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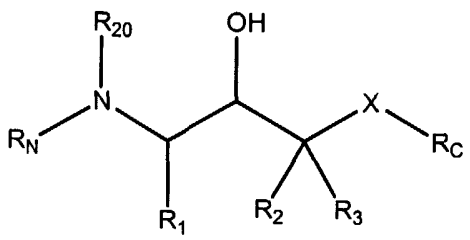
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(54) Title: BETA-HYDROXYAMINE DERIVATIVES USEFUL IN TREATMENT OF ALZHEIMER'S DISEASE



(I)

(57) Abstract: The invention relates to substituted alcohol compounds of the formula (I), wherein X, R_1, R_2, R_3, R_N, R_{20} et R_C are defined herein. The compounds are useful in the treatment or prevention 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 Alzhaimer's sufferers.

BETA-HYDROXYAMINE DERIVATIVES USEFUL IN THE TREATMENT OF ALZHEIMER'S DISEASE

(Case No. 01-1704-D)

This application claims priority to U.S. Provisional Application Ser. No. 60/301210, filed June 27, 2001; U.S. Provisional Application Ser. No. 60/323396, filed September 18, 2001 and U.S. Provisional Application Ser. No. 60/332736, filed November 19, 2001.

Background of the Invention

Field of the Invention

The invention relates to hydroxy alkylamine derivates and to such compounds that are useful in the treatment of Alzheimer's disease and similar diseases. More specifically the invention is directed to such 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.

Description of the Related Art

Alzheimer's disease (AD) is a progressive degenerative disease of the brain primarily associated with aging. Clinical 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 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 aggregate of a peptide fragment known 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 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 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 neurogenerative disorders. Beta-amyloid is a 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 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 beta-secretase and at the C-terminus by one or more gamma-secretases 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 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 responsible for processing of APP at the beta-secretase cleavage site. The beta-secretase enzyme has been disclosed using varied nomenclature, including BACE, Asp, am Mamepsin. See, for 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 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* 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 treatement of AD. *In vivo* processing of APP at the beta-secretase cleavage site is 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 overexpress 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 for the treatment of AD and other beta amyloid disorders.

Published PCT application WO00/47618 entitled "Beta-Secretase Enzyme Compositions and Methods" identifies the beta-secretase enzyme and methods of its use. This publication also discloses oligopeptide inhibitors that bind the enzyme's active site and are useful in affinity column purification of the enzyme. In addition, WO00/77030 discloses tetrapeptide inhibitors of beta-secretase activity that are based on a statine molecule.

Various pharmaceutical agents have been proposed for the treatment of Alzheimer's disease but without any real success. US Patent 5,175,281 discloses 21-aminosteroids as being useful for treating Alzheimer's disease. US Patent 5,502,187 discloses bicyclic heterocyclic amines as being useful for treating Alzheimer's disease.

The hydroxyethylene "nucleus" or isostere, of which the compounds of the invention are a modified analogs, has been used with success in the area of HIV protease inhibition. Many of these hydroxyethylene-based compounds are known as well as how to make them. See for example, *J. Med.Chem.*, 37, 3100-3107 (1994). European Patent 603309 by Dreyer, et al. are directed to similar isosteric strategies directed at HIV inhibition, although all contain an additional amino acid on the N-terminus that is lacking in the compounds of the invention.

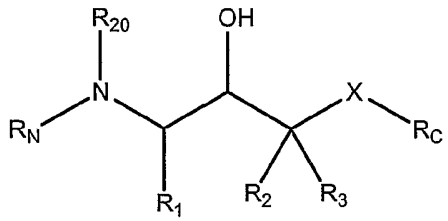
At present there are no effective treatments for halting, preventing, or reversing the progression of Alzheimer's disease. Therefore, there is an urgent need for pharmaceutical agents capable of slowing the progression of Alzheimer's disease and/or preventing it in the first place.

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

Summary of the Invention

The invention encompasses the substituted alcohol 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 pharmaceutically acceptable salts or esters thereof,

wherein X is C_{1-6} alkyl or alkenyl, O, S, SO, or SO_2;

wherein R_1 is

(I) C_1-C_6 alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, C_1-C_7 alkyl (optionally substituted with C_1-C_3 alkyl and C_1-C_3 alkoxy), –F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are independently -H or C_1-C_6 alkyl, and $-OC{=}O\ NR_{1-a}R_{1-b}$,

(II) $-CH_2$-$S(O)_{0-2}$-(C_1-C_6 alkyl),

(III) $-CH_2$-CH_2-$S(O)_{0-2}$-(C_1-C_6 alkyl),

(IV) 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, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1-a}R_{1-b}$,

(V) 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, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1-a}R_{1-b}$,

(VI) -$(CH_2)_{n1}$-($R_{1\text{-aryl}}$) where n_1 is zero or one and where $R_{1\text{-aryl}}$ is phenyl, 1-naphthyl, 2-naphthyl and indanyl, indenyl, 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 C_1-C_3 alkyl, –F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(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, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(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, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(D) -F, Cl, -Br or –I,

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

(G) –$NR_{N\text{-}2}R_{N\text{-}3}$ where $R_{N\text{-}2}$ and $R_{N\text{-}3}$ are as defined below,

(H) –OH,

(I) -C≡N,

(J) C_3-C_7 cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(K) –CO-(C_1-C_4 alkyl),

(L) –SO_2-$NR_{1\text{-}a}R_{1\text{-}b}$,

(M) –CO-$NR_{1\text{-}a}R_{1\text{-}b}$,

(N) –SO_2-(C_1-C_4 alkyl),

(VII) -$(CH_2)_{n1}$-($R_{1\text{-heteroaryl}}$) where n_1 is as defined above and where $R_{1\text{-heteroaryl}}$ is selected from the group consisting of:

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

isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, coumarinyl, isocoumarinyl, chromonyl, chromanonyl, pyridinyl-N-oxide, tetrahydroquinolinyl, dihydroquinolinyl, 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, quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-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,

where the $R_{1\text{-heteroaryl}}$ group is bonded to $-(CH_2)_{n1}-$ by any ring atom of the parent $R_{N\text{-heteroaryl}}$ 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:

(1) 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≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1\text{-}a}R_{1\text{-}b}$,

(2) 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, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1\text{-}a}R_{1\text{-}b}$,

(3) 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, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1\text{-}a}R_{1\text{-}b}$,

(4) -F, Cl, -Br or –I,

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

(7) $-NR_{N\text{-}2}R_{N\text{-}3}$ where $R_{N\text{-}2}$ and $R_{N\text{-}3}$ are as defined below,

(8) –OH,

(9) -C≡N,

(10) C_3-C_7 cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(11) –CO-(C_1-C_4 alkyl),

(12) –SO_2-$NR_{1\text{-}a}R_{1\text{-}b}$,

(13) –CO-$NR_{1\text{-}a}R_{1\text{-}b}$, or

(14) –SO_2-(C_1-C_4 alkyl), with the proviso that when n_1 is zero $R_{1\text{-heteroaryl}}$ is not bonded to the carbon chain by nitrogen, or

(VIII) -$(CH_2)_{n1}$-($R_{1\text{-heterocycle}}$) where n_1 is as defined above and $R_{1\text{-heterocycle}}$ 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, homomorpholinyl, homomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl dihydropyrazinyl dihydropyridinyl dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide, homothiomorpholinyl S-oxide,

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

(1) 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≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(2) 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, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(3) 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, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(4) -F, Cl, -Br, or –I,

(5) C_1-C_6 alkoxy,

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

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

(8) –OH,

(9) -C≡N,

(10) C_3-C_7 cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1-a}R_{1-b}$,

(11) –CO-(C_1-C_4 alkyl),

(12) $-SO_2-NR_{1-a}R_{1-b}$,

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

(14) $-SO_2-(C_1$-C_4 alkyl),

(15) =O, with the proviso that when n_1 is zero $R_{1\text{-heterocycle}}$ is not bonded to the carbon chain by nitrogen;

wherein R_2 is

(I)-H,

(II) 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≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1-a}R_{1-b}$,

(III) $-(CH_2)_{0-4}-R_{2-1}$ where R_{2-1} is $R_{1\text{-aryl}}$ or $R_{1\text{-heteroaryl}}$;

(IV) 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, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1-a}R_{1-b}$,

(V) 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, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1-a}R_{1-b}$,

(VI) $-(CH_2)_{0-4}$- C_3-C_7 cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1-a}R_{1-b}$;

wherein R_3 is

(I)-H,

(II) 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≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(III) -$(CH_2)_{0\text{-}4}$-$R_{2\text{-}1}$ where $R_{2\text{-}1}$ is $R_{1\text{-}aryl}$ or $R_{1\text{-}heteroaryl}$;

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

(V) C_2-C_6 alkynyl with one or two triple bonds, or

(VI) -$(CH_2)_{0\text{-}4}$- C_3-C_7 cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

and where R_2 and R_3 are taken together with the carbon to which they are attached to form a carbocycle of three, four, five, six, or seven carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of –O-, -S-, -SO_2-, and -$NR_{N\text{-}2}$-, where $R_{N\text{-}2}$ is as defined below;

wherein R_N is

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

(A) –CO-,

(B) –SO_2-,

(C) -$(CR'R'')_{1\text{-}6}$ where R' and R" are the same or different and are –H and C_1-C_4 alkyl,

(D) –CO-$(CR'R'')_{1\text{-}6}$-$X_{N\text{-}1}$ where $X_{N\text{-}1}$ is selected from the group consisting of –O-, -S- and –NR'- and where R' and R" are as defined above, or

(E) a single bond;

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

(A) $R_{N\text{-}aryl}$ where $R_{N\text{-}aryl}$ is phenyl, 1-naphthyl, 2-naphthyl, tetralinyl, indanyl, 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 same or different and are:

(1) 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≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(2) –OH,

(3) –NO_2,

(4) –F, -Cl, -Br, or -I,

(5) -CO-OH,

(6) -C≡N,

(7) $-(CH_2)_{0-4}$-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 consisting of:

(a) -H,

(b) -C_1-C_6 alkyl optionally substituted with one substitutent selected from the group consisting of:

(i) -OH, and

(ii) $-NH_2$,

(c) -C_1-C_6 alkyl optionally substituted with one, two, or three –F, -Cl, -Br, or -I,

(d) -C_3-C_7 cycloalkyl,

(e) -(C_1-C_2 alkyl)-(C_3-C_7 cycloalkyl),

(f) -(C_1-C_6 alkyl)-O-(C_1-C_3 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,

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

(j) $-R_{1\text{-aryl}}$, and

(k) $-R_{1\text{-heteroaryl}}$,

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

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

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

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

(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, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homomorpholinyl 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:

(a) C_1-C_6 alkyl,

(b) -$(CH_2)_{0-2}$-($R_{1\text{-aryl}}$),

(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

(f) -$(CH_2)_{0-2}$-($R_{1\text{-heteroaryl}}$),

(17) $-(CH_2)_{0-4}$-SO_2-$NR_{N-2}R_{N-3}$,

(18) $-(CH_2)_{0-4}$-SO-(C_1-C_8 alkyl),

(19) $-(CH_2)_{0-4}$-SO_2-(C_1-C_{12} alkyl),

(20) $-(CH_2)_{0-4}$-SO_2-(C_3-C_7 cycloalkyl),

(21) $-(CH_2)_{0-4}$-N(H or R_{N-5})-CO-O-R_{N-5} where R_{N-5} can be the same or different,

(22) $-(CH_2)_{0-4}$-N(H or R_{N-5})-CO-N(R_{N-5})$_2$, where R_{N-5} can be the same or different,

(23) $-(CH_2)_{0-4}$-N-CS-N(R_{N-5})$_2$, where R_{N-5} can be the same or different,

(24) $-(CH_2)_{0-4}$–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) $-(CH_2)_{0-4}$-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} can be the same or different,

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

(27) $-(CH_2)_{0-4}$–O-CO-(C_1-C_6 alkyl),

(28) $-(CH_2)_{0-4}$-O-P(O)-($OR_{N\text{-aryl-}1}$)$_2$ where $R_{N\text{-aryl-}1}$ 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})$_2$,

(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 alkyl optionally substituted with one, two, three, four, or five of –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, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, or -$NR_{1-a}R_{1-b}$,

(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≡N, -CF_3, C_1-C_3 alkoxy, or -$NR_{1-a}R_{1-b}$,

(38) -$(CH_2)_{0-4}$–N(-H or R_{N-5})-SO_2-R_{N-2} where R_{N-5} and R_{N-2} can be the same of different, or

