NR}_{1-a}\text{R}_{1-b}$,
 (L) $-\text{CO-NR}_{1-a}\text{R}_{1-b}$, or
 (M) $-\text{SO}_2-(\text{C}_1\text{-C}_4 \text{ alkyl})$.

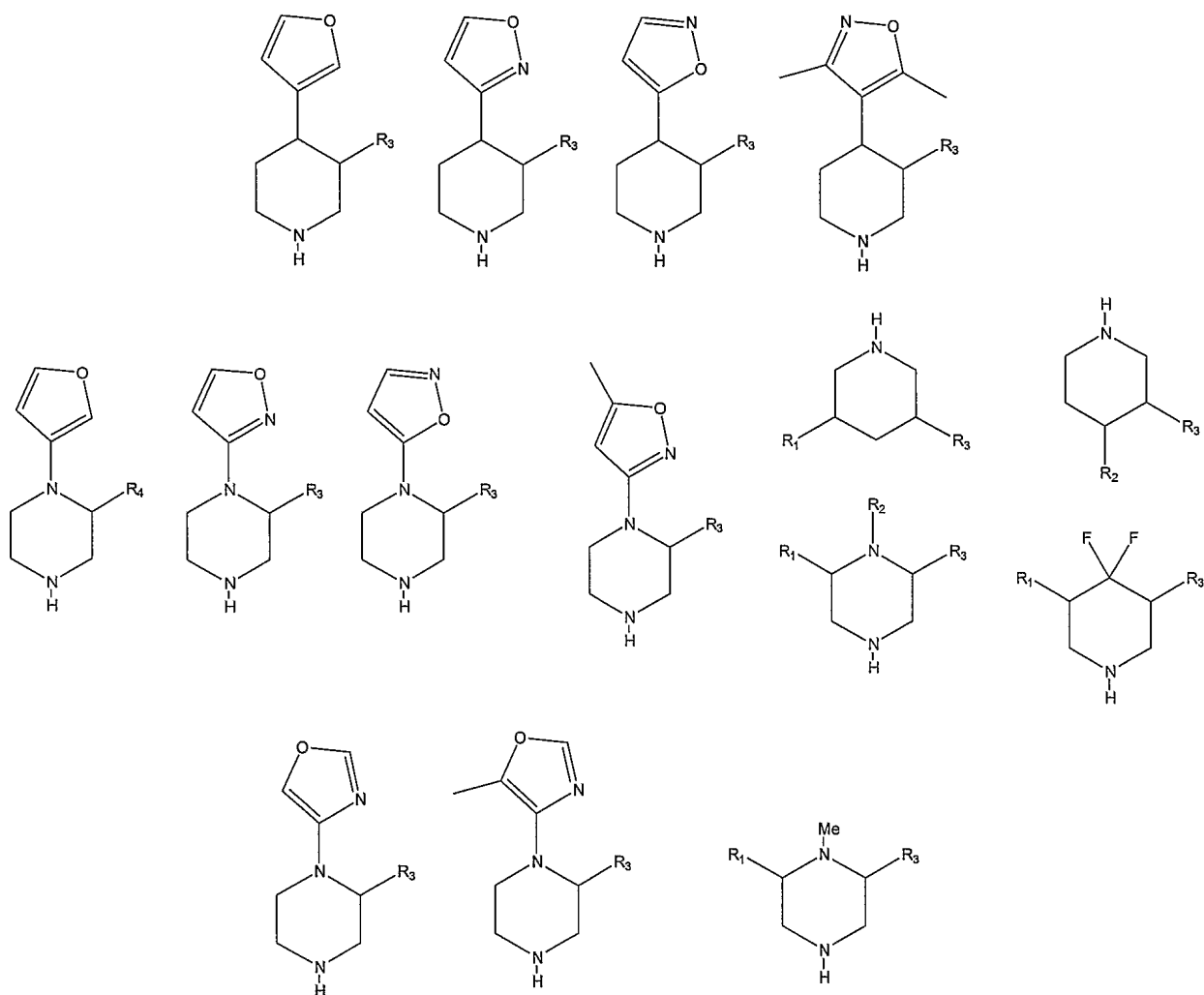
11. A compounds according to claim 1, wherein R_1 and R_3
 20 are independently phenyl($\text{C}_1\text{-C}_6$)alkyl groups where the phenyl is
 optionally substituted with one or two groups independently
 selected from

- (A) $\text{C}_1\text{-C}_6$ alkyl optionally substituted with one,
 two or three substituents selected from the group consisting of
 25 $\text{C}_1\text{-C}_3$ alkyl, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1\text{-C}_3$
 alkoxy, and $-\text{NR}_{1-a}\text{R}_{1-b}$, $\text{C}_1\text{-C}_3$ alkoxy- $(R_1\text{-aryl})$, $\text{C}_1\text{-C}_3$ alkoxy- $(R_1\text{-}$
 $\text{heteroaryl})$,
 (B) $-\text{F}$, Cl , $-\text{Br}$, or $-\text{I}$,
 (C) $-\text{C}_1\text{-C}_6$ alkoxy optionally substituted with
 30 one, two, or three $-\text{F}$,
 (D) $-\text{NR}_{N-2}\text{R}_{N-3}$, where R_{N-2} and R_{N-3} are independently
 selected from the group consisting of:
 (1) $-\text{H}$,
 (2) $-\text{C}_1\text{-C}_6$ alkyl optionally substituted with
 35 one substituent selected from the group consisting of:
 (a) $-\text{OH}$, and
 (b) $-\text{NH}_2$,

- 5 (3) -C₁-C₆ alkyl optionally substituted with
one to three -F, -Cl, -Br, or -I,
(4) -C₃-C₇ cycloalkyl,
(5) -(C₁-C₂ alkyl)-(C₃-C₇ cycloalkyl),
(6) -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl),
10 (9) -C₁-C₆ alkyl chain with one double bond
and one triple bond,
(E) -OH,
(F) -C≡N,
(G) C₃-C₇ cycloalkyl, optionally substituted with
15 one, two or three substituents selected from the group
consisting of -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃
alkoxy, and -NR_{1-a}R_{1-b}, C₁-C₃ alkoxy-(R_{1-aryl}), C₁-C₃ alkoxy-(R₁₋
heteroaryl),
(H) -CO-(C₁-C₄ alkyl),
20 (I) -SO₂-NR_{1-a}R_{1-b}, where R_{1-a} and R_{1-b} are as
defined above, or
(J) -CO-NR_{1-a}R_{1-b}, where R_{1-a} and R_{1-b} are as defined
above.
- 25 12. A compound according to claim 1, wherein R₁ and R₃ are
independently benzyl, 4-hydroxybenzyl, 2-fluoro-4-propylbenzyl,
3-amino-4-bromobenzyl; 3-chloro-5-methylphenethyl, 3,5-
difluorobenzyl, 2-methylphenylpropyl, 4-trifluoromethylbenzyl,
4-trifluoromethylphenethyl, 2,3-dichlorobenzyl, and 2-chloro-4-
30 cyanobenzyl.

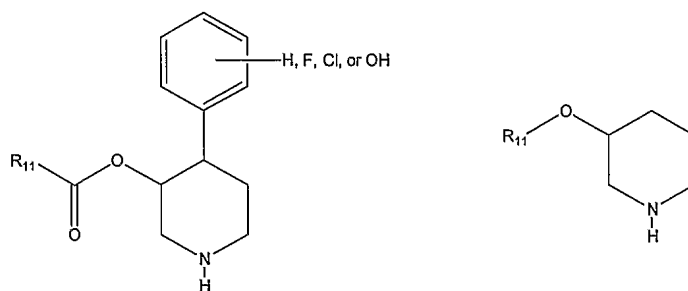
13. A compound of the formula:

5



10 wherein R₁, R₂ and R₃ are as defined in claim 1.

14. A compound of the formula:

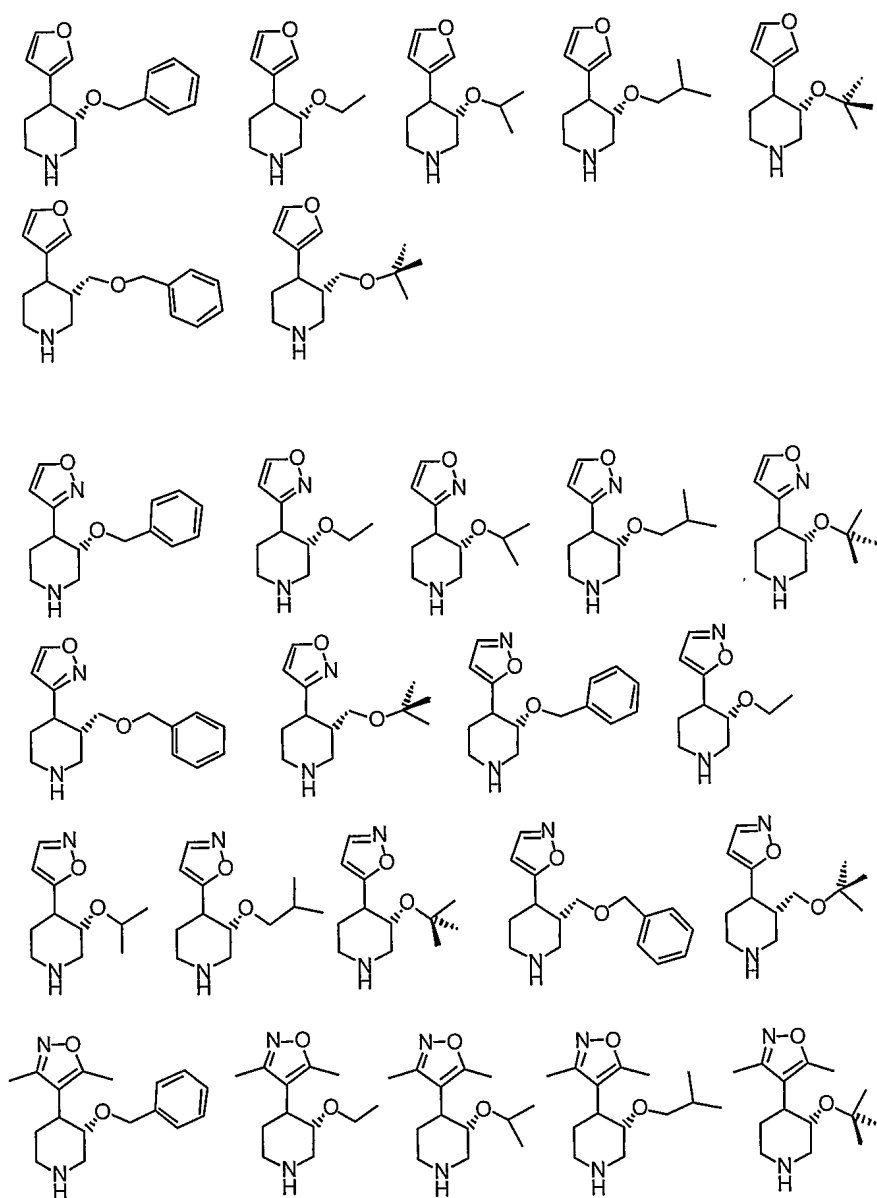


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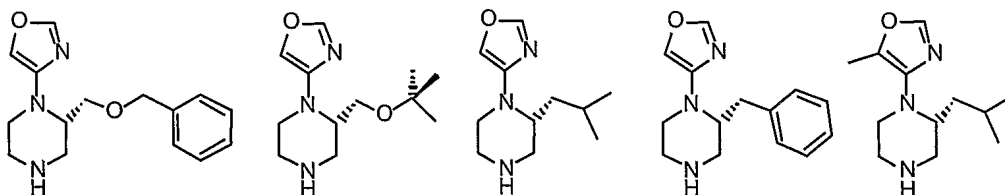
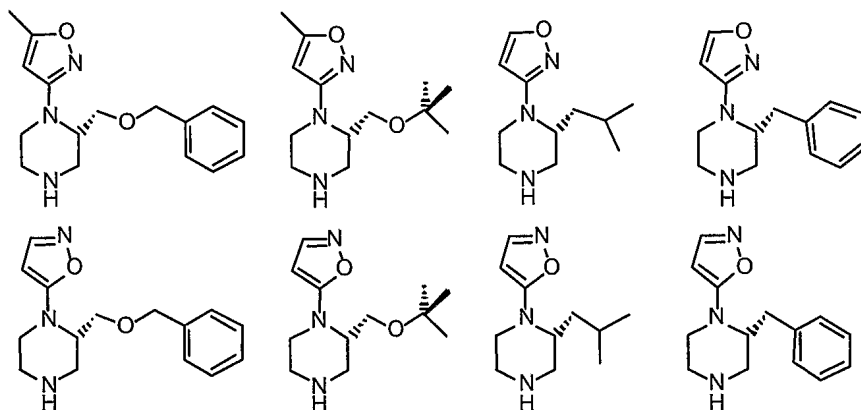
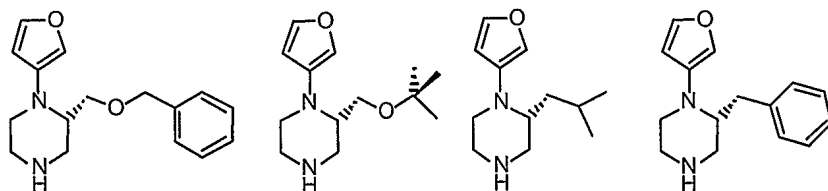
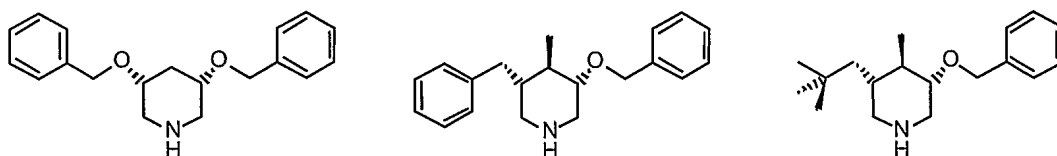
wherein R₁₁ is $-(CH_2)_{n1}-(R_{1-aryl})$, or $-(CH_2)_{n1}-O-(R_{1-aryl})$, wherein n₁ and R_{1-aryl} are as defined in claim 1.

5

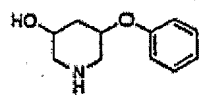
15. A compound of the formula:



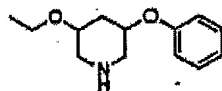
5 16. A compound of the formula:



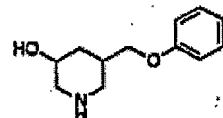
5 17. A compound of the formula:



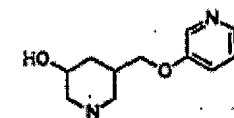
5-Phenoxy-piperidin-3-ol



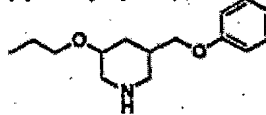
3-Ethoxy-5-phenoxy-piperidine



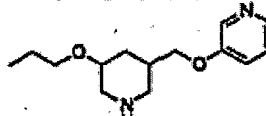
5-Phenoxymethyl-piperidin-3-ol



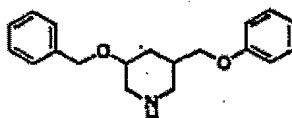
5-(Pyridin-3-yloxymethyl)-piperidin-3-ol



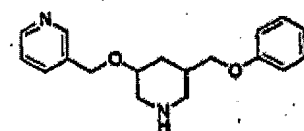
3-Phenoxymethyl-5-propoxy-piperidine



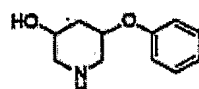
3-(5-Propoxy-piperidin-3-ylmethoxy)-pyridine



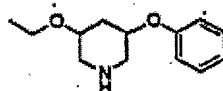
3-Benzoyloxy-5-phenoxy-methyl-piperidine



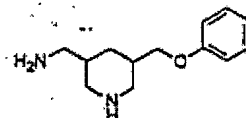
3-(5-Phenoxymethyl-piperidin-3-yloxymethyl)-pyridine



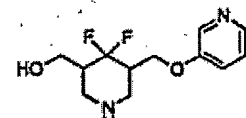
5-Phenoxy-piperidin-3-ol



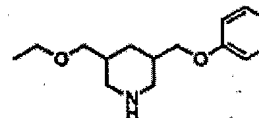
3-Ethoxy-5-phenoxy-piperidine



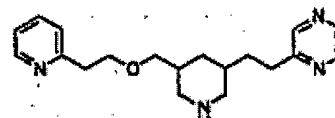
C-(5-Phenoxymethyl-piperidin-3-yl)-methylamine



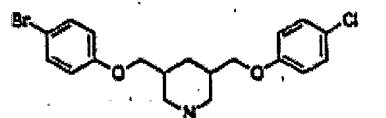
[4,4-Difluoro-5-(pyridin-3-yloxymethyl)-piperidin-3-yl]-methanol



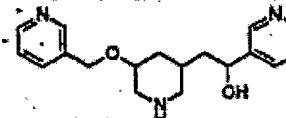
3-Ethoxymethyl-5-phenoxy-methyl-piperidine



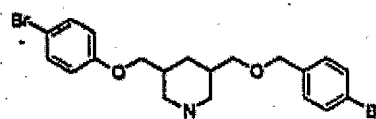
2-[5-(2-Pyridin-2-yl-ethoxymethyl)-piperidin-3-yl]-ethyl-pyrazine



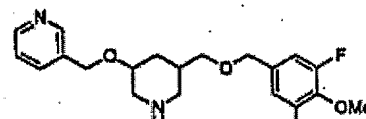
3-(4-Bromo-phenoxy-methyl)-5-(4-chloro-phenoxy-methyl)-piperidine



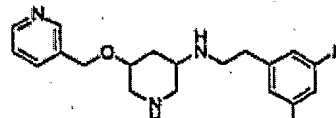
1-Pyridin-3-yl-2-[5-(pyridin-3-ylmethoxy)-piperidin-3-yl]-ethanol



3-(4-Bromo-benzoyloxymethyl)-5-(4-bromo-phenoxy-methyl)-piperidine



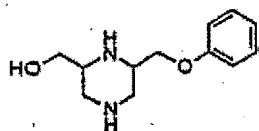
3-(5-(3,5-Difluoro-4-methoxy-benzoyloxymethyl)-piperidin-3-yloxymethyl)-pyridine



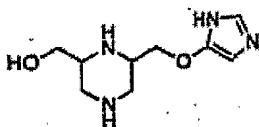
[2-(3,5-Difluoro-phenyl)-ethyl]-[5-(pyridin-3-ylmethoxy)-piperidin-3-yl]-amine

5

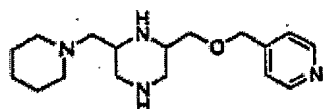
18. A compound of the formula:



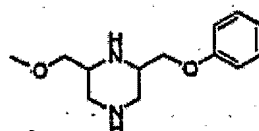
(6-Phenoxymethyl-piperazin-2-yl)-methanol



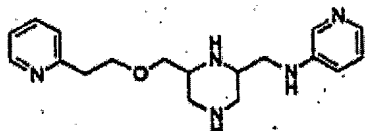
[5-(3H-imidazol-4-ylloxymethyl)-piperazin-2-yl]-methanol



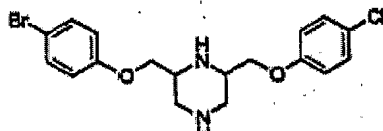
2-Piperidin-1-ylmethyl-6-(pyridin-4-ylmethoxymethyl)-piperazine



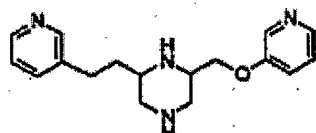
2-Methoxymethyl-6-phenoxymethyl-piperazine



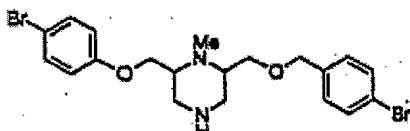
Pyridin-3-yl-[6-(2-pyridin-2-yl-ethoxymethyl)-piperazin-2-ylmethyl]-amine



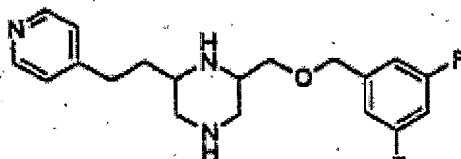
2-(4-Bromo-phenoxymethyl)-6-(4-chloro-phenoxymethyl)-piperazine



2-(2-Pyridin-3-yl-ethyl)-6-(pyridin-3-ylloxymethyl)-piperazine



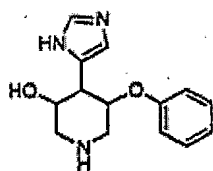
2-(4-Bromo-benzyloxymethyl)-6-(4-bromo-phenoxymethyl)-1-methyl-piperazine



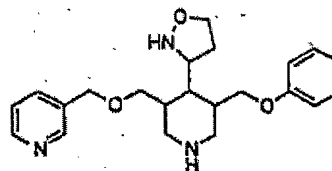
2-(3,5-Difluoro-benzyloxymethyl)-6-(2-pyridin-4-yl-ethyl)-piperazine

5

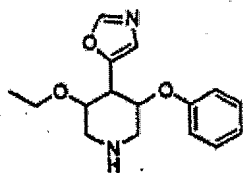
19. A compound of the formula:



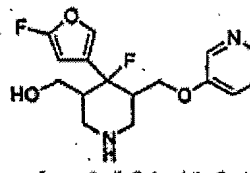
4-(3H-imidazol-4-yl)-5-phenoxy-piperidin-3-ol



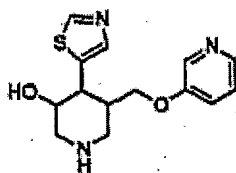
3-(4-isoxazolidin-3-yl-5-phenoxy-methyl-piperidin-3-ylmethoxymethyl)-pyridine



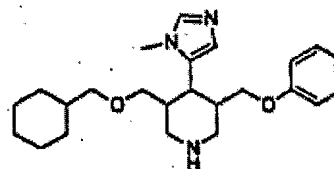
3-Ethoxy-4-oxazol-5-yl-5-phenoxy-piperidine