(39) -$(CH_2)_{0-4}$- C_3-C_7 cycloalkyl,

(B) -$R_{N\text{-}heteroaryl}$ where $R_{N\text{-}heteroaryl}$ is selected from the group consisting of: pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pryidazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, coumarinyl, isocoumarinyl, chromonyl, chromanonyl, pyridinyl-N-oxide,

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

(1) 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≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1-a}R_{1-b}$,

(2) –OH,

(3) –NO_2,

(4) –F, -Cl, -Br, or -I,

(5) -CO-OH,

(6) -C≡N,

(7) $-(CH_2)_{0-4}$-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 consisting of:

(a) -H,

(b) -C_1-C_6 alkyl optionally substituted with one substitutent selected from the group consisting of:

(i) -OH, and

(ii) $-NH_2$,

(c) -C_1-C_6 alkyl optionally substituted with one, two, or three –F, -Cl, -Br, or -I,

(d) -C_3-C_7 cycloalkyl,

(e) -(C_1-C_2 alkyl)-(C_3-C_7 cycloalkyl),

(f) -(C_1-C_6 alkyl)-O-(C_1-C_3 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,

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

(j) $-R_{1\text{-aryl}}$, and

(k) $-R_{1\text{-heteroaryl}}$,

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

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

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

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

(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, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homomorpholinyl 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:

(a) C_1-C_6 alkyl,

(b) -$(CH_2)_{0-2}$-($R_{1\text{-aryl}}$),

(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

(f) -$(CH_2)_{0-2}$-($R_{1\text{-heteroaryl}}$),

(17) $-(CH_2)_{0-4}$-SO_2-$NR_{N-2}R_{N-3}$,

(18) $-(CH_2)_{0-4}$-SO-(C_1-C_8 alkyl),

(19) $-(CH_2)_{0-4}$-SO_2-(C_1-C_{12} alkyl),

(20) $-(CH_2)_{0-4}$-SO_2-(C_3-C_7 cycloalkyl),

(21) $-(CH_2)_{0-4}$-N(H or R_{N-5})-CO-O-R_{N-5} where R_{N-5} can be the same or different,

(22) $-(CH_2)_{0-4}$-N(H or R_{N-5})-CO-N(R_{N-5})$_2$, where R_{N-5} can be the same or different,

(23) $-(CH_2)_{0-4}$-N-CS-N(R_{N-5})$_2$, where R_{N-5} can be the same or different,

(24) $-(CH_2)_{0-4}$–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) $-(CH_2)_{0-4}$-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} can be the same or different,

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

(27) $-(CH_2)_{0-4}$–O-CO-(C_1-C_6 alkyl),

(28) $-(CH_2)_{0-4}$-O-P(O)-($OR_{N\text{-aryl-}1}$)$_2$ where $R_{N\text{-aryl-}1}$ 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})$_2$,

(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 alkyl optionally substituted with one, two, three, four, or five of –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, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, or -$NR_{1-a}R_{1-b}$,

(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≡N, -CF_3, C_1-C_3 alkoxy, or -$NR_{1-a}R_{1-b}$,

(38) -$(CH_2)_{0-4}$–N(-H or R_{N-5})-SO_2-R_{N-2} where R_{N-5} and R_{N-2} can be the same of different,,

(39) -$(CH_2)_{0-4}$- C_3-C_7 cycloalkyl,

(C) $R_{N\text{-}aryl}$-W-$R_{N\text{-}aryl}$,

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

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

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

(G) $R_{N\text{-}heteroaryl}$-W-$R_{N\text{-}heteroaryl}$,

(H) $R_{N\text{-}heteroaryl}$-W-$R_{N\text{-}1\text{-}heterocycle}$,

(I) $R_{N\text{-}heterocycle}$-W-$R_{N\text{-}aryl}$, where $R_{N\text{-}heterocycle}$ is the same as $R_{1\text{-}heterocycle}$,

(J) $R_{N\text{-}heterocycle}$-W-$R_{N\text{-}heteroaryl}$,

(K) $R_{N\text{-}heterocycle}$-W-$R_{N\text{-}1\text{-}heterocycle}$,

where W is

(1) –$(CH_2)_{0-4}$-,

(2) –O-,

(3) –$S(O)_{0-2}$-,

(4) –$N(R_{N-5})$- where R_{N-5} is as defined above, or

(5) –CO-;

(II) –CO-(C_1-C_{10} alkyl) where alkyl is optionally substituted with one three substitutents selected from the group consisting of:

(A) -OH,

(B)-C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or –phenyl,

(E) –CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(F) -CO-R_{N-4} where R_{N-4},

(G) -SO_2-(C_1-C_8 alkyl),

(H) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8},

(K) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(L) -R_{N-4},

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where the R_{N-8}s are the same or different,

(O) -O-(C_1-C_5 alkyl)-COOH,

(P) –O-(C_1-C_6 alkyl optionally substitued with one, two, or three of -F, -Cl, -Br, or -I),

(Q) -NH-SO_2-(C_1-C_6 alkyl), and

(R) -F, -Cl,

(III) –CO-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl) where alkyl is optionally substituted with one, two, or three substitutents selected from the group consisting of

(A) -OH,

(B)-C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -φ,

(E) –CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) -SO_2-(C_1-C_8 alkyl),

(H) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8},

(K) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(L) -R_{N-4},

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where R_{N-8} are the same or different,

(O) -O-(C_1-C_5 alkyl)-COOH,

(P) –O-(C_1-C_6 alkyl optionally substitued with one, two, or three of -F, -Cl, -Br, or -I),

(Q) -NH-SO_2-(C_1-C_6 alkyl), and

(R) -F, or -Cl,

(IV) –CO-(C_1-C_6 alkyl)-S-(C_1-C_6 alkyl) where alkyl is optionally substituted with one, two, or three of substitutents selected from the group consisting of

(A) -OH,

(B) -C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8},

(E) –CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) -SO_2-(C_1-C_8 alkyl),

(H) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,

(K) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(L) -R_{N-4} where R_{N-4} is as defined above,

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where the R_{N-8}s are the same or different,

(O) -O-(C_1-C_5 alkyl)-COOH,

(P) –O-(C_1-C_6 alkyl optionally substitued with one, two, or three of –F, -Cl, -Br, or -I),

(Q) -NH-SO_2-(C_1-C_6 alkyl), and

(R) -F, or -Cl,

(V) –CO-CH(-$(CH_2)_{0-2}$-O-R_{N-10})-$(CH_2)_{0-2}$-$R_{N\text{-}aryl}$/$R_{N\text{-}heteroaryl}$), where R_{N-10} is selected from the group consisting of:

(A) –H,

(B) C_1-C_6 alkyl,

(C) C_3-C_7 cycloalkyl,

(D) C_2-C_6 alkenyl with one double bond,

(E) C_2-C_6 alkynyl with one triple bond,

(F) $R_{1\text{-}aryl}$, and

(G) $R_{N\text{-}heteroaryl}$, or

(VI) –CO-(C_3-C_8 cycloalkyl) where alkyl is optionally substituted with one or two substitutents selected from the group consisting of:

(A) -$(CH_2)_{0-4}$-OH,

(B) -$(CH_2)_{0-4}$-C_1-C_6 alkoxy,

(C) -$(CH_2)_{0-4}$-C_1-C_6 thioalkoxy,

(D) -$(CH_2)_{0-4}$-CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -phenyl,

(E) -$(CH_2)_{0-4}$-CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

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

(G) -$(CH_2)_{0-4}$-SO_2-(C_1-C_8 alkyl),

(H) -$(CH_2)_{0-4}$-SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(I) -$(CH_2)_{0-4}$-NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8},

(K) -$(CH_2)_{0-4}$-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

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

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where R_{N-8} are the same or different,

(O) -O-(C_1-C_5 alkyl)-COOH,

(P) –O-(C_1-C_6 alkyl optionally substitued with one, two, or three of –F, -Cl, -Br, or -I),

(Q) -NH-SO_2-(C_1-C_6 alkyl), and

(R) -F, or -Cl,

wherein R_C is:

(I)-C_1-C_{10} 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≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, -$NR_{1-a}R_{1-b}$, -OC=O $NR_{1-a}R_{1-b}$, -$S(=O)_{0-2}$, - NR_{1-a}C=O $NR_{1-a}R_{1-b}$, -C=O $NR_{1-a}R_{1-b}$, and -$S(=O)_2$ $NR_{1-a}R_{1-b}$,

(II) -$(CH_2)_{0-3}$-(C_3-C_8) cycloalkyl where cycloalkyl can be 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≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, -CO-OH, -CO-O-(C_1-C_4 alkyl), and -$NR_{1-a}R_{1-b}$,

(III) -$(CR_{C-x}R_{C-y})_{0-4}$-R_{C-aryl} where R_{C-x} and R_{C-y} are

(A) –H,

(B) C_1-C_4 alkyl optionally substituted with one or two –OH,

(C) C_1-C_4 alkoxy optionally substituted with one, two, or three -F,

(D) -$(CH_2)_{0-4}$-C_3-C_7 cycloalkyl,

(E) C_2-C_6 alkenyl containing one or two double bonds,

(F) C_2-C_6 alkynyl contianing one or two triple bonds,

(G) phenyl,

and where R_{C-x} and R_{C-y} are taken together with the carbon to which they are attached to form a carbocycle of three, four, five, six or seven carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of –O-, -S-, -SO_2-, and -NR_{N-2}- and R_{C-aryl} is the same as R_{N-aryl};

(IV) -$(CR_{C-x}R_{C-y})_{0-4}$-$R_{C-heteroaryl}$ where $R_{C-heteroaryl}$ is the same as $R_{N-heteroaryl}$,

(V) -$(CR_{C-x}R_{C-y})_{0-4}$-R_{C-aryl}-R_{C-aryl} ,

(VI) -$(CR_{C-x}R_{C-y})_{0-4}$-R_{C-aryl}-$R_{C-heteroaryl}$,

(VII) -$(CR_{C-x}R_{C-y})_{0-4}$-$R_{C-heteroaryl}$-R_{C-aryl},

(VIII) -$(CR_{C-x}R_{C-y})_{0-4}$-$R_{C-heteroaryl}$-$R_{C-heteroaryl}$,

(IX) -$(CR_{C-x}R_{C-y})_{0-4}$-R_{C-aryl}-$R_{C-heterocycle}$ and where $R_{C-heterocycle}$ is the same as $R_{1-heterocycle}$,

(X) -$(CR_{C-x}R_{C-y})_{0-4}$-$R_{C-heteroaryl}$-$R_{C-heterocycle}$,

(XI) -$(CR_{C-x}R_{C-y})_{0-4}$-$R_{C-heterocycle}$-R_{C-aryl},

(XII) -$(CR_{C-x}R_{C-y})_{0-4}$-$R_{C-heterocycle}$-$R_{C-heteroaryl}$,

(XIII) -$(CR_{C-x}R_{C-y})_{0-4}$-$R_{C-heterocycle}$-$R_{C-heterocycle}$,

(XIV) -$(CR_{C-x}R_{C-y})_{0-4}$-$R_{C-heterocycle}$,

(XV) -$[C(R_{C-1})(R_{C-2})]_{1-3}$-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:

(A) -H,

(B) -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≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, and -$NR_{1-a}R_{1-b}$,

(C) 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 C_1-C_3 alkyl, –F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, and -$NR_{1-a}R_{1-b}$,

(D) 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 C_1-C_3 alkyl, –F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, and -$NR_{1-a}R_{1-b}$,

(E) $-(CH_2)_{1-2}-S(O)_{0-2}-(C_1-C_6$ alkyl),

(F) $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl, 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≡N, $-CF_3$, C_1-C_6 alkoxy, -O-phenyl, and $-NR_{1-a}R_{1-b}$,

(G) $-(C_1-C_4$ alkyl)$-R_{C'-aryl}$ where $R_{C'-aryl}$ is as defined for R_{1-aryl},

(H) $-(C_1-C_4$ alkyl)$-R_{C-heteroaryl}$,

(I) $-(C_1-C_4$ alkyl)$-R_{C-heterocycle}$,

(J) $-R_{C-heteroaryl}$,

(K) $-R_{C-heterocycle}$,

(M) $-(CH_2)_{1-4}-R_{C-4}-(CH_2)_{0-4}-R_{C'-aryl}$ where R_{C-4} is –O-, -S- or $-NR_{C-5}-$ where R_{C-5} is C_1-C_6 alkyl,