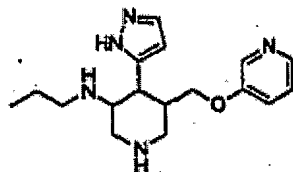
[4-Fluoro-4-(5-fluoro-furan-3-yl)-5-(pyridin-3-ylmethoxymethyl)-piperidin-3-yl]-methanol



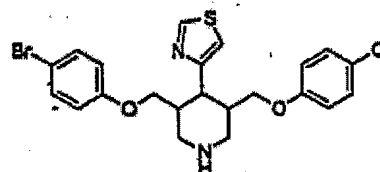
5-(Pyridin-3-ylmethoxymethyl)-4-thiazol-5-yl-piperidin-3-ol



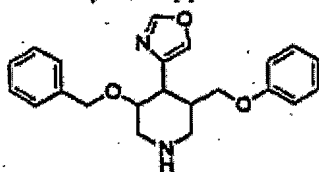
3-Cyclohexylmethoxymethyl-4-(3-methyl-3H-imidazol-4-yl)-5-phenoxy-methyl-piperidine



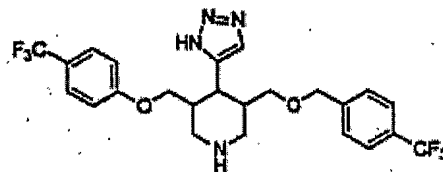
Propyl-[4-(2H-pyrazol-3-yl)-5-(pyridin-3-ylmethoxymethyl)-piperidin-3-yl]-amine



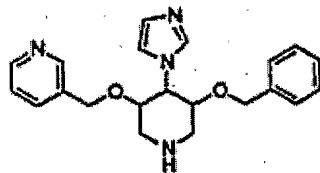
3-(4-Bromo-phenoxy-methyl)-5-(4-chloro-phenoxy-methyl)-4-thiazol-4-yl-piperidine



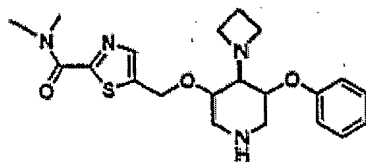
3-Benzoyloxy-4-oxazol-4-yl-5-phenoxy-methyl-piperidine



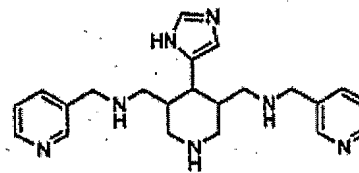
4-(3H-[1,2,3]Triazol-4-yl)-3-(4-trifluoromethyl-benzoyloxymethyl)-5-(4-trifluoromethyl-phenoxy-methyl)-piperidine



3-(5-Benzoyloxy-4-imidazol-1-yl-piperidin-3-ylmethoxymethyl)-pyridine



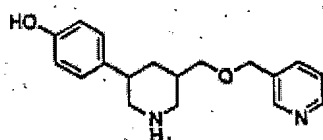
5-(4-Azetidin-1-yl-5-phenoxy-piperidin-3-ylmethoxymethyl)-thiazole-2-carboxylic acid dimethylamide



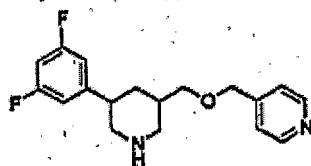
4-(3H-imidazol-4-yl)-5-(((pyridin-3-ylmethyl)-amino)-methyl)-piperidin-3-ylmethyl-pyridin-3-ylmethyl-amine

5

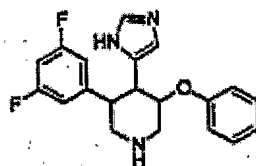
20. A compound of the formula:



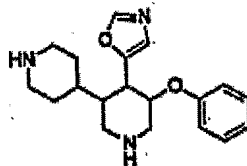
4-{5-(Pyridin-3-ylmethoxymethyl)-piperidin-3-yl}-phenol



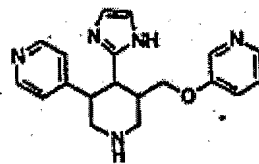
4-{5-(3,5-Difluoro-phenyl)-piperidin-3-ylmethoxymethyl}-pyridine



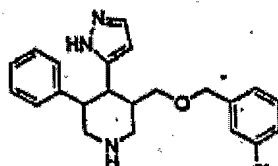
3-(3,5-Difluoro-phenyl)-4-(3H-imidazol-4-yl)-5-phenoxy-piperidine



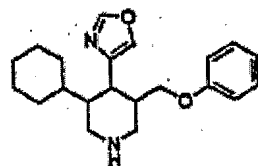
4-Oxazol-5-yl-5-phenoxy-(3,4'-bipiperidinyl)



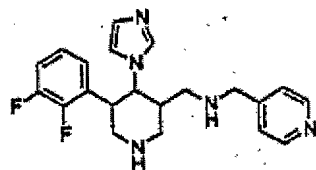
4-(1H-imidazol-2-yl)-5-(pyridin-3-ylloxymethyl)-1,2,3,4,5,6-hexahydro-[3,4']bipyridinyl



3-(3-Chloro-benzoyloxymethyl)-5-phenyl-4-(2H-pyrazol-3-yl)-piperidine



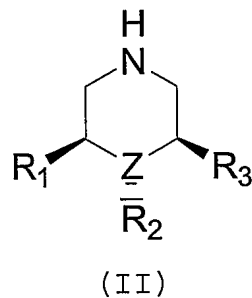
3-Cyclohexyl-4-oxazol-4-yl-5-phenoxy-methyl-piperidine



[5-(2,3-Difluoro-phenyl)-4-imidazol-1-yl-piperidin-3-ylmethyl]-pyridin-4-ylmethyl-amine

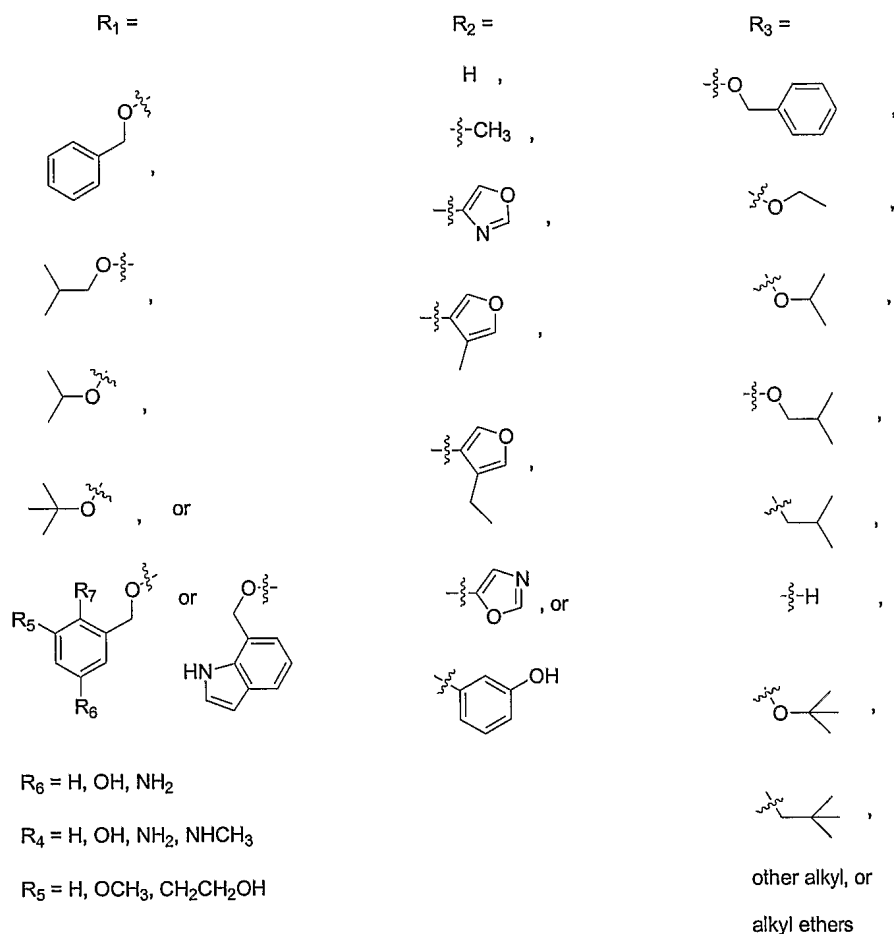
5

21. A compound according to Formula II:



10

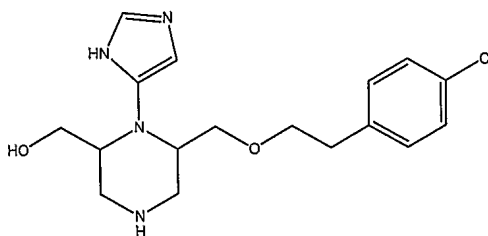
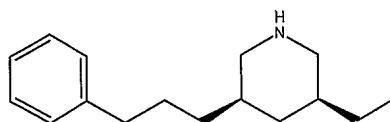
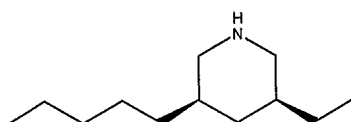
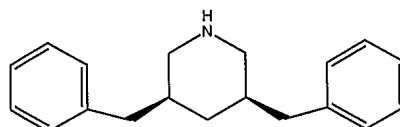
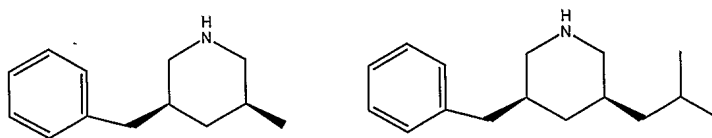
or a pharmaceutically acceptable salt or ester thereof,
wherein Z is CH or N, and R₁, R₂ and R₃ are defined as follows:



15

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22. A compound of the formula:



10

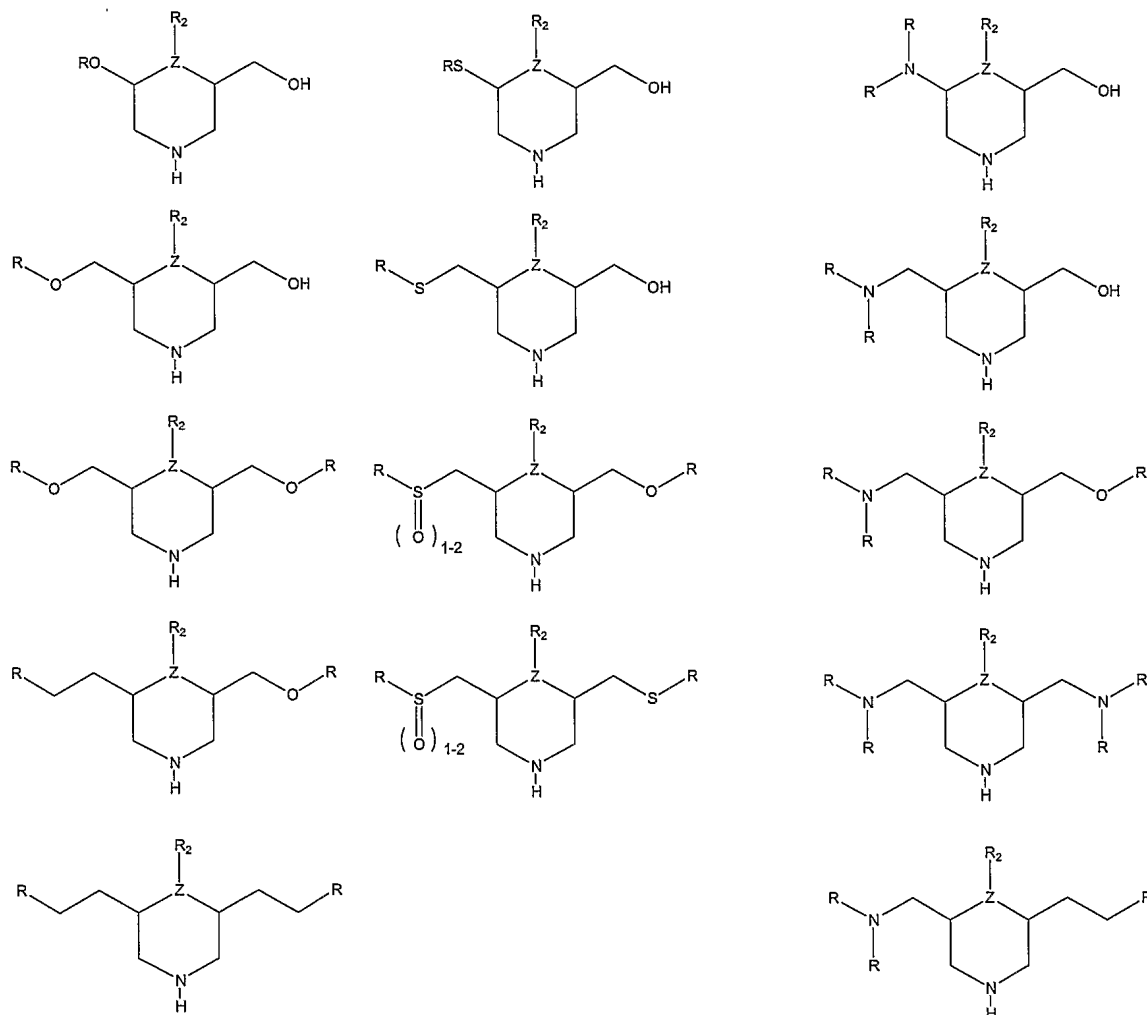
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17 MAY 2006

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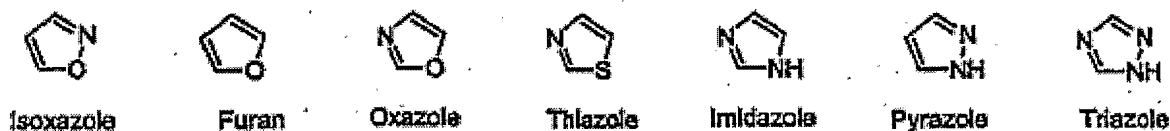
23. A compound of the formula:



where R in each compound may independently be R_1 or R_3 , wherein Z is CH or N, and wherein R_1 , R_2 and R_3 are as defined in claim

10 1.

24. A compound according to claim 1, wherein R_2 is an optionally substituted five-membered heterocycle of the formula:



15

25. A compound according to claim 1, wherein R_2 is an optionally substituted six-membered heterocycle of the formula:



Pyridine



Pyrimidine



Pyrazine



Triazine

5

26. A compound according to claim 1, wherein R_2 is an optionally substituted phenol.

10

27. A compound according to claim 1, wherein R_2 is not a halogenated phenyl, benzyl, aryl or heteroaryl.

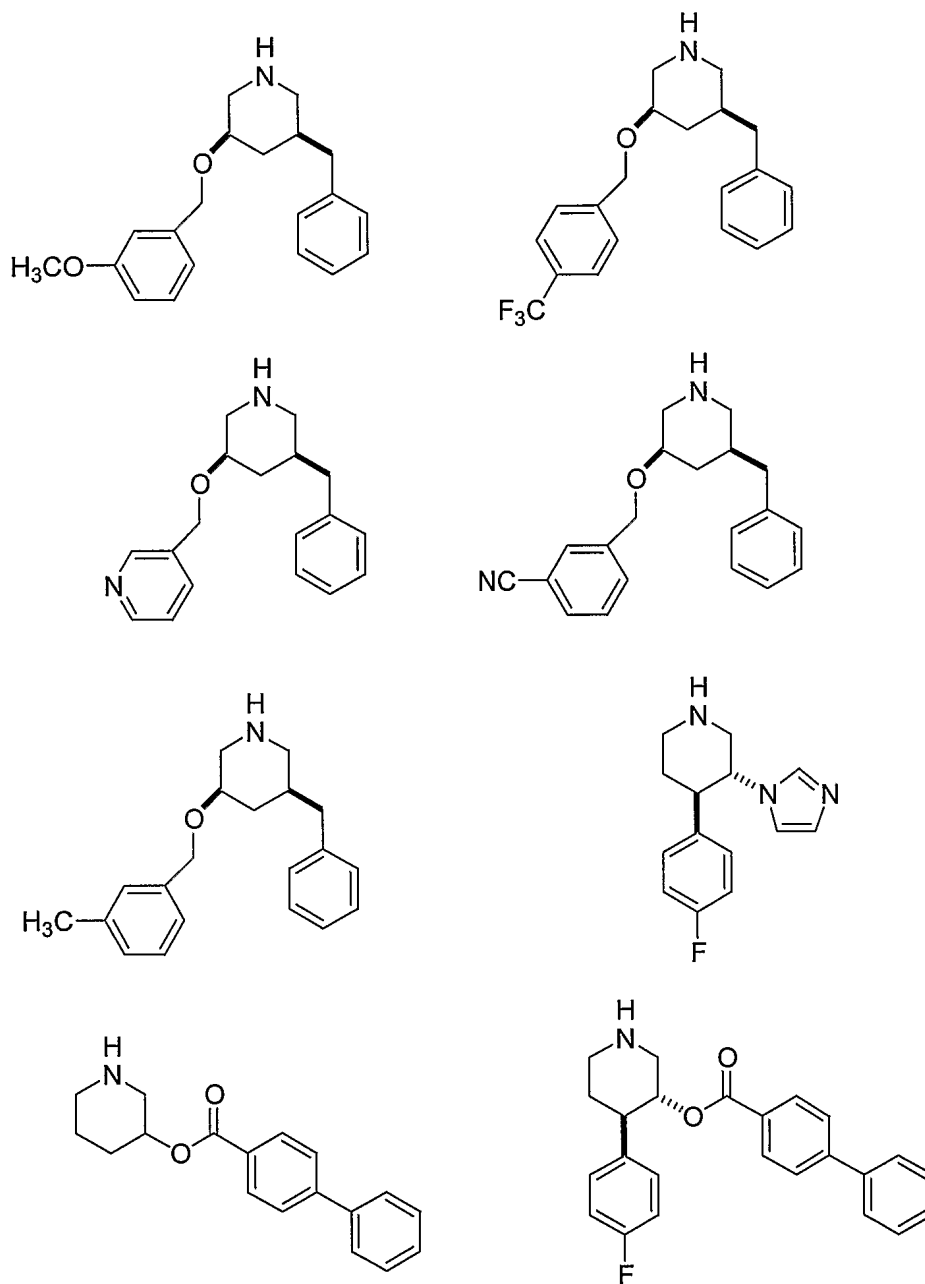
15

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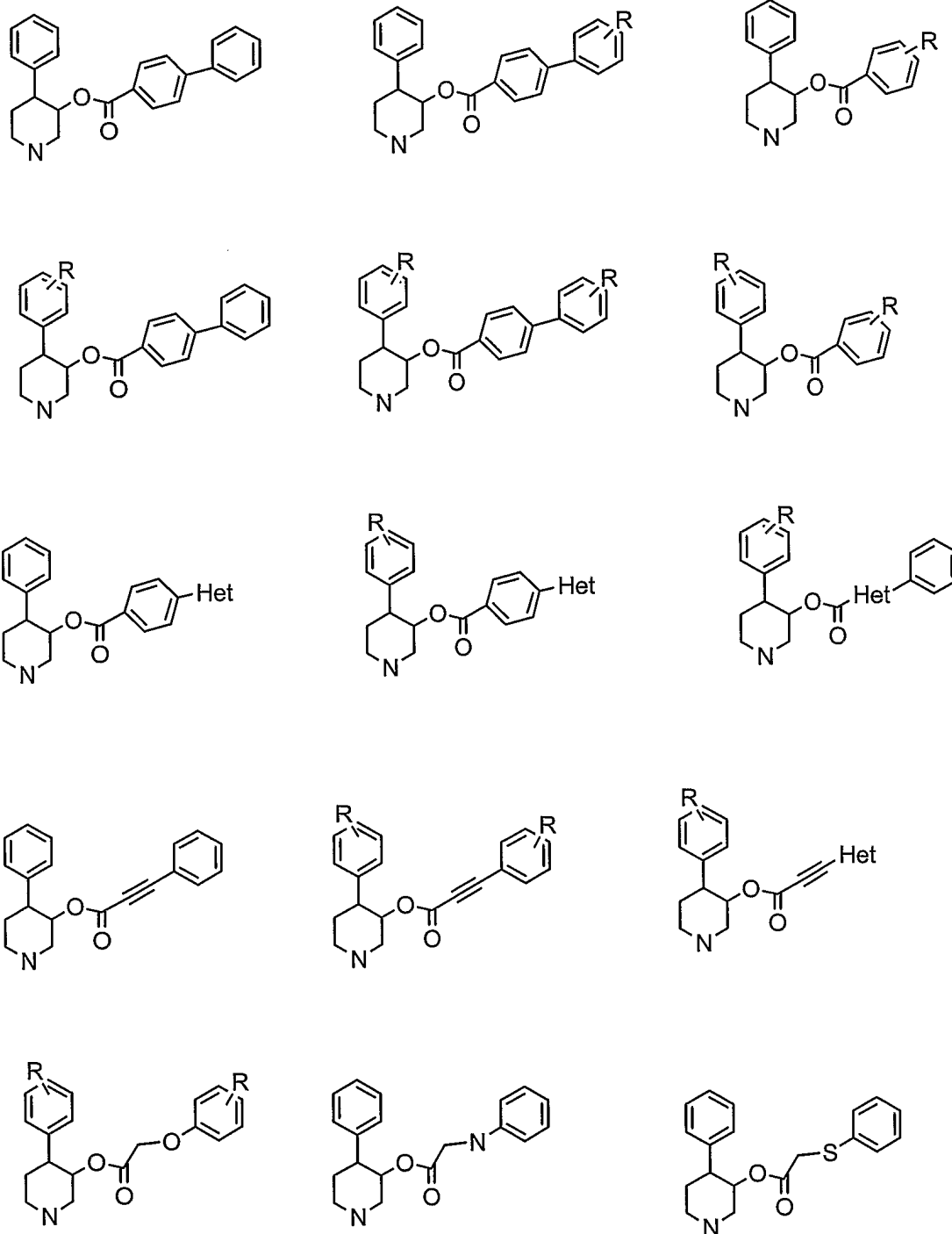
5 28. A compound of the formula:



wherein the imidazole ring, when present is optionally substituted with an aryl or alkyl group.