(N) $-(CH_2)_{1-4}-R_{C-4}-(CH_2)_{0-4}-R_{C-heteroaryl}$, and

(O) $-R_{C'-aryl}$,

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

(A) -H,

(B) $-C_1-C_6$ 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≡N, $-CF_3$, C_1-C_6 alkoxy, -O-phenyl, and $-NR_{1-a}R_{1-b}$,

(C) 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 C_1-C_3 alkyl, –F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_6 alkoxy, -O-phenyl, and $-NR_{1-a}R_{1-b}$,

(D) 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 C_1-C_3 alkyl, –F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_6 alkoxy, -O-phenyl, and $-NR_{1-a}R_{1-b}$,

(E) $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl, 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≡N, $-CF_3$, C_1-C_6 alkoxy, -O-phenyl, and $-NR_{1-a}R_{1-b}$,

(F) $-R_{C'-aryl}$,

(G) $-R_{C-heteroaryl}$,

(H) $-R_{C-heterocycle}$,

(I) $-(C_1-C_4$ alkyl)$-R_{C'-aryl}$,

(J) $-(C_1-C_4$ alkyl)$-R_{C-heteroaryl}$, or

(K) $-(C_1-C_4$ alkyl)$-R_{C-heterocycle}$,

(XVI) $-CH(R_{C\text{-}aryl})_2$ where $R_{C\text{-}aryl}$ are the same or different and are as defined above,

(XVII) $-CH(R_{C\text{-}heteroaryl})_2$ where $R_{C\text{-}heteroaryl}$ are the same or different and are as defined above,

(XVIII) $-CH(R_{C\text{-}aryl})(R_{C\text{-}heteroaryl})$,

(XIX) -cyclopentyl, -cyclohexyl, or -cycloheptyl ring fused to $R_{C\text{-}aryl}$ or $R_{C\text{-}heteroaryl}$ or $R_{C\text{-}heterocycle}$ where one carbon of cyclopentyl, cyclohexyl, or -cycloheptyl is optionally replaced with NH, $NR_{N\text{-}5}$, O, or $S(=O)_{0\text{-}2}$, and where cyclopentyl, cyclohexyl, or -cycloheptyl can be optionally substituted with one or two -C_1-C_3 alkyl, –F, -OH, -SH, -C≡N, -CF_3, C_1-C_6 alkoxy, =O, or -$NR_{1\text{-}a}R_{1\text{-}b}$,

(XX) C_2-C_{10} alkenyl containing one or two double bonds 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≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(XXI) C_2-C_{10} alkynyl containing one or two triple bonds 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≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(XXI) $-(CH_2)_{0\text{-}1}$-$CHR_{C\text{-}6}$-$(CH_2)_{0\text{-}1}$-$R_{C\text{-}aryl}$ and $R_{C\text{-}6}$ is -$(CH_2)_{0\text{-}6}$-OH,

(XXII) $-(CH_2)_{0\text{-}1}$-$CHR_{C\text{-}6}$-$(CH_2)_{0\text{-}1}$-$R_{C\text{-}heteroaryl}$,

(XXIII) –CH(-$R_{C\text{-}aryl}$ or $R_{C\text{-}heteroaryl}$)-CO-O(C_1-C_4 alkyl),

(XXIV) $-CH(-CH_2\text{-}OH)\text{-}CH(-OH)\text{-}NO_2$,

(XXV) (C_1-C_6 alkyl)-O-(C_1-C_6 alkyl)-OH,

(XXVII) $-CH_2\text{-}NH\text{-}CH_2\text{-}CH(-O\text{-}CH_2\text{-}CH_3)_2$,

(XXVIII) –H,

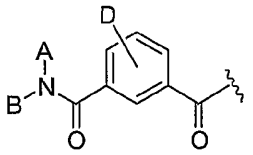
(XXIX) -$(CH_2)_{0\text{-}6}$-$C(=NR_{1\text{-}a})(NR_{1\text{-}a}R_{1\text{-}b})$; and

wherein R_{20} is H or $C_{1\text{-}6}$ alkyl or alkenyl.

In a preferred aspect of the invention, X is -CH_2-, -S- or -SO_2-. In a more preferred aspect of the invention, X is S or -SO_2-. Still more preferably, X is SO_2.

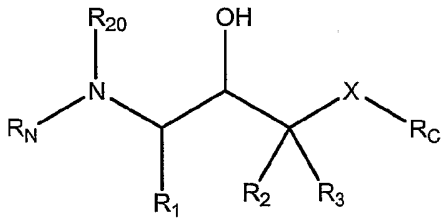
In a preferred aspect of the invention, R_{20} is H or C_1-C_4 alkyl or C_2-C_4 alkenyl. More preferably, R_{20} is H or methyl. Still more preferably, R_{20} is H. In particularly preferred compounds of Formula I, R_{20} is hydrogen and the remaining groups are as defined for formula I.

In a preferred aspect, R_N is $R_{N\text{-}1}$-X_N-. More preferably R_N is



wherein A and B are independently H or C_1-C_6 alkyl and D is H, C_1-C_4 alkoxy, or C_1-C_4 alkyl and the remaining groups are as defined for formula I. Still more preferably, D is H, methyl, or ethyl. Still more preferably, A and B are C_1-C_4 alkyl and D is H or methyl

Disclosed is 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 (MCI) and/or 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 angiopathy and/or 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 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 comprises administration of a therapeutically effective amount of a compound selected from the group consisting of a substituted alcohol of formula (I)

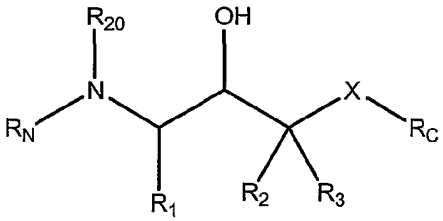


(I)

where R_1, R_2, R_3, X, R_N, R_{20} and R_C are as defined above, and pharmaceutically acceptable salts or esters thereof.

Also disclosed are 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 inhibiting production of amyloid beta peptide (A beta) in a cell, for

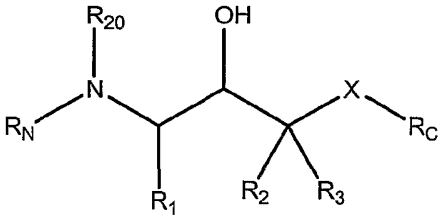
inhibiting the production of beta-amyloid plaque in an animal, and for treating or preventing a disease characterized by beta-amyloid deposits in the brain which comprise administration of a therapeutically effective amount of a substituted alcohol of formula (I)



(I)

where R_1, R_2, R_3, X, R_N, R_{20} and R_C are as defined above, and pharmaceutically acceptable salts thereof.

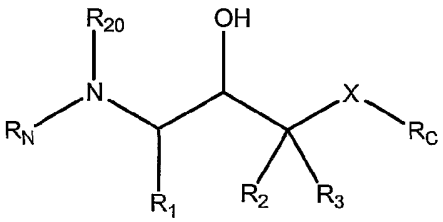
Disclosed is a pharmaceutical composition that comprises a substituted alcohol of formula (I)



(I)

where R_1, R_2, R_3, X, R_N, R_{20} and R_C are as defined above, and pharmaceutically acceptable salts or esters thereof, and one or more pharmaceutically acceptable inert carriers.

Disclosed is the use of a substituted alcohol of formula (I),



(I)

where R_1, R_2, R_3, X, R_N, R_{20} and R_C are as defined above, and pharmaceutically acceptable salts or esters 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 Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI) and/or 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 angiopathy and/ot 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 palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease and who is in need of such treatment.

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 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 patients with mild cognitive impairment (MCI), and/or 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-amyloid angiopathy and/or 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 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 one or more of the assays described herein or known in the art.

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 (MCI) and/or 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 angiopathy and/or 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 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 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.

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 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.

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.

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.

In an embodiment, this method of treatment can employ therapeutically effective amounts: for oral administration from about 0.1 mg/day to about 1,000 mg/day; for parenteral, sublingual, intranasal, intrathecal administration from about 0.5 to 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 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 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.

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 Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI) an/or 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 angiopathy and/or 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 palsy, dementia associated with cortical basal degeneration, diffuse Lewy body 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.

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.

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.

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.

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, CH_3-$(CH_2)_n$-COOH where n is 0 thru 4, HOOC-(CH_2)n-COOH where n is as defined above, HOOC-CH=CH-COOH, and phenyl-COOH.

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 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 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 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.

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 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 formula I or a pharmaceutically acceptable salt or ester thereof.

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 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.

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 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 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 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.

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 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.

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 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 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.

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 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 that is a cell.

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

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 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.

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 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.

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.

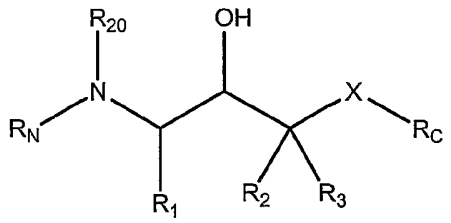
In an embodiment, this composition includes a carrier that is an oil.

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

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 treat or prevent any human or veterinary disease or condition associated with a pathological form of A beta peptide.

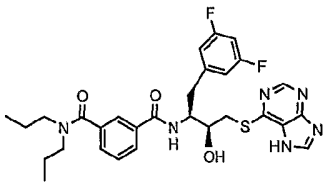
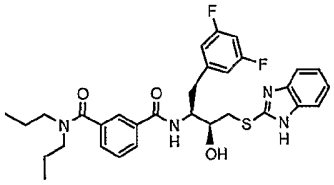
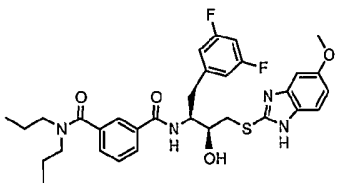
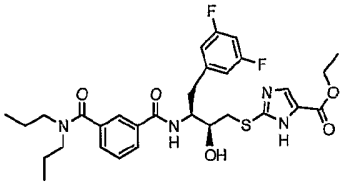
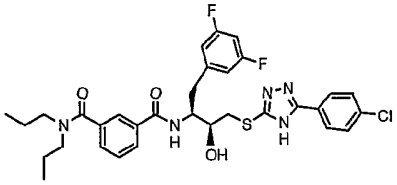
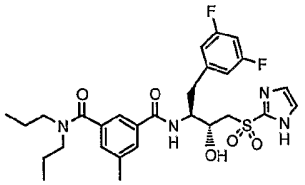
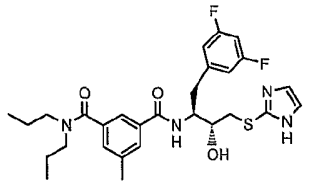
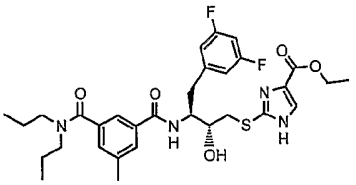
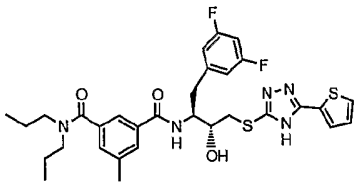
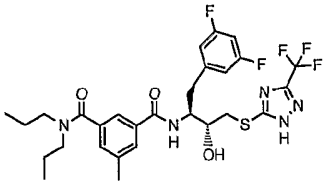
The invention also provides intermediates and methods useful for preparing the compounds of Formula I. The invention also provides a method for making a compound of formula (I)



or a pharmaceutically acceptable salt or ester thereof, wherein R_1, R_2, R_3, X, R_N, R_{20} and R_C are as defined above.