10

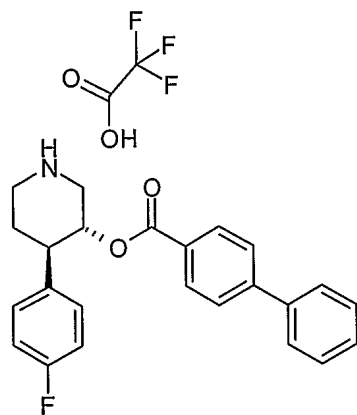
5 29. A compound of the formula:



5

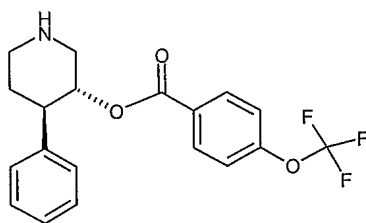
30. A compound of the formula:

	(+/-) - (3R,4R) -4- (3-hydroxyphenyl)piperidin-3-yl 1,1'-biphenyl-4-carboxylate hydrochloride
	(+/-) - (3R,4R) -4- (4-chlorophenyl)piperidin-3-yl 1,1'-biphenyl-4-carboxylate trifluoroacetate
	(+/-) - (3R,4R) -4- (4-chlorophenyl)piperidin-3-yl (3,5-difluorophenyl)acetate
	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 1-naphthoate hydrochloride

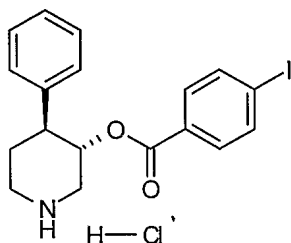


(+/-) - (3R,4R) - 4 - (4 -
fluorophenyl)piperidin-3-yl 1,1'-
biphenyl-4-carboxylate
trifluoroacetate

OH

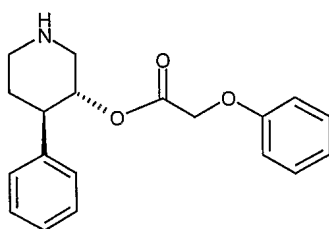


(+/-) - (3R,4R) - 4-phenylpiperidin-3-yl
4 - (trifluoromethoxy)benzoate
hydrochloride

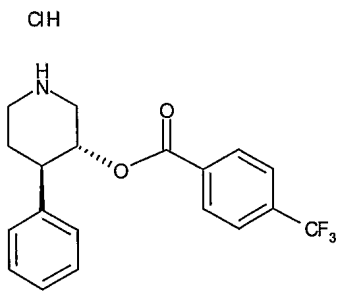
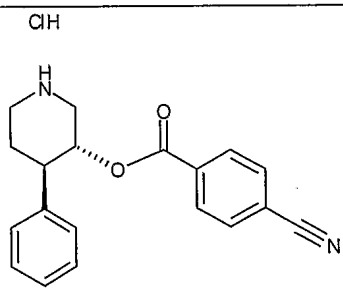
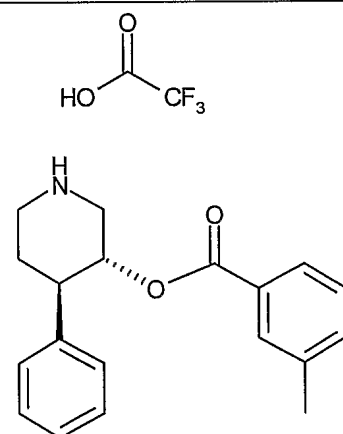
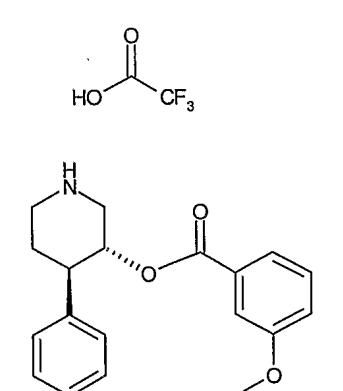


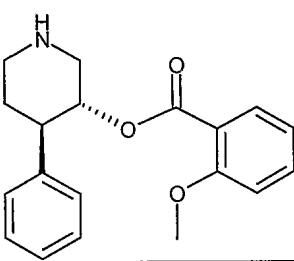
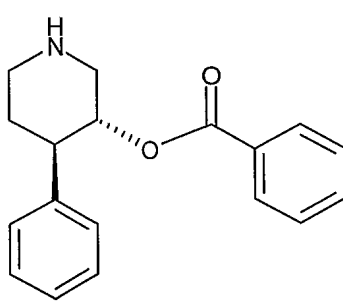
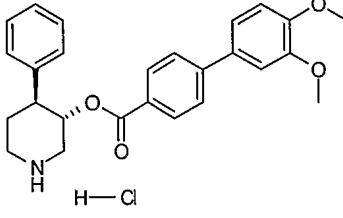
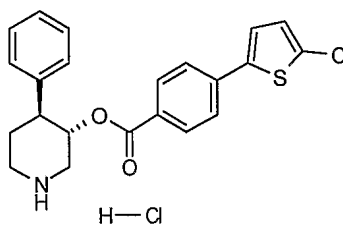
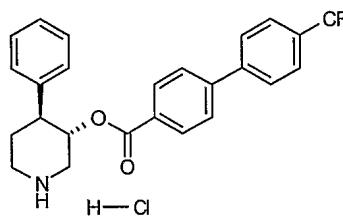
(+/-) - (3S,4S) - 4-phenylpiperidin-3-yl
4-iodobenzoate hydrochloride

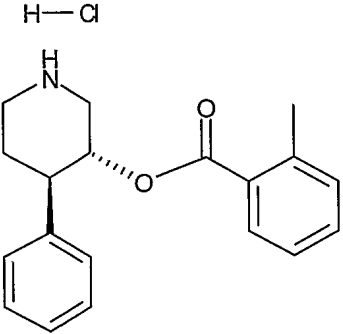
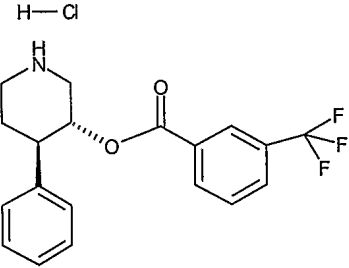
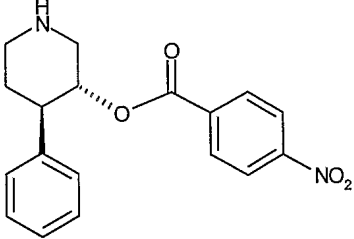
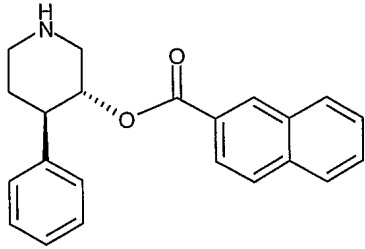
OH

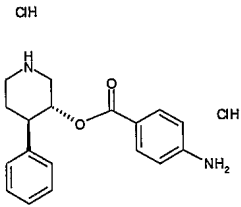
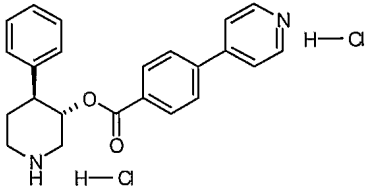
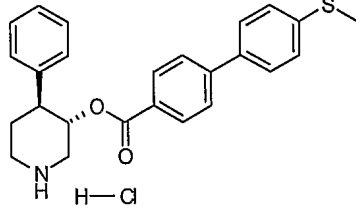
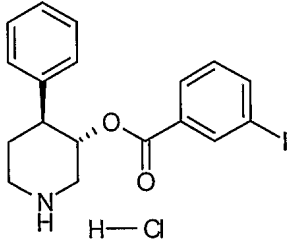
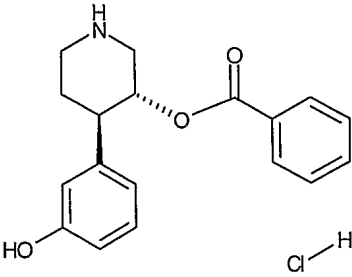


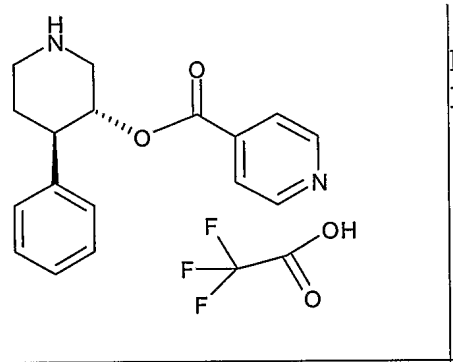
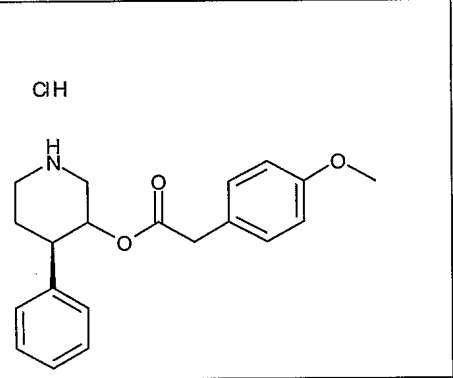
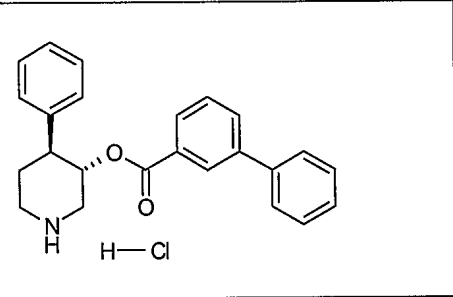
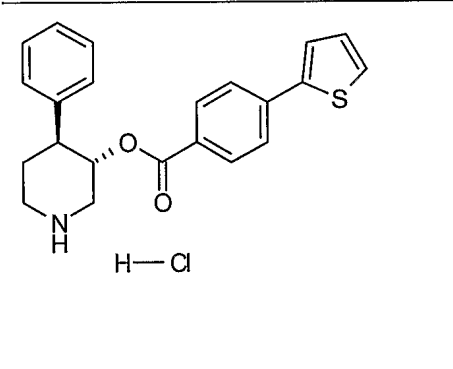
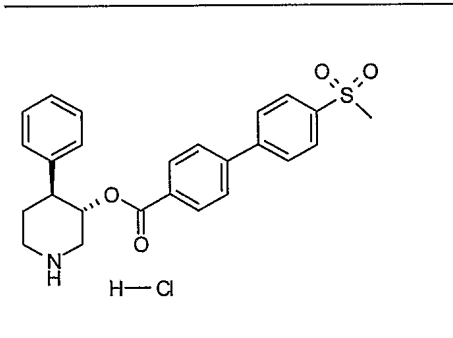
(+/-) - (3R,4R) - 4-phenylpiperidin-3-yl
phenoxyacetate hydrochloride

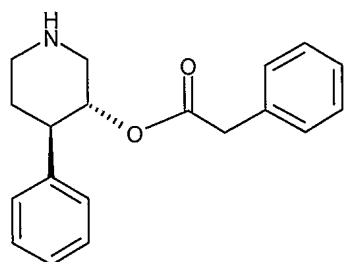
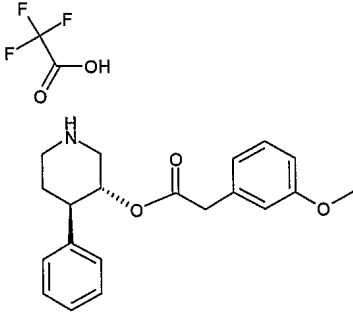
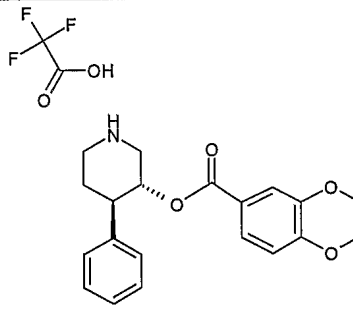
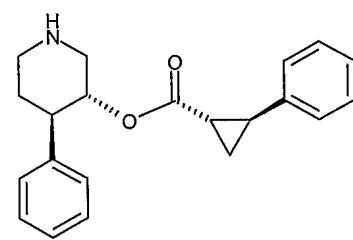
OH 	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 4-(trifluoromethyl)benzoate hydrochloride
OH 	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 4-cyanobenzoate hydrochloride
	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 3-methylbenzoate trifluoroacetate
	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 3-methoxybenzoate trifluoroacetate

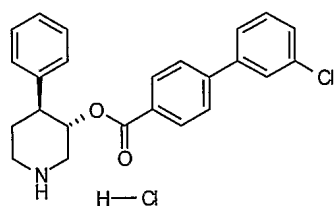
ClH 	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 2-methoxybenzoate hydrochloride
ClH 	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl benzoate hydrochloride
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 3',4'-dimethoxy-1,1'-biphenyl-4- carboxylate hydrochloride
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4-(5-chlorothiophen-2-yl)benzoate hydrochloride
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4'-(trifluoromethyl)-1,1'-biphenyl-4- carboxylate hydrochloride

H-Cl 	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 2-methylbenzoate hydrochloride
H-Cl 	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 3-(trifluoromethyl)benzoate hydrochloride
HCl 	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 4-nitrobenzoate hydrochloride
ClH 	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 2-naphthoate hydrochloride

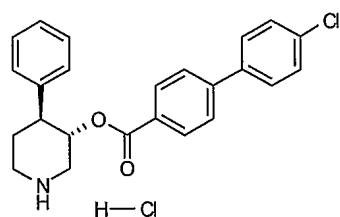
	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 4-aminobenzoate dihydrochloride
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4-pyridin-4-ylbenzoate dihydrochloride
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4'-(methylthio)-1,1'-biphenyl-4- carboxylate hydrochloride
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 3-iodobenzoate hydrochloride
	(+/-) - (3R,4R) -4-(3- hydroxyphenyl)piperidin-3-yl benzoate hydrochloride

	(+/-) - (3R,4R) -4- (3-hydroxyphenyl)piperidin-3-yl benzoate hydrochloride
	(3R,4R) -4-phenylpiperidin-3-yl 1,1'-biphenyl-4-carboxylate
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 1,1'-biphenyl-3-carboxylate hydrochloride
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4-thien-2-ylbenzoate hydrochloride
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4'-(methylsulfonyl)-1,1'-biphenyl-4-carboxylate hydrochloride

ClH 	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl phenylacetate hydrochloride
	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl (3-methoxyphenyl) acetate trifluoroacetate
	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 3,4-dimethoxybenzoate trifluoroacetate
ClH 	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl (1R,2S) -2- phenylcyclopropanecarboxylate hydrochloride

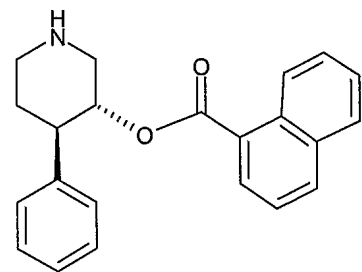


(+/-) - (3S,4S) -4-phenylpiperidin-3-yl
3'-chloro-1,1'-biphenyl-4-carboxylate
hydrochloride

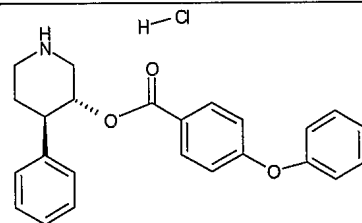


(+/-) - (3S,4S) -4-phenylpiperidin-3-yl
4'-chloro-1,1'-biphenyl-4-carboxylate
hydrochloride

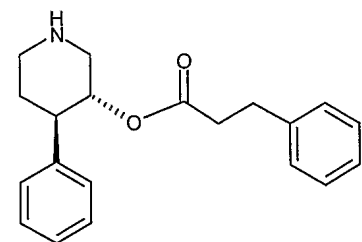
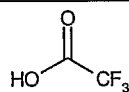
CH



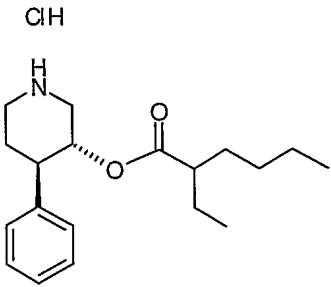
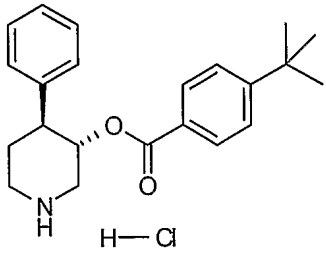
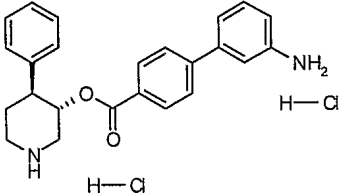
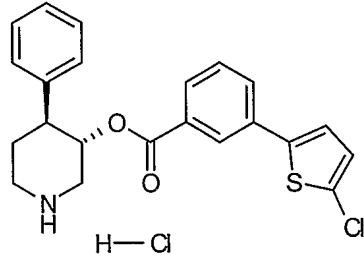
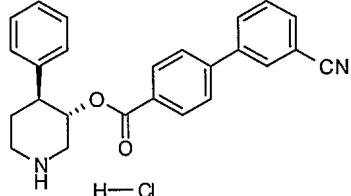
(+/-) - (3R,4R) -4-phenylpiperidin-3-yl
1-naphthoate hydrochloride

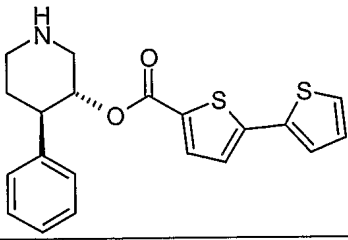
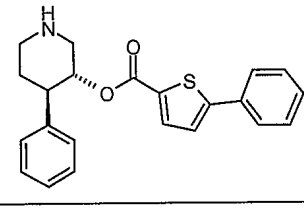
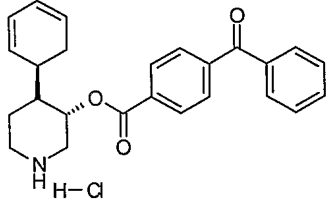
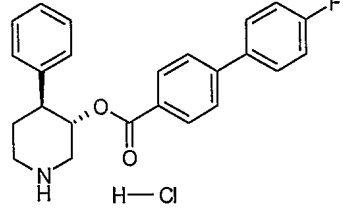
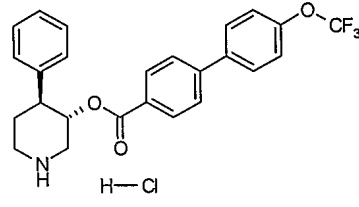
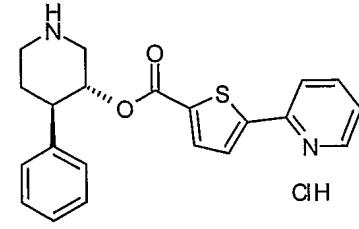


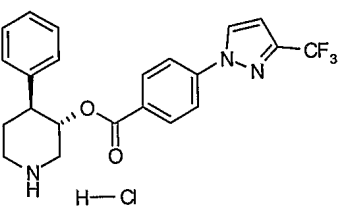
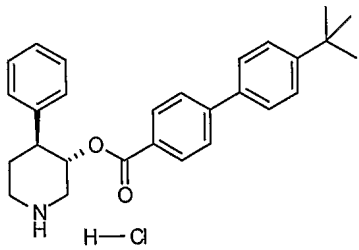
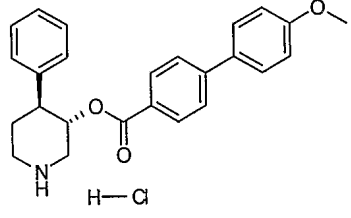
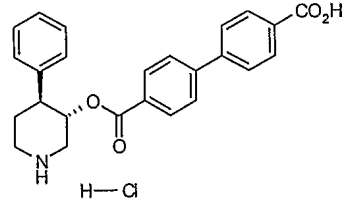
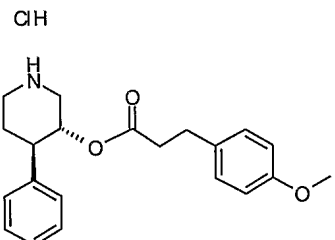
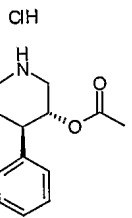
(+/-) - (3R,4R) -4-phenylpiperidin-3-yl
4-phenoxybenzoate hydrochloride

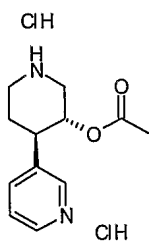


(+/-) - (3R,4R) -4-phenylpiperidin-3-yl
3-phenylpropanoate trifluoroacetate

	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 2-ethylhexanoate hydrochloride
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4-tert-butylbenzoate hydrochloride
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 3'-amino-1,1'-biphenyl-4-carboxylate dihydrochloride
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 3-(5-chlorothiophen-2-yl)benzoate hydrochloride
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 3'-cyano-1,1'-biphenyl-4-carboxylate hydrochloride (Generated by ACD/Name software)

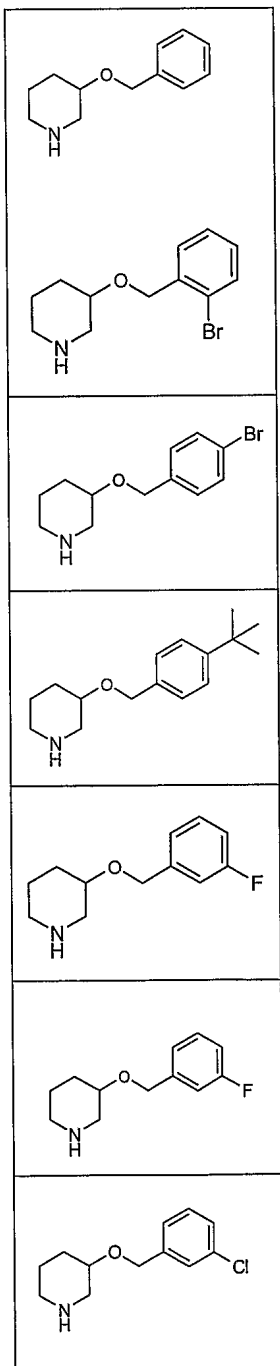
ClH 	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 2,2'-bithiophene-5-carboxylate hydrochloride
ClH 	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 5-phenylthiophene-2-carboxylate hydrochloride
	(+/-) - (3S,4R) -4-[(1R) -cyclohexa-2,4- dien-1-yl]piperidin-3-yl 4- benzoylbenzoate hydrochloride)
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4'-fluoro-1,1'-biphenyl-4-carboxylate hydrochloride
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4'-(trifluoromethoxy)-1,1'-biphenyl- 4-carboxylate hydrochloride
ClH 	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 5-pyridin-2-ylthiophene-2-carboxylate dihydrochloride