Detailed Description Of The Invention

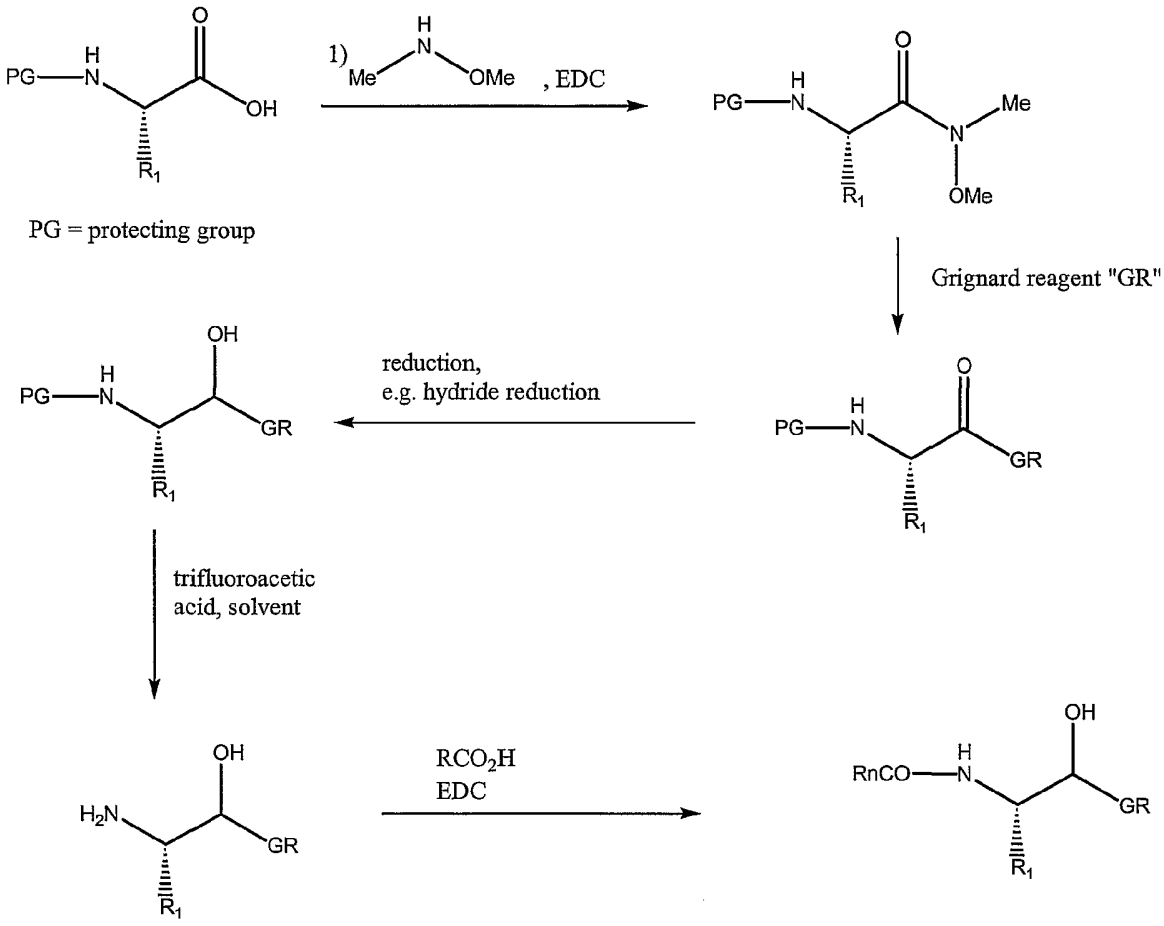
As noted above, a broad aspect of the invention is directed to compounds of (I), or pharmaceutically acceptable salts or esters thereof. In a preferred aspect, the invention provides compounds of the formula:

The invention is directed to the substituted alcohols (I) that are useful in treating or preventing Alzheimer's disease. The anti-Alzheimer's substituted alcohols (I) are made by methods well known to those skilled in the art from starting compounds that are also known to those skilled in the art. The process chemistry is well known to those skilled in the art. An example of a general process to prepare the substituted alcohols (I) of the invention is set forth in Scheme I.

Scheme I

Preparation of substituted alcohols of the invention



The chemistry is straight forward and in summary involves the steps of N-protecting an amino acid starting material to produce the corresponding protected amino acid, coupling of the protected amino acid with methoxymethylamine using an amide-bond-forming coupling agent such as EDC, followed by reaction of the resulting activated amide, known as a Weinreb amide, with a Grignard reagent to form the protected amino ketone. Reduction of the protected aminoketone to the corresponding alcohol via a hydride reduction, using a mild reducing agent such as $NaBH_4$ (sodium borohydride), followed by coupling of the amine released from deprotection of the N-terminus with isopthalic amides and other acylating groups to yield the substitued alcohols (I) of the invention. One skilled in the art will appreciate that these are all well known reactions in organic chemistry. A chemist skilled in the art, knowing the chemical

structure of the biologically active substituted alcohol end product (I) of the invention would be able to prepare them by known methods from known starting materials without any additional information.

Scheme I sets forth a general method used in the invention to prepare the appropriately substituted alcohols (I). The anti-Alzheimer substituted alcohols (I) of the invention are prepared by starting with the appropriately selected amino acid having the desired alpha substituent. The amino acids are well known to those skilled in the art and/or can be readily prepared from known compounds by methods well known to those skilled in the art. Natural amino acids (and having the L configuration) are available in abundance, and a great array of non-naturally occurring amino acids have been prepared by techniques well known to those skilled in the art of organic synthesis or are available commercially. Roberts and Vellaccio provide a comprehensive listing of non-natural amino acids, and techniques for the synthesis of many variations thereof in *The Peptides*, Vol. 5: Analysis, Synthesis, Biology; Academic Press, NY 1983. A more recent description of additional routes to chirally pure non-natural amino acids is in: *Asymmetric synthesis of α-amino acids from carbohydrates as chiral templates*; Cintas, P., *Tetrahedron*, **47** (32), 6079-111 (1991). Thus one skilled in the art can synthesize the amino acid precursors used in the preparation of the compounds of the invention by a judicious selection of one or more of the methods outlined above, which articles are hereby incorporated by reference. Alternatively, many amino acid derived compounds may advantageously be purchased commercially. Such amino acid derivatives are available having a wide variety of alpha substituents. Such derivatives are available, by way of example from Synthetech, Inc. (1290 Industrial Way, P. O. Box 646, Albany, OR 97321 USA) which publishes catalogs of available compounds.

The substituted alcohols (I) of the invention have at least two enantiomeric centers which give four enantiomers. There could be additional enantiomeric centers depending on nature of R2 and R3. The first of these enantiomeric centers derives from the amino acid starting material. It is preferred to commercially obtain or produce the desired enantiomer (S) rather than produce an enantiomerically impure mixture and then have to separate out the desired enantiomer (S). It is preferred to start the process with enantiomerically pure (S)-amino acid of the same configuration as that of the substituted alcohol (I) product.

The first step of the process is to protect the free amino group of the (S)-amino acid with an amino protecting group to produce the (S)-protected amino acid by methods well known to those skilled in the art. Amino protecting groups are well known to those skilled in the art. See

for example, "Protecting Groups in Organic Synthesis", John Wiley and sons, New York, N.Y., 1981, Chapter 7; "Protecting Groups in Organic Chemistry", Plenum Press, New York, N.Y., 1973, Chapter 2. The function of the amino protecting group is to protect the free amino functionality ($-NH_2$) during subsequent reactions on the (S)-amino acid which would not proceed well either because the amino group would react and be functionalized in a way that is inconsistent with its need to be free for subsequent reactions or the free amino group would interfere in the reaction. When the amino protecting group is no longer needed, it is removed by methods well known to those skilled in the art. By definition the amino protecting group must be readily removable as is known to those skilled in the art by methods well known to those skilled in the art. Suitable amino protecting group is selected from the group consisting of *t*-butoxycarbonyl, benzyloxycarbonyl, formyl, trityl, acetyl, trichloroacetyl, dichloroacetyl, chloroacetyl, trifluoroacetyl, difluoroacetyl, fluoroacetyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-ethoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-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-(*p*-toluyl)prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycabonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)ethoxycarbonyl, fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxyl)benzyloxycarbonyl, isobornyloxycarbonyl and 1-piperidyloxycarbonyl, 9-fluorenylmethyl carbonate, $-CH-CH=CH_2$ and phenyl-C(=N-)-H. It is preferred that the protecting group be *t*-butoxycarbonyl (BOC) and benzyloxycarbony (CBZ), it is more preferred that the protecting group be *t*-butoxycarbonyl. One skilled in the art will understand the preferred methods of introducing a *t*-butoxycarbonyl or benzyloxycarbonyl protecting group and may additionally consult T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry," John Wiley and Sons, 1991 for guidance.

Suitable means for removal of the amine protecting group depends on the nature of the protecting group. Those skilled in the art, knowing the nature of a specific protecting group, know which reagent is preferable for its removal. For example, it is preferred to remove the

preferred protecting group, BOC, by dissolving the (S,R)-protected alcohol in a trifluoroacetic acid/dichloromethane mixture. When complete, the solvents are removed under reduced pressure to give the corresponding (S,R)-amine (as the corresponding salt, i.e. trifluoroacetic acid salt) which is used without further purification. However, if desired, the (S,R)-amine can be purified further by means well known to those skilled in the art, such as for example, recrystallization, or by HPLC purification optionally using chiral-selective solid supports. Further, if the non-salt form is desired that also can be obtained by means known to those skilled in the art, such as for example, preparing the free base amine via treatment of the salt with mild basic conditions. Additional BOC deprotection conditions and deprotection conditions for other protecting groups can be found in T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry," John Wiley and Sons, 1991, p. 309. Typical chemically suitable salts include trifluoroacetate, and the anion of mineral acids such as chloride, sulfate, phosphate; preferred is trifluoroacetate and chloride.

Many Grignard reagents are available for purchase; others are prepared by methods known to those skilled in the art. The Grignard reagents are then applied in the method for preparing the amino ketone intermediates by preparation of the Weinreb amide, either from the acid directly as depicted in Scheme I or by way of acid halide followed by treatment with N,O-dimethylhydroxylamine to give Weinreb amide and then treating the Weinreb amide with the Grignard reagent, by methods known to those skilled in the art.

The compounds of the invention may contain geometric or optical isomers as well as tautomers. Thus, the invention includes all tautomers and pure geometric isomers, such as the *E* and *Z* geometric isomers, as well as mixtures thereof. Futhermore, the invention includes pure enantiomers and diastereoisomers as well as mixtures thereof, including racemic mixtures. The individual geometric isomers, enantiomers, or diastereoisomers may be prepared or isolated by methods known in the art.

The (R,S)-substituted alcohol (I) may have basic functions and as such form salts when reacted with acids. Pharmaceutically acceptable salts are preferred over the free base substituted alcohol (I) since they produce compounds which are more water soluble, stable and/or more crystalline. Pharmaceutically acceptable salts are any salt which retains the activity of the parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Pharmaceutically acceptable salts include salts of both inorganic and organic acids. The preferred pharmaceutically acceptable salts include salts of the following acids acetic, aspartic, benzenesulfonic, benzoic, bicarbonic, bisulfuric, bitartaric, butyric, calcium edetate, camsylic, carbonic,

chlorobenzoic, citric, edetic, edisylic, estolic, esyl, esylic, formic, fumaric, gluceptic, gluconic, glutamic, glycollylarsanilic, hexamic, hexylresorcinoic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxynaphthoic, isethionic, lactic, lactobionic, maleic, malic, malonic, mandelic, methanesulfonic, methylnitric, methylsulfuric, mucic, muconic, napsylic, nitric, oxalic, p-nitromethanesulfonic, pamoic, pantothenic, phosphoric, monohydrogen phosphoric, dihydrogen phosphoric, phthalic, polygalactouronic, propionic, salicylic, stearic, succinic, succinic, sulfamic, sulfanilic, sulfonic, sulfuric, tannic, tartaric, teoclic and toluenesulfonic. For other acceptable salts, see *Int. J. Pharm.*, 33, 201-217 (1986) and *J.Pharm.Sci.*, 66(1), 1, (1977).

The invention provides compounds, compositions, kits, and methods for inhibiting beta-secretase enzyme activity and A beta peptide production. Inhibition of beta-secretase enzyme activity halts or reduces the production of A beta from APP and reduces or eliminates the formation of beta-amyloid deposits in the brain.

Methods of the Invention

The compounds of the invention, and pharmaceutically acceptable salts or esters thereof, are useful for treating humans or animals suffering from a condition characterized by a pathological form of beta-amyloid peptide, such as beta-amyloid plaques, and for helping to prevent or delay the onset of such a condition. For example, the compounds are useful for treating Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with MCI (mild cognitive impairment) and/or 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 angiopathy and/or preventing its potential consequences, i.e. single and recurrent lobal 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, and diffuse Lewy body type Alzheimer's disease. The compounds and compositions of the invention are particularly useful for treating or preventing Alzheimer's disease. When treating or preventing these diseases, the compounds of the invention can either be used individually or in combination, as is best for the patient.

As used herein, the term "treating" means that the compounds of the invention can be used in humans with at least a tentative diagnosis of disease. The compounds of the invention will delay or slow the progression of the disease thereby giving the individual a more useful life span.