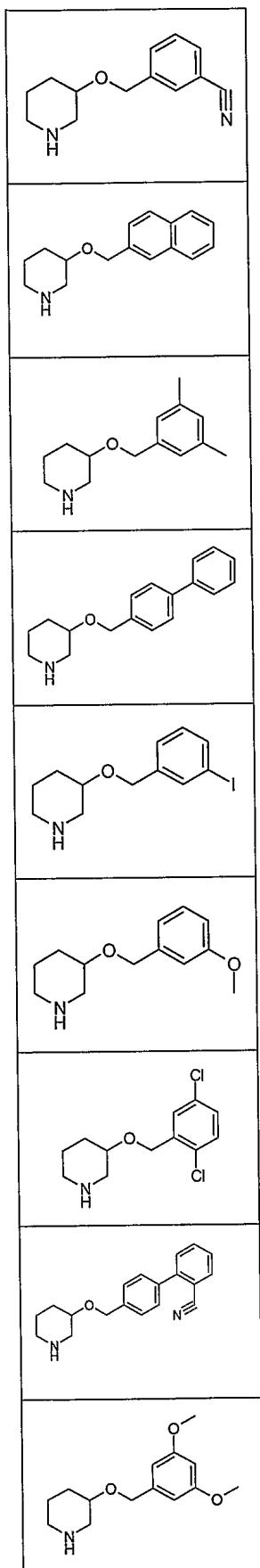
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]benzoate hydrochloride
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4'-tert-butyl-1,1'-biphenyl-4- carboxylate hydrochloride
	(+/-) - (3S,4S) -4-phenylpiperidin-3-yl 4'-methoxy-1,1'-biphenyl-4- carboxylate hydrochloride
	(+/-) - 4' - ({ [(3S,4S) -4- phenylpiperidin-3-yl]oxy } carbonyl) - 1,1'-biphenyl-4-carboxylic acid hydrochloride
	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl 3-(4-methoxyphenyl)propanoate hydrochloride
	(+/-) - (3R,4R) -4-phenylpiperidin-3-yl acetate hydrochloride

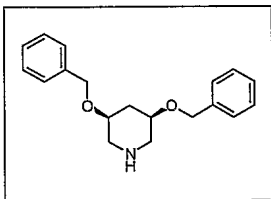


(+/-) - (3R,4R) -4-pyridin-3-ylpiperidin-3-yl acetate dihydrochloride

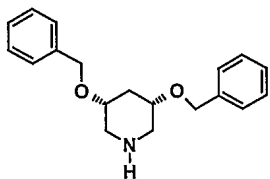
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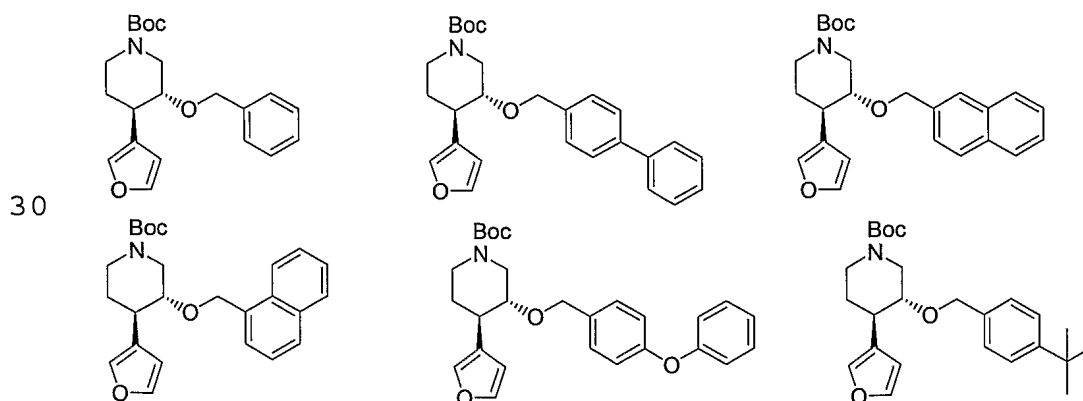


10 31. A compound selected from the group consisting of 3-benzyl-5-[(3,5-difluorobenzyl)oxy]piperidine hydrochloride; 3-benzyl-5-[(3-methylbenzyl)oxy]piperidine hydrochloride; 3-benzyl-5-{[4-(trifluoromethyl)benzyl]oxy}piperidine hydrochloride; 3-({5-benzylpiperidin-3-yl}oxy)methyl benzonitrile; 3-benzyl-5-[(3-methoxybenzyl)oxy]piperidine hydrochloride; 5-benzylpiperidin-3-yl 1,1'-biphenyl-4-carboxylate
15 trifluoroacetate.

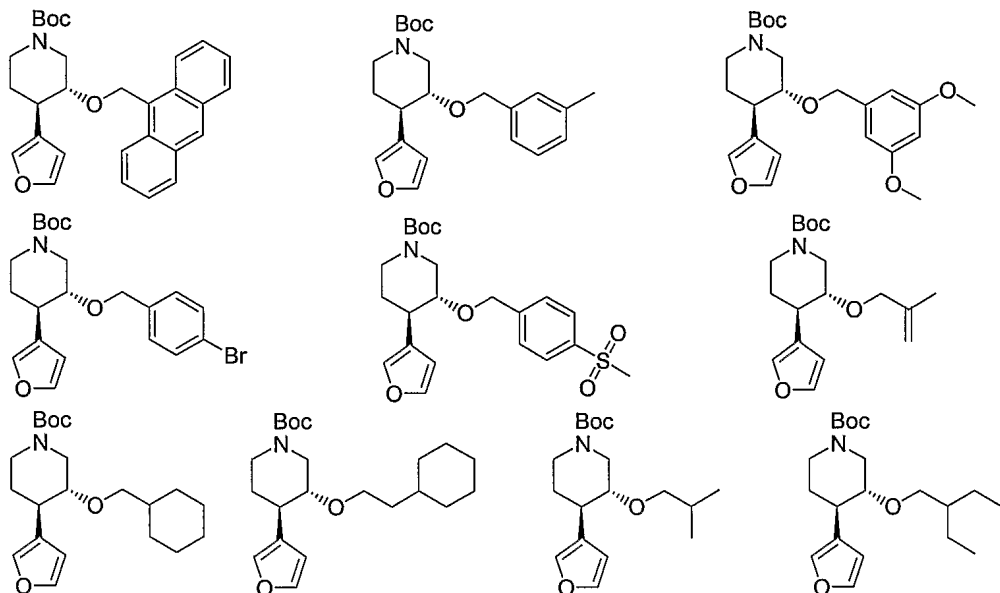
32. A compound selected from the group consisting of 3-Benzyl-5-[(3,5-difluorobenzyl)oxy]piperidine hydrochloride; 3-Benzyl-5-[(3-methylbenzyl)oxy]piperidine hydrochloride; 3-Benzyl-5-{[4-(trifluoromethyl)benzyl]oxy}piperidine hydrochloride; 3-({5-benzylpiperidin-3-yl}oxy)methyl benzonitrile; 3-Benzyl-5-[(3-methoxybenzyl)oxy]piperidine hydrochloride; 5-Benzylpiperidin-3-yl 1,1'-biphenyl-4-carboxylate trifluoroacetate.
20 Benzyloxy-4-furan-3-yl-piperidine-1-carboxylic acid tert-butyl ester; 3-(Biphenyl-4-ylmethoxy)-4-furan-3-yl-piperidine-1-carboxylic acid tert-butyl ester; 4-Furan-3-yl-3-(naphthalen-2-ylmethoxy)-piperidine-1-carboxylic acid tert-butyl ester; 4-Furan-3-yl-3-(naphthalen-1-ylmethoxy)-piperidine-1-carboxylic acid tert-butyl ester; 4-Furan-3-yl-3-(4-phenoxy-benzyloxy)-piperidine-1-carboxylic acid tert-butyl ester; 3-(4-tert-Butyl-benzyloxy)-4-furan-3-yl-piperidine-1-carboxylic acid tert-butyl ester; 3-(Anthracen-9-ylmethoxy)-4-furan-3-yl-piperidine-1-carboxylic acid tert-butyl ester; 4-Furan-3-yl-3-(3-methyl-benzyloxy)-piperidine-1-carboxylic acid tert-butyl ester; 3-(3,5-Dimethoxy-benzyloxy)-4-furan-3-yl-piperidine-1-carboxylic acid tert-butyl ester; 3-(4-Bromo-benzyloxy)-4-furan-3-yl-piperidine-
25 30

5 1-carboxylic acid tert-butyl ester; 4-Furan-3-yl-3-(4-methanesulfonyl-benzyloxy)-piperidine-1-carboxylic acid tert-butyl ester; 4-Furan-3-yl-3-(2-methyl-allyloxy)-piperidine-1-carboxylic acid tert-butyl ester; 3-Cyclohexylmethoxy-4-furan-3-yl-piperidine-1-carboxylic acid tert-butyl ester; 3-(2-Cyclohexyl-ethoxy)-4-furan-3-yl-piperidine-1-carboxylic acid tert-butyl ester; 4-Furan-3-yl-3-isobutoxy-piperidine-1-carboxylic acid tert-butyl ester; 3-(2-Ethyl-butoxy)-4-furan-3-yl-piperidine-1-carboxylic acid tert-butyl ester; 3-Benzyloxy-4-furan-3-yl-piperidine; 3-(Biphenyl-4-ylmethoxy)-4-furan-3-yl-piperidine; 4-Furan-3-yl-3-(naphthalen-2-ylmethoxy)-piperidine; 4-Furan-3-yl-3-(naphthalen-1-ylmethoxy)-piperidine; 4-Furan-3-yl-3-(4-phenoxy-benzyloxy)-piperidine; 3-(4-tert-Butyl-benzyloxy)-4-furan-3-yl-piperidine; 3-(Anthracen-9-ylmethoxy)-4-furan-3-yl-piperidine; 4-Furan-3-yl-3-(3-methyl-benzyloxy)-piperidine; 3-(3,5-Dimethoxy-benzyloxy)-4-furan-3-yl-piperidine; 3-(4-Bromobenzyloxy)-4-furan-3-yl-piperidine; 4-Furan-3-yl-3-(2-methyl-allyloxy)-piperidine; 3-Cyclohexylmethoxy-4-furan-3-yl-piperidine; 3-(2-Cyclohexyl-ethoxy)-4-furan-3-yl-piperidine; 4-Furan-3-yl-3-isobutoxy-piperidine; 3-(2-Ethyl-butoxy)-4-furan-3-yl-piperidine.

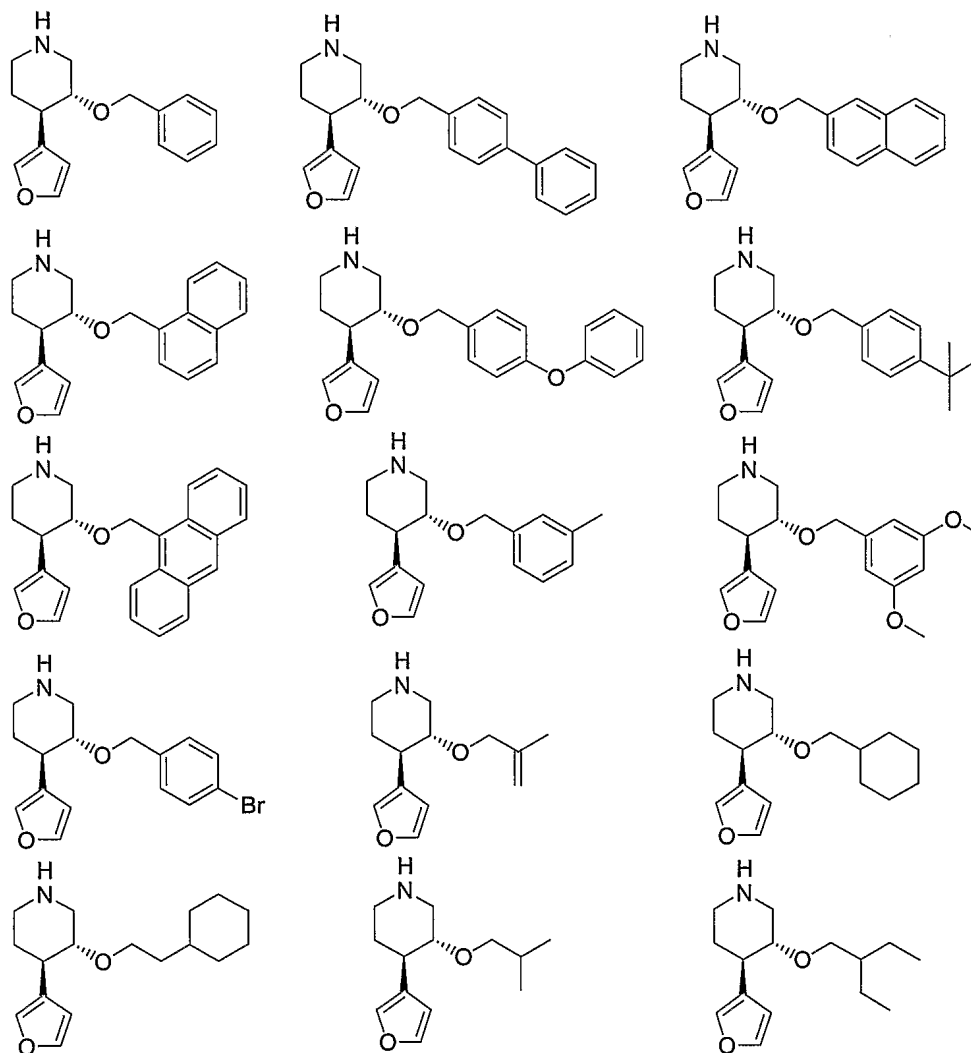
33. A compound of the formula:



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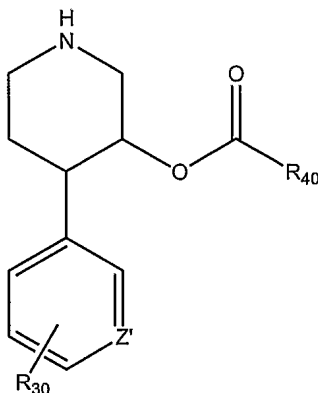
5

34. A method for treating a patient who has, or in preventing a patient from getting, a disease or condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for
10 treating patients with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid
15 angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear
20 palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease and who is in need of such treatment, comprising administering to such patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof, wherein
25 Z, R₁, R₂ and R₃ are as defined in claim 1.

30

35. A method for making a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof, wherein Z, R₁, R₂ and R₃ are as defined in claim 1.

36. A compound of the formula:



5

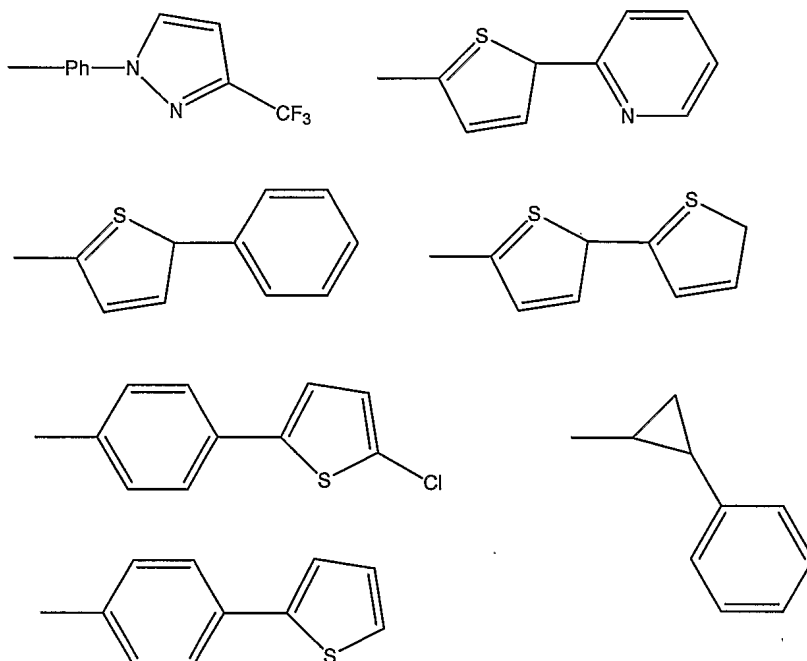
or a pharmaceutically acceptable salt or ester thereof,
wherein Z' is CH or N;

wherein R₃₀ is absent, -OH, or halo;

10 wherein R₄₀ is C₁₋₈ alkyl, C₁₋₈ alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycl, substituted heterocycl, phenyl, substituted phenyl, C₁₋₈ alkyl-phenyl, or C₁₋₈ alkyl-substituted phenyl.

15 37. A compound according to claim 36, wherein R₃₀ is absent, -OH, or Cl, Br, I or F.

38. A compound according to claim 37, wherein R₄₀ is selected from the group consisting essentially of -CH₃, -CH₂CH₂-
20 Ph-O-CH₃, -Ph-Ph-CO₂H, -Ph-Ph-OCH₃, -Ph-Ph-C(CH₃)₃, -Ph-Ph-OCF₃, -Ph-Ph-F, -Ph-C(=O)-Ph, -Ph-Ph-CN, -Ph-Ph-NH₂, -Ph-C(CH₃)₃, -CH(CH₂CH₃)(CH₂CH₂CH₂CH₃), -CH₂CH₂Ph, -Ph-O-Ph, naphthalene, -Ph-Ph-Cl, -Ph-(OCH₃)₂, -CH₂-Ph-OCH₃, -CH₂-Ph, -Ph-Ph-S(=O)₂CH₃, -Ph-Ph, pyridyl, Ph, Ph-I, -Ph-Ph-S-CH₃, -Ph-pyridyl, -Ph-NH₂, -Ph-
25 NO₂, -Ph-CF₃, -Ph-CH₃, -Ph-Ph-CF₃, -Ph-Ph-(OCH₃)₂, -Ph-OCH₃, -Ph-CN, -CH₂-O-Ph, -Ph-OCF₃, -CH₂-PhF₂,



5

39. A compound according to claim 38, wherein Z is CH.

10 40. A compound according to claim 39, wherein a single substituent attached to a Ph-ring is in the ortho position.

41. A compound according to claim 39, wherein a single substituent attached to a Ph-ring is in the meta position.

15

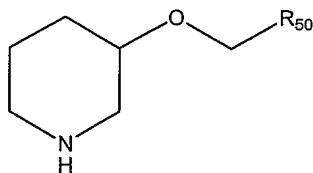
42. A compound according to claim 39, wherein a single substituent attached to a Ph-ring is in the para position.

20 43. A compound according to claim 39, wherein di-substituents attached to a Ph-ring are in di-meta positions.

44. A compound according to claim 39, wherein di-substituents attached to a Ph-ring are in a meta and para position.

25

45. A compound of the formula



5

wherein R₅₀ is aryl or substituted aryl.

46. A compound according to claim 45, wherein R₅₀ is selected from the group consisting of -Ph, -PhBr, -Ph-C(CH₃)₃, -
10 PhF, -PhCl, -PhCN, naphthyl, -Ph(CH₃)₂, -Ph-Ph, -PhI, -Ph-OCH₃, -PhCl₂, -Ph-PhCN, and -Ph-(OCH₃)₂.

47. A compound according to claim 46, wherein a single
15 substituent attached to a Ph-ring is in the ortho position.

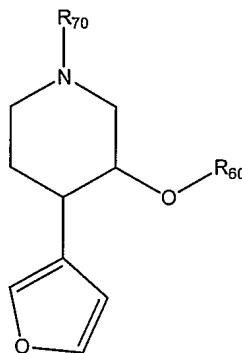
48. A compound according to claim 46, wherein a single
substituent attached to a Ph-ring is in the meta position.

49. A compound according to claim 46, wherein a single
20 substituent attached to a Ph-ring is in the para position.

50. A compound according to claim 46, wherein di-
substituents attached to a Ph-ring are in di-meta positions.

25 51. A compound according to claim 46, wherein di-
substituents attached to a Ph-ring are in a meta and para
position.

52. A compound of the formula
30



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wherein R_{60} is aryl, substituted aryl, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} cycloalkyl, C_{1-6} alkyl- C_{1-6} cycloalkyl; and
 wherein R_{70} is t-butoxycarbonyl or H.

10

53. A compound according to claim 52, wherein R_{60} is selected from the group consisting of -Ph, -Ph-Ph, naphthyl, -Ph-O-Ph, -PhC(CH₃)₃, anthracinyl, -PhCH₃, -Ph(OCH₃)₂, -PhBr, -PhS(=O)₂CH₃, C(=CH₂)CH₃, cyclohexyl, -CH₂-cyclohexyl, -CH(CH₃)₂,
 15 and -CH(CH₂CH₃)₂.

54. A compound according to claim 53, wherein a single substituent attached to a Ph-ring is in the ortho position.

20 55. A compound according to claim 53, wherein a single substituent attached to a Ph-ring is in the meta position.

56. A compound according to claim 53, wherein a single substituent attached to a Ph-ring is in the para position.

25

57. A compound according to claim 53, wherein di-substituents attached to a Ph-ring are in di-meta positions.

58. A compound according to claim 53, wherein di-substituents attached to a Ph-ring are in a meta and para position.

30