The term "preventing" means that the compounds of the invention are useful when administered to a patient who has not been diagnosed as possibly having the disease at the time of administration, but who would normally be expected to develop the disease or be at increased risk for the disease. The compounds of the invention will slow the development of disease symptoms, delay the onset of the disease, or prevent the individual from developing the disease at all. Preventing also includes administration of the compounds of the invention to those individuals thought to be predisposed to the disease due to age, familial history, genetic or chromosomal abnormalities, and/or due to the presence of one or more biological markers for the disease, such as a known genetic mutation of APP or APP cleavage products in brain tissues or fluids.

In treating or preventing the above diseases, the compounds of the invention are administered in a therapeutically 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 displaying any of the diagnosed above conditions a physician may administer a compound of the invention immediately and continue administration indefinitely, as needed. In treating patients who are not diagnosed as having Alzheimer's disease, but who are believed to be at substantial risk for Alzheimer's disease, the physician should preferably 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 may be determined to be at risk for developing Alzheimer's through the detection of a genetic marker such as APOE4 or other biological indicators that are predictive for Alzheimer's disease. In these situations, even though the patient does not have symptoms of the disease, administration of the compounds of the invention may be started before symptoms appear, and treatment may be continued indefinitely to prevent or delay the outset of the disease.

Dosage forms and amounts

The compounds of the invention can be administered orally, parenternally, (IV, IM, depo-IM, SQ, and depo SQ), sublingually, intranasally (inhalation), intrathecally, topically, or rectally. Dosage forms known to those of skill in the art are suitable for delivery of the compounds of the invention.

Compositions are provided that contain therapeutically effective amounts of the compounds of the invention. The compounds are preferably formulated into suitable pharmaceutical preparations such as tablets, capsules, or elixirs for oral administration or in sterile solutions or suspensions for parenternal administration. Typically the compounds

described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art.

About 1 to 500 mg of a compound or mixture of compounds of the invention or a physiologically acceptable salt or ester is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in those compositions or preparations is such that a suitable dosage in the range indicated is obtained. The compositions are preferably formulated in a unit dosage form, each dosage containing from about 2 to about 100 mg, more preferably about 10 to about 30 mg of the active ingredient. The term "unit dosage from" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

To prepare compositions, one or more compounds of the invention are mixed with a suitable pharmaceutically acceptable carrier. Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion, or the like. Liposomal suspensions may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for lessening or ameliorating at least one symptom of the disease, disorder, or condition treated and may be empirically determined.

Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration. In addition, the active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, or have another action. The compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients.

Where the compounds exhibit insufficient solubility, methods for solubilizing may be used. Such methods are known and include, but are not limited to, using cosolvents such as dimethylsulfoxide (DMSO), using surfactants such as Tween®, and dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as salts or esters or prodrugs may also be used in formulating effective pharmaceutical compositions.

The concentration of the compound is effective for delivery of an amount upon administration that lessens or ameliorates at least one symptom of the disorder for which the compound is administered. Typically, the compositions are formulated for single dosage administration.

The compounds of the invention may be prepared with carriers that protect them against rapid elimination from the body, such as time-release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, microencapsulated delivery systems. The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in known *in vitro* and *in vivo* model systems for the treated disorder.

The compounds and compositions of the invention can be enclosed in multiple or single dose containers. The enclosed compounds and compositions can be provided in kits, for example, including component parts that can be assembled for use. For example, a compound inhibitor in lyophilized form and a suitable diluent may be provided as separated components for combination prior to use. A kit may include a compound inhibitor and a second therapeutic agent for co-administration. The inhibitor and second therapeutic agent may be provided as separate component parts. A kit may include a plurality of containers, each container holding one or more unit dose of the compound of the invention. The containers are preferably adapted for the desired mode of administration, including, but not limited to tablets, gel capsules, sustained-release capsules, and the like for oral administration; depot products, pre-filled syringes, ampules, vials, and the like for parenternal administration; and patches, medipads, creams, and the like for topical administration.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the active compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art.

The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the

professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

If oral administration is desired, the compound should be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

Oral compositions will generally include an inert diluent or an edible carrier and may be compressed into tablets or enclosed in gelatin capsules. For the purpose of oral therapeutic administration, the active compound or compounds can be incorporated with excipients and used in the form of tablets, capsules, or troches. Pharmaceutically compatible binding agents and adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches, and the like can contain any of the following ingredients or compounds of a similar nature: a binder such as, but not limited to, gum tragacanth, acacia, corn starch, or gelatin; an excipient such as microcrystalline cellulose, starch, or lactose; a disintegrating agent such as, but not limited to, alginic acid and corn starch; a lubricant such as, but not limited to, magnesium stearate; a gildant, such as, but not limited to, colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; and a flavoring agent such as peppermint, methyl salicylate, or fruit flavoring.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials, which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings, and flavors.

The active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action.

Solutions or suspensions used for parenternal, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent such as water for injection, saline solution, fixed oil, a naturally occurring vegetable oil such as sesame oil, coconut oil, peanut oil, cottonseed oil, and the like, or a synthetic fatty vehicle such as ethyl oleate, and the like, polyethylene glycol, glycerine, propylene glycol, or other synthetic solvent;

antimicrobial agents such as benzyl alcohol and methyl parabens; antioxidants such as ascorbic acid and sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates, and phosphates; and agents for the adjustment of tonicity such as sodium chloride and dextrose. Parenternal preparations can be enclosed in ampoules, disposable syringes, or multiple dose vials made of glass, plastic, or other suitable material. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Where administered intravenously, suitable carriers include physiological saline, phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents such as glucose, polyethylene glycol, polypropyleneglycol, and mixtures thereof. Liposomal suspensions including tissue-targeted liposomes may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known for example, as described in U.S. Patent No. 4,522,811.

The active compounds may be prepared with carriers that protect the compound against rapid elimination from the body, such as time-release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid, and the like. Methods for preparation of such formulations are known to those skilled in the art.

The compounds of the invention can be administered orally, parenternally (IV, IM, depo-IM, SQ, and depo-SQ), sublingually, intranasally (inhalation), intrathecally, topically, or rectally. Dosage forms known to those skilled in the art are suitable for delivery of the compounds of the invention.

Compounds of the invention may be administered enterally or parenterally. When administered orally, compounds of the 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 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 invention need to be administered only once or twice daily.

The oral dosage forms are administered to the patient 1, 2, 3, or 4 times daily. It is preferred that the compounds of the invention be administered either three or fewer times, more preferably once or twice daily. Hence, it is preferred that the compounds of the invention be administered in oral dosage form. It is preferred that whatever oral dosage form is used, that it

be designed so as to protect the compounds of the invention from the acidic environment of the 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.

When administered orally, an administered amount therapeutically effective to inhibit beta-secretase activity, to inhibit A beta production, to inhibit A beta deposition, or to treat or prevent AD is from about 0.1 mg/day to about 1,000 mg/day. It is preferred that the 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 started at one dose, that dose may be varied over time as the patient's condition changes.

Compounds of the invention may also be advantageously delivered in a nano crystal dispersion formulation. Preparation of such formulations is described, for example, in U.S. Patent 5,145,684. Nano crystalline dispersions of HIV protease inhibitors and their method of use are described in US 6,045,829. The nano crystalline formulations typically afford greater bioavailability of drug compounds.

The compounds of the invention can be administered parenterally, for example, by IV, IM, depo-IM, SC, or depo-SC. When administered parenterally, a therapeutically effective amount of about 0.5 to about 100 mg/day, preferably from about 5 to about 50 mg daily should be delivered. When a depot formulation is used for injection once a month or once every two weeks, the dose should be about 0.5 mg/day to about 50 mg/day, or a monthly dose of from about 15 mg to about 1,500 mg. In part because of the forgetfulness of the patients with Alzheimer's disease, it is preferred that the parenteral dosage form be a depo formulation.

The compounds of the invention can be administered sublingually. When given sublingually, the compounds of the invention should be given one to four times daily in the amounts described above for IM administration.

The compounds of the invention can be administered intranasally. When given by this route, 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 invention for intranasal administration is the amount described above for IM administration.

The compounds of the invention can be administered intrathecally. When given by this route the appropriate dosage form can be a parenternal dosage form as is known to those skilled in the art. The dosage of the compounds of the invention for intrathecal administration is the amount described above for IM administration.

The compounds of the invention can be administered topically. When given by this route, the appropriate dosage form is a cream, ointment, or patch. Because of the amount of the compounds of the invention to be administered, the patch is preferred. When administered topically, the dosage is from about 0.5 mg/day to about 200 mg/day. Because the amount that can be delivered by a patch is limited, two or more patches may be used. The number and size of the patch is not important, what is important is that a therapeutically effective amount of the compounds of the invention be delivered as is known to those skilled in the art. The compounds of the 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.

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

The invention here is the new compounds of the invention and new methods of using the compounds of the invention. Given a particular compound of the invention and a desired dosage form, one skilled in the art would know how to prepare and administer the appropriate dosage form.

The compounds of the invention are used in the same manner, by the same routes of administration, using the same pharmaceutical dosage forms, and at the same dosing schedule as described above, for preventing disease or treating patients with MCI (mild cognitive impairment) and/or preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating or preventing Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and/or 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 palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type of Alzheimer's disease.

The compounds of the invention can be used in combination, with each other or with other therapeutic agents or approaches used to treat or prevent the conditions listed above. Such agents or approaches include: acetylcholine esterase inhibitors such as tacrine (tetrahydroaminoacridine, marketed as COGNEX®), donepezil hydrochloride, (marketed as Aricept® and rivastigmine (marketed as Exelon®); gamma-secretase inhibitors; anti-inflammatory agents such as cyclooxygenase II inhibitors; anti-oxidants such as Vitamin E and

ginkolides; immunological approaches, such as, for example, immunization with A beta peptide or administration of anti-A beta peptide antibodies; statins; and direct or indirect neurotropic agents such as Cerebrolysin®, AIT-082 (Emilieu, 2000, *Arch. Neurol.* 57:454), and other neurotropic agents of the future.

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 invention administered, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, and other medication the individual may be taking as is well known to administering physicians who are skilled in this art.

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 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). Inhibitory activity is 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 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 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 A beta can be analyzed *in vitro* or *in vivo,* using natural, 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, animal models expressing native APP and enzyme, or may utilize transgenic animal models expressing the substrate and 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 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 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 No. 5,744,346 and published PCT patent applications WO98/22597, WO00/03819, WO01/23533, and WO00/17369, as well as in literature publications (Hussain et.al., 1999, *Mol.Cell.Neurosci.* 14:419-427; Vassar et.al., 1999, *Science* 286:735-741; Yan et.al., 1999, *Nature* 402:533-537; Sinha et.al., 1999, *Nature* 40:537-540; and Lin et.al., 2000, *PNAS USA* 97:1456-1460). Synthetic forms of the enzyme have also been described (WO98/22597 and WO00/17369). Beta-secretase can be extracted and purified from human brain tissue and can be produced in cells, for example mammalian cells expressing recombinant enzyme.

Preferred inhibitory compounds are effective to inhibit 50% of beta-secretase enzymatic activity at a concentration of less than 100 micromolar, more preferably 50 micromolar, even more preferably at a concentration of 10 micromolar or less, more highly preferably 1 micromolar or less, and most preferably 10 nanomolar or less.

APP substrate

Assays that demonstrate inhibition of beta-secretase-mediated cleavage of APP can utilize any of the known forms of APP, including the 695 amino acid "normal" isotype described by Kang et.al., 1987, *Nature* 325:733-6, the 770 amino acid isotype described by Kitaguchi et. al., 1981, *Nature* 331:530-532, and variants such as the Swedish Mutation (KM670-1NL) (APP-SW), the London Mutation (V7176F), and others. See, for example, U.S. Patent No. 5,766,846 and also Hardy, 1992, *Nature Genet.* 1:233-234, 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 form, e.g., SW, as described, for example, in U.S. Patent No 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 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, a binding substrate, and the like.

Antibodies

Products characteristic of APP cleavage can be measured by immunoassay using various antibodies, as described, for example, in Pirttila et.al., 1999, *Neuro.Lett.* 249:21-4, and in U.S. Patent No. 5,612,486. Useful antibodies to detect A beta include, for example, the monoclonal antibody 6E10 (Senetek, St. Louis, MO) that specifically recognizes an epitope on amino acids 1-16 of the A beta 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 recognize the junction region of beta-amyloid peptide, the site between residues 16 and 17, as described in U.S. Patent No. 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 of APP and its cleavage products, as described in U.S. Patent Nos. 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 described, for example, in U.S. Patent Nos. 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 described, for example, in WO00/17369, WO 00/03819, and U.S. Patents No. 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.

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 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 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 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* 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 degrees C, for a time period of approximately 10 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 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 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 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 antibody SW192. This assay is described, for example, in U.S. Patent No 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. 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 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 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 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 A beta from APP 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 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 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 APP cleavage products such as A beta.

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 processing of APP to A beta, 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.

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 A beta released into the 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 include primary human neuronal cells, primary transgenic animal neuronal cells where the transgene is APP, 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 activity and /or processing of APP to release A beta, 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 U.S. Patent Nos: 5,877,399; 5,612,486; 5,387,742; 5,720,936; 5,850,003; 5,877,015,, and 5,811,633, and in Ganes et.al., 1995, *Nature* 373:523. 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 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.

Inhibition of beta-secretase mediated cleavage of APP at the beta-secretase cleavage site and of A beta 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 A beta deposits or plaques is 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 A beta from the substrate, the 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 A beta. 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 A beta deposition in brain tissues of the animal, and to reduce the number and/or size of beta amyloid plaques. Where such administration is to a human subject, the compounds are effective to inhibit or slow the progression of disease characterized by enhanced amounts of A beta, 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.

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.

Definitions And Conventions

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

Conventions For Formulas And Definitions Of Variables

The chemical formulas representing various compounds or molecular fragments in the specification and claims may contain variable substituents in addition to expressly defined structural features. These variable substituents are identified by a letter or a letter followed by a numerical subscript, for example, "Z_1" or "R_i" where "i" is an integer. These variable substituents are either monovalent or bivalent, that is, they represent a group attached to the formula by one or two chemical bonds. For example, a group Z_1 would represent a bivalent variable if attached to the formula CH_3-C(=Z_1)H. Groups R_i and R_j would represent monovalent variable substituents if attached to the formula CH_3-CH_2-C(R_i)(R_j)H_2. When chemical formulas are drawn in a linear fashion, such as those above, variable substituents contained in parentheses are bonded to the atom immediately to the left of the variable substituent enclosed in

parenthesis. When two or more consecutive variable substituents are enclosed in parentheses, each of the consecutive variable substituents is bonded to the immediately preceding atom to the left which is not enclosed in parentheses. Thus, in the formula above, both R_i and R_j are bonded to the preceding carbon atom. Also, for any molecule with an established system of carbon atom numbering, such as steroids, these carbon atoms are designated as C_i, where "i" is the integer corresponding to the carbon atom number. For example, C_6 represents the 6 position or carbon atom number in the steroid nucleus as traditionally designated by those skilled in the art of steroid chemistry. Likewise the term "R_6" represents a variable substituent (either monovalent or bivalent) at the C_6 position.

Chemical formulas or portions thereof drawn in a linear fashion represent atoms in a linear chain. The symbol "-" in general represents a bond between two atoms in the chain. Thus CH_3-O-CH_2-CH(R_i)-CH_3 represents a 2-substituted-1-methoxypropane compound. In a similar fashion, the symbol "=" represents a double bond, e.g., CH_2=C(R_i)-O-CH_3, and the symbol "≡" represents a triple bond, e.g., HC≡C-CH(R_i)-CH_2-CH_3. Carbonyl groups are represented in either one of two ways: -CO- or -C(=O)-, with the former being preferred for simplicity.

When a variable substituent is bivalent, the valences may be taken together or separately or both in the definition of the variable. For example, a variable R_i attached to a carbon atom as -C(=R_i)- might be bivalent and be defined as oxo or keto (thus forming a carbonyl group (-CO-) or as two separately attached monovalent variable substituents alpha-R_{i-j} and beta-R_{i-k}.

The carbon atom content of variable substituents is indicated in one of two ways. The first method uses a prefix to the entire name of the variable such as "C_1-C_4", where both "1" and "4" are integers representing the minimum and maximum number of carbon atoms in the variable. The prefix is separated from the variable by a space. For example, "C_1-C_4 alkyl" represents alkyl of 1 through 4 carbon atoms, (including isomeric forms thereof unless an express indication to the contrary is given). Whenever this single prefix is given, the prefix indicates the entire carbon atom content of the variable being defined. Thus C_2-C_4 alkoxycarbonyl describes a group CH_3-(CH_2)$_n$-0-CO- where n is one, two or three. By the second method the carbon atom content of only each portion of the definition is indicated separately by enclosing the "C_i-C_j" designation in parentheses and placing it immediately (no intervening space) before the portion of the definition being defined. By this optional convention (C_1-C_3)alkoxycarbonyl has the same meaning as C_2-C_4 alkoxycarbonyl because the "C_1-C_3" refers only to the carbon atom content of the alkoxy group. If the notation "C_0-C_3" is for example, this indicates that the alkyl chain may be absent of consist of on to three carbon atoms.

In a divalent chain, i.e. where "C_0-C_3" is connected to two substituents, then C_0 is defined as a bond to allow connection of the two groups. Similarly while both C_2-C_6 alkoxyalkyl and (C_1-C_3)alkoxy(C_1-C_3)alkyl define alkoxyalkyl groups containing from 2 to 6 carbon atoms, the two definitions differ since the former definition allows either the alkoxy or alkyl portion alone to contain 4 or 5 carbon atoms while the latter definition limits either of these groups to 3 carbon atoms.

When the claims contain a fairly complex (cyclic) substituent, at the end of the phrase naming/designating that particular substituent will be a notation in (parentheses) which will correspond to the same name/designation in one of the CHARTS which will also set forth the chemical structural formula of that particular substituent.

Definitions

All temperatures are in degrees Celsius.

TLC refers to thin-layer chromatography.

psi refers to pounds/in^2.

HPLC refers to high pressure liquid chromatography.

THF refers to tetrahydrofuran.

DMF refers to dimethylformamide.

EDC refers to ethyl-1-(3-dimethylaminopropyl)carbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

HOBt refers to 1-hydroxy benzotriazole hydrate.

NMM refers to N-methylmorpholine.

NBS refers to N-bromosuccinimide.

TEA refers to triethylamine.

BOC refers to 1,1-dimethylethoxy carbonyl or *t*-butoxycarbonyl, represneted schematically as-CO-O-C(CH_3)$_3$.

CBZ refers to benzyloxycarbonyl, –CO-O-CH_2-φ.

FMOC refers to 9-fluorenylmethyl carbonate.

TFA refers to trifluoracetic acid, CF_3-COOH.

CDI refers to 1,1'-carbonyldiimidazole.

Saline refers to an aqueous saturated sodium chloride solution.

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

CMR refers to C-13 magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from TMS.

NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm (d) downfield from TMS.

IR refers to infrared spectroscopy.

-phenyl refers to phenyl (C_6H_5).

MS refers to mass spectrometry expressed as m/e, m/z or mass/charge unit. MH^+ refers to the positive ion of a parent plus a hydrogen atom. EI refers to electron impact. CI refers to chemical ionization. FAB refers to fast atom bombardment.

HRMS refers to high resolution mass spectrometry.

Ether refers to diethyl ether.

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a 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.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

BOP refers to benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate.

TBDMSCl refers to *t*-butyldimethylsilyl chloride.

TBDMSOTf refers to *t*-butyldimethylsilyl trifluosulfonic acid ester.

Trisomy 21 refers to Down's Syndrome.

APP, amyloid precursor protein, is defined as any APP polypeptide, including APP variants, mutations, and isoforms, for example, as disclosed in U.S. Patent No. 5,766,846.

A beta, amyloid beta peptide, is defined as any peptide resulting from beta-secretase mediated cleavage of APP, 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.

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

"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

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 disease being treated or to reduce or delay onset of one or more clinical markers or symptoms of the disease.

BIOLOGY EXAMPLES

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 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 described in WO00/47618. Human brain -Secretase from concentrated HiQ pool prepared 7/16/97 in 0.20% Triton was used in the assay.

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 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 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.

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 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, 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 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 NaAc, 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 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. 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 compound.

Example B

Cell Free Inhibition Assay Utilizing a Synthetic APP Substrate

A synthetic APP substrate that can be cleaved by beta-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:

Biotin-SEVNL-DAEFRC[Oregon green]KK [SEQ ID NO: 1]

Biotin-SEVKM-DAEFRC[Oregon green]KK [SEQ ID NO: 2]

Biotin-GLNIKTEEISEISY-EVEFRC[Oregon green]KK [SEQ ID NO: 3]

Biotin-ADRGLTTRPGSGLTNIKTEEISEVNL-DAEFRC[Oregon green]KK [SEQ ID NO:4]

Biotin-FVNQHLCoxGSHLVEALY-LVCoxGERGFFYTPKAC[Oregon green]KK [SEQ ID NO: 5]

(Note: The Oregon green is covalently attached to the preceding Cysteine residue and ox means oxidized cysteine)

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 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 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 Acqurest (Ex485 nm/ Em530 nm). The activity of the beta-secretase enzyme 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.

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 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]

(biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNL [SEQ ID NO: 7]

Briefly, the biotin-coupled synthetic substrates are 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 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 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 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. 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 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 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 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 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 SEVNL-DAEF [SEQ ID NO: 8], and the cleavage site is between residues 5 and 6. Another preferred substrate has the sequence ADRGLTTRPGSGLTNIKTEEISEVNL-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 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

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 to Asn651Leu652 (numbered for APP751), commonly called the Swedish mutation and shown to overproduce A beta (Citron et.al., 1992, *Nature* 360:672-674), as described in USPN 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 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 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 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 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 A beta release in the presence of putative inhibitory compounds. As described in USPN 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 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 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 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 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 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 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.

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 plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated patients.

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 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. 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 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.

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 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.

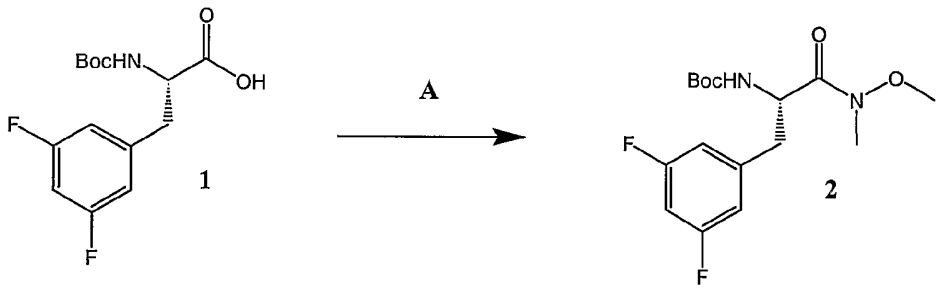
Unless defined otherwise, all scientific and technical terms used herein have the same meaning as commonly understood by one of skill in the art to which this invention belongs.

All patents and publications referred to herein are hereby incorporated by reference for all purposes.

Examples

The following examples are offered as non-limiting illustrations of the invention.

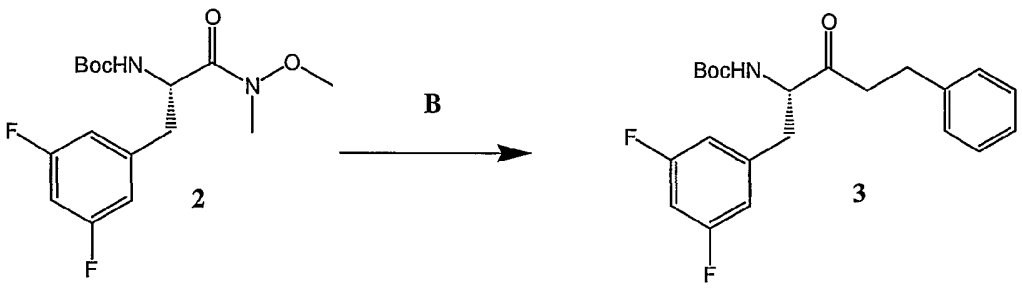
Synthesis Of Activated Amide (2) With Representative Boc-Protected Alpha Amino Acid



Procedure A

Amino acid **1** (2g, 6.6 mmol) was dissolved in anhydrous dichloromethane (35 mL). Triethylamine (4.8 mL, 33 mmol), O, N-di-Methyl hydroxylamine hydrochloride (0.650 g, 6.6 mmol) and 1-hydroxybenzotriazole (1.07 g, 8 mmol) were added with stirring, followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1. 52 g, 8 mmol). The reaction mixture was allowed to stir at 20-25 degrees Centigrade for 15 h and was then quenched with 10% aqueous $NaHCO_3$, and extracted 3x with EtOAc. The combined organic extracts were washed (sat'd $NaHCO_3$, H_2O, sat'd NaCl), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the crude product **2** which was used in the next step without further purification (mass spec (ES) (MNa+): 367.1.)

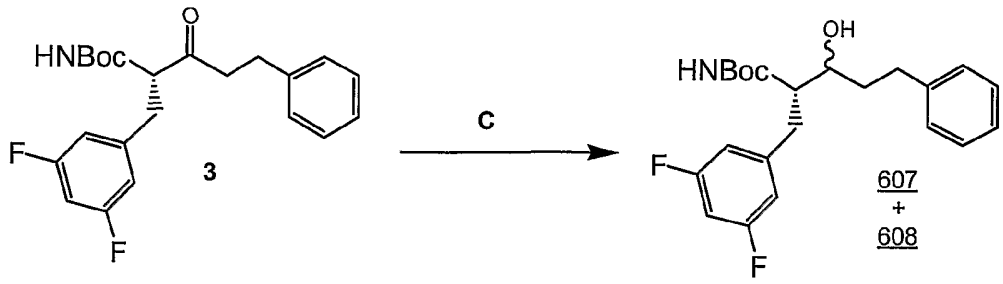
Reaction Of Activated Amide (2) With A Grignard Reagent To Provide Ketone Compond (3)



Procedure B

To a stirred solution of compound **2** (2.1 g) in anhydrous THF (30 ml) under N_2 at 0 °C was added 1.0 M phenethylmagnesium chloride in Et_2O (18 ml, 3 eqs.). After 1 hr of stirring at 0 °C, the mixture was gradually warmed to room temperature and stirred for an additional 3 h. The reaction mixture was then poured onto 1 N HCl (20 ml). The organic layer was separated and the aqueous layer was extracted with Et_20 (3x 30 ml). The combined organic phase was dried (Na_2SO_4) and concentrated to give a crude product, which was used in the next step without further purification (1.7 g): mass spec. (ES) (MNa+): 412.1

Reduction Of The Ketone Compoud (3) To Provide Amino Alchols

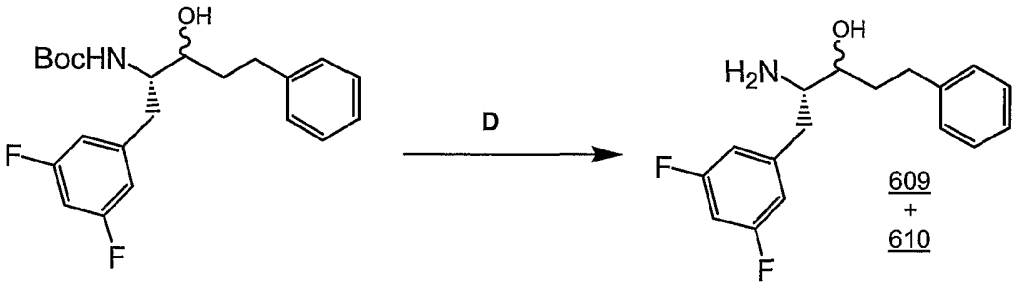


Procedure C

To a solution of **3** (1.7 g.) in THF (25 ml) under nitrogen at 0 °C was added $NaBH_4$ (190 mg, 1.2 eq.). The solution was gradually warmed to room temperature in 3 hrs and then poured onto NH_4Cl (10 ml). The mixture was extracted with Et_20 (3x 30 ml). The combined organic phase was washed with 1 N HCl (2 x 20 ml), saturated $NaHCO_3$ (2x 20 ml), dried (Na_2SO_4), and concentrated to give as a crude product a 3:1 mixture of diastereoisomers as determined by HPLC. Purification by reverse phase HPLC of half of the crude material gave compounds **607** and **608** .

mass spec (ES) (MNa+): 414.1

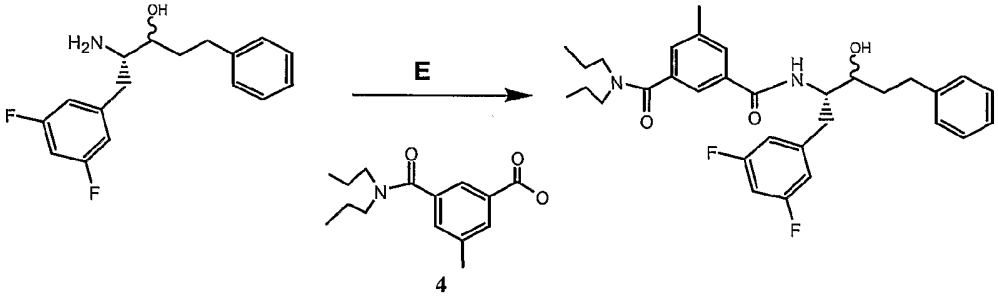
Removal Of Protecting Groups



Procedure D

30 mgs of **607** and **608** were separately dissolved in CH_2Cl_2 (2 mL) at 0 °C degree, and CF_3COOH (0.4 ml) was added with stirring under N_2. This was stirred at room temperature for 3 h, whereupon the reaction mixture was concentrated under vacuum. The resulting oils were purified by reverse phase HPLC to yield respectively compounds **609** and **610**.

Mass spec (ES) MH+ = 314

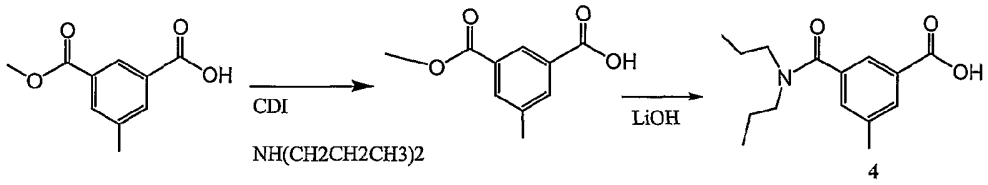


Procedure E

Free amine (1.0eq) was dissolved in dichloromethane (5ml) and isophthalic acid **4** (1.0 eq), hydroxybenzotriazol (1.5 eq) and N-methylmorphiline (5 eq) were added thereto. The resulting solution was stirred at room temperature for 15 min. and then EDC (1.2 eq) was added. Stirring was continued overnight under nitrogen. Solvents were removed under pressure, residue dissolved in ethylacetate (15 ml), washed with saturated aqueous Sodium carbonate,

brine and dried with magnesium sulfate. After removal, the residue was purified using flash chromatography on silica gel followed by HPLC. MH+: 560.1

Synthesis Of The Isopthalic Amide (4)



Procedure F

One preferred method of making these compounds is set forth as follows. An ester, preferably the monomethyl ester of isophthalic acid or methyl 5-methyl-1,3-isophthalate is dissolved in a THF/DMF mixture. 1,1'-Carbonyldiimidazole is added at 20-25 degrees C. The diisopropyl amide is added. After 3-24 hr of stirring at 20 degrees C to the reflux temperature of the solvent, the reaction mixture is partitioned between saturated aqueous ammonium chloride and a water immiscible organic solvent such as ethyl acetate. The aqueous layer is separated and extracted twice more with the organic solvent (ethyl acetate). The solvent is removed and the residue thus obtained is basified to yield the isophthalic amide **(4)** in 80% yield.

Enzyme Inhibition Assay

The inhibitory concentration data was obtained by use of the MBP-C125 assay, which determines the relative inhibition of β-secretase cleavage of an MPB-C125 substrate by the compounds assayed. Human brain β-secretase from concentrated HiQ pool prepared in 0.20% Triton was used in the assay.

Inhibition data was obtained from an ELISA which uses an anti-MBP capture antibody (on precoated and blocked 96-well high binding plates) followed by incubation with diluted enzyme reaction supernatant, incubation with an anti-SW192 specific biotinylated reporter antibody and incubation with streptavidin/alkaline phosphatase. Detection was effected by a fluorescent substrate signal on cleavage by the phosphatase. ELISA only detected cleavage following Leu 596 at the substrate's Swedish APP 751 mutation site.

Compounds were diluted in a 1:1 dilution series to a six-point concentration curve (two wells per concentration) which took up one 96-plate row per compound tested. Relative compound inhibition potency was determined by calculating the concentration of compound that

showed a fifty- percent reduction in detected signal compared to the enzyme reaction signal in the control wells with no added compound.

Procedure

Each of the test compounds was weighed out into a vial and DMSO was added to make up a 10mM solution. To obtain a final compound concentration of 200 μM at the high point of a 6-point dilution curve, 100 μL of the 10 mM solution was added to well C1 of a 96-well V-bottom plate. Fifty μL of DMSO was added to odd wells of row C across the plate and 1:1 serial dilutions were made. 10 μL of each dilution was added to each of two wells on row C of a corresponding V-bottom plate to which 190 μL of 52 mM NaOAc/7.9% DMSO, pH 4.5 were pre-added. The NaOAc diluted compound plate was spun down to pellet precipitant and 20 μL/well was transferred to a corresponding flat-bottom plate to which 30 μL of ice-cold enzyme-substrate mixture (2.5 μL MBP-C125 substrate, 0.03 μL enzyme and 24.5 ice cold 0.09% TX100 per 30 l) was added. The compound concentration in the final enzyme reaction was thus 50 times less than the starting concentration. The final reaction mixture of 200 M compound for the highest curve point was in 5% DMSO, 20 mM NaAc, 0.06% TX100, at pH 4.5. The enzyme reaction was started by warming the plates to 37° C. After 90 minutes at 37° C, 200 μL/well cold specimen diluent was added to stop the reaction and 20 μL/well was transferred to a corresponding -MBP coated ELISA plate, containing 80 μL/well specimen diluent. This reaction was incubated overnight at 4 degrees C and the ELISA was developed the next day using a 2 hr. incubation with -192SW followed by Streptavidin-AP conjugate and fluorescent substrate. The signal was read on a fluorescent plate reader.

Additional Examples

As previously stated, 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 chemistry is known to those skilled in the art. In fact, there is more than one process to prepare the compounds of the invention. Additional compounds were prepared where X is a heteroatoms, as shown below.

Experimental Procedures for Compounds 1 – 7 Below

A mixture of 0.2 mmol of a heterocyclic thiol, 0.2 mmol of epoxide **21**, and 0.2 mmol of triethylamine (DBU was substituted for triethylamine in the preparation of compound **1**) in 1 mL of methanol was stirred at 25 °C for 1 hour and then at 50° C for 6 hours. The product was isolated by preparative reverse phase chromatography eluting with a gradient of acetonitrile/water containing 0.1% trifluoroacetic acid as an ion pairing agent, or by trituration with methanol. The isolated products were treated with methanolic hydrogen chloride for 8

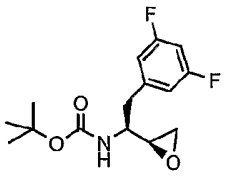
hours and then the solvent was evaporated in a stream of nitrogen. (In the case of compound **1** neat trifluoroacetic acid was used instead of methanolic HCl). The residue was weighed and treated with a dimethylformamide solution containing 1.1 equivalent of the carboxylic acid **23**, 1.1 equivalent of EDC hydrochloride salt, 1.1 equivalent of HOBt, and 4.4 equivalent of triethylamine. After six hours the solvent was evaporated at reduced pressure and the desired product was isolated by reverse phase chromatography eluting with a gradient of acetonitrile/water containing 0.1% trifluoroacetic acid as an ion pairing agent.

Experimental Procedure for Compounds 8-14 Below

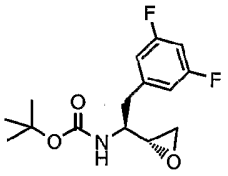
Compounds **1** – **7** were individually disssolved in 0.5 mL of dichloromethane. (A few drops of methanol were added if necessary to obtain a clear solution.) To each solution was then added 1.5 equivalents of meta chloroperbenzoic acid, and the mixtures were agitated for 12 hours. To each solution was then added 0.1 mL of a saturated aqueous solution of sodium bisulfite. After agitating for 5 minutes the phases were separated. The organic phase was washed with distilled water and then the solvent was evaporated at reduced pressure. The residue was purified by reverse phase HPLC, eluting with a gradient of acetonitrile/water containing 0.1% trifluoroacetic acid as an ion pairing agent.

Experimental Procedure for Compounds 15-20 Below

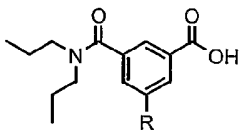
These compounds were prepared analogously to compounds **1** – **7** except that the epoxide **22** was used in place of **21**, and the acid **24** was used in place of **23**. Compounds 21-24 are shown below:



21



22

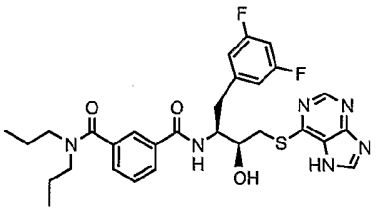


23 R = H
24 R = CH_3

Analytical Results for Compounds 1-21

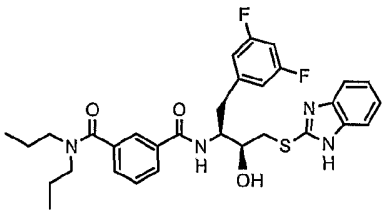
Compound 1:

Mass Spectrum (ESI): m/z = 583.3



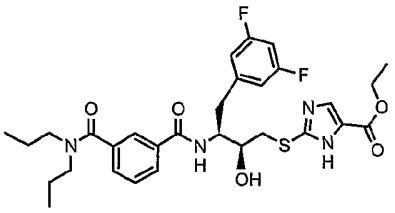
Compound 2:

Mass Spectrum (ESI): $m/z = 581.3$



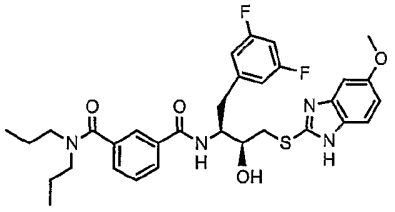
Compound 3:

Mass Spectrum (ESI): $m/z = 603.3$



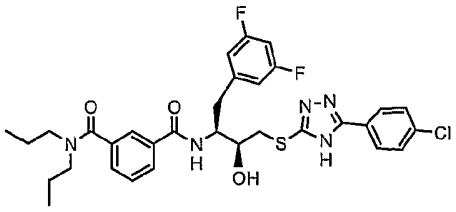
Compound 4:

Mass Spectrum (ESI): $m/z = 611.4$



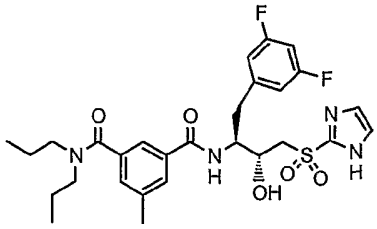
Compound 5:

Mass Spectrum (ESI): *m/z* = 642.4



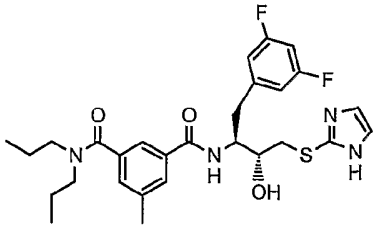
Compound 6

Mass Spectrum (ESI): *m/z* = not measured



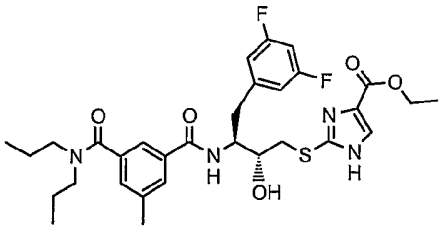
Compound 7:

Mass Spectrum (ESI): *m/z* = 545.3



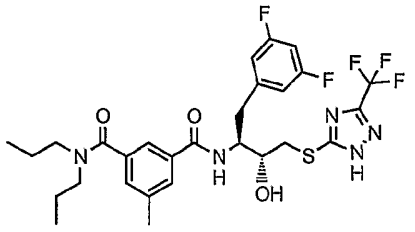
Compound 8:

Mass Spectrum (ESI): *m/z* =617.3



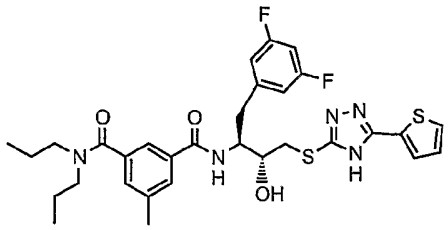
Compound 9:

Mass Spectrum (ESI): *m/z* = 614.3



Compound 10:

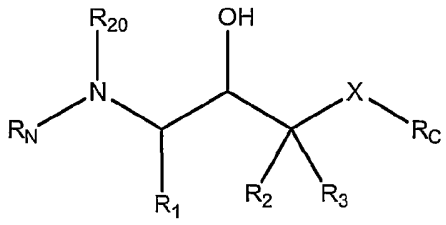
Mass Spectrum (ESI): *m/z* = 628.3



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.

WHAT IS CLAIMED IS:

1. A compound of the formula I:



(I)

wherein X is CR_2R_3, C_{1-6} alkyl or alkenyl, O, S, SO, or SO_2;

wherein R_1 is

(I) C_1-C_6 alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, C_1-C_7 alkyl (optionally substituted with C_1-C_3 alkyl and C_1-C_3 alkoxy), –F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, $-NR_{1\text{-}a}R_{1\text{-}b}$ where $R_{1\text{-}a}$ and $R_{1\text{-}b}$ are independently -H or C_1-C_6 alkyl, and -OC=O $NR_{1\text{-}a}R_{1\text{-}b}$,

(II) $–CH_2\text{-}S(O)_{0\text{-}2}\text{-}(C_1\text{-}C_6$ alkyl),

(III) $–CH_2\text{-}CH_2\text{-}S(O)_{0\text{-}2}\text{-}(C_1\text{-}C_6$ alkyl),

(IV) 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, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1\text{-}a}R_{1\text{-}b}$,

(V) 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, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1\text{-}a}R_{1\text{-}b}$,

(VI) $-(CH_2)_{n1}\text{-}(R_{1\text{-}aryl})$ where n_1 is zero or one and where $R_{1\text{-}aryl}$ is phenyl, 1-naphthyl, 2-naphthyl and indanyl, indenyl, 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 C_1-C_3 alkyl, –F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1\text{-}a}R_{1\text{-}b}$,

(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, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(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, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(D) -F, Cl, -Br or –I,

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

(G) –$NR_{N\text{-}2}R_{N\text{-}3}$ where $R_{N\text{-}2}$ and $R_{N\text{-}3}$ are as defined below,

(H) –OH,

(I) -C≡N,

(J) C_3-C_7 cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(K) –CO-(C_1-C_4 alkyl),

(L) –SO_2-$NR_{1\text{-}a}R_{1\text{-}b}$,

(M) –CO-$NR_{1\text{-}a}R_{1\text{-}b}$,

(N) –SO_2-(C_1-C_4 alkyl),

(VII) -$(CH_2)_{n1}$-($R_{1\text{-heteroaryl}}$) where n_1 is as defined above and where $R_{1\text{-heteroaryl}}$ is selected from the group consisting of:

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

pyridinyl-N-oxide, tetrahydroquinolinyl, dihydroquinolinyl, 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, quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-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,

where the $R_{1\text{-heteroaryl}}$ group is bonded to $-(CH_2)_{n1}-$ by any ring atom of the parent $R_{N\text{-heteroaryl}}$ 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:

(1) 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≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1\text{-}a}R_{1\text{-}b}$,

(2) 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, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1\text{-}a}R_{1\text{-}b}$,

(3) 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, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1\text{-}a}R_{1\text{-}b}$,

(4) -F, Cl, -Br or –I,

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

(7) $-NR_{N\text{-}2}R_{N\text{-}3}$ where $R_{N\text{-}2}$ and $R_{N\text{-}3}$ are as defined below,

(8) –OH,

(9) -C≡N,

(10) C_3-C_7 cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1\text{-}a}R_{1\text{-}b}$,

(11) –CO-(C_1-C_4 alkyl),

(12) $-SO_2$-$NR_{1\text{-}a}R_{1\text{-}b}$,

(13) –CO-$NR_{1\text{-}a}R_{1\text{-}b}$, or

(14) –SO_2-(C_1-C_4 alkyl), with the proviso that when n_1 is zero $R_{1\text{-heteroaryl}}$ is not bonded to the carbon chain by nitrogen, or

(VIII) -$(CH_2)_{n1}$-($R_{1\text{-heterocycle}}$) where n_1 is as defined above and $R_{1\text{-heterocycle}}$ 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, homomorpholinyl, homomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl dihydropyrazinyl dihydropyridinyl dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide, homothiomorpholinyl S-oxide,

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

(1) 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≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(2) 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, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(3) 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, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(4) -F, Cl, -Br, or –I,

(5) C_1-C_6 alkoxy,

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

(7) –$NR_{N\text{-}2}R_{N\text{-}3}$ where $R_{N\text{-}2}$ and $R_{N\text{-}3}$ are as defined below,

(8) –OH,

(9) -C≡N,

(10) C_3-C_7 cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(11) –CO-(C_1-C_4 alkyl),

(12) –SO_2-$NR_{1\text{-}a}R_{1\text{-}b}$,

(13) –CO-$NR_{1\text{-}a}R_{1\text{-}b}$,

(14) –SO_2-(C_1-C_4 alkyl),

(15) =O, with the proviso that when n_1 is zero $R_{1\text{-heterocycle}}$ is not bonded to the carbon chain by nitrogen;

wherein R_2 is

(I)-H,

(II) 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≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(III) -$(CH_2)_{0\text{-}4}$-$R_{2\text{-}1}$ where $R_{2\text{-}1}$ is $R_{1\text{-aryl}}$ or $R_{1\text{-heteroaryl}}$;

(IV) 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, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(V) 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, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(VI) -$(CH_2)_{0\text{-}4}$- C_3-C_7 cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$;

wherein R_3 is

(I)-H,

(II) 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≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(III) -$(CH_2)_{0\text{-}4}$-$R_{2\text{-}1}$ where $R_{2\text{-}1}$ is $R_{1\text{-aryl}}$ or $R_{1\text{-heteroaryl}}$;

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

(V) C_2-C_6 alkynyl with one or two triple bonds, or

(VI) -$(CH_2)_{0-4}$- C_3-C_7 cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1-a}R_{1-b}$,

and where R_2 and R_3 are taken together with the carbon to which they are attached to form a carbocycle of three, four, five, six, or seven carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of –O-, -S-, -SO_2-, and -NR_{N-2}-, where R_{N-2} is as defined below;

wherein R_N is

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

(A) –CO-,

(B) –SO_2-,

(C) -$(CR'R'')_{1-6}$ where R' and R" are the same or different and are –H and C_1-C_4 alkyl,

(D) –CO-$(CR'R'')_{1-6}$-X_{N-1} where X_{N-1} is selected from the group consisting of –O-, -S- and –NR'- and where R' and R" are as defined above, or

(E) a single bond;

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

(A) $R_{N\text{-}aryl}$ where $R_{N\text{-}aryl}$ is phenyl, 1-naphthyl, 2-naphthyl, tetralinyl, indanyl, 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 same or different and are:

(1) 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≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1-a}R_{1-b}$,

(2) –OH,

(3) –NO_2,

(4) –F, -Cl, -Br, or -I,

(5) -CO-OH,

(6) -C≡N,

(7) –$(CH_2)_{0-4}$-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 consisting of:

(a) -H,

(b) -C_1-C_6 alkyl optionally substituted with one substitutent selected from the group consisting of:

(i) -OH, and

(ii) $-NH_2$,

(c) $-C_1$-C_6 alkyl optionally substituted with one, two, or three –F, -Cl, -Br, or -I,

(d) $-C_3$-C_7 cycloalkyl,

(e) $-(C_1$-C_2 alkyl)-(C_3-C_7 cycloalkyl),

(f) $-(C_1$-C_6 alkyl)-O-(C_1-C_3 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,

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

(j) $-R_{1\text{-aryl}}$, and

(k) $-R_{1\text{-heteroaryl}}$,

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

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

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

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

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

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

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

(15) $-(CH_2)_{0\text{-}4}$-CO-$R_{N\text{-}4}$ where $R_{N\text{-}4}$ is selected from the group consisting of morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homomorpholinyl 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) $-(CH_2)_{0\text{-}4}$-CO-O-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is selected from the group consisting of:

(a) C_1-C_6 alkyl,

(b) $-(CH_2)_{0\text{-}2}$-($R_{1\text{-aryl}}$),

(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

(f) $-(CH_2)_{0\text{-}2}$-($R_{1\text{-heteroaryl}}$),

(17) $-(CH_2)_{0-4}-SO_2-NR_{N-2}R_{N-3}$,

(18) $-(CH_2)_{0-4}-SO-(C_1-C_8$ alkyl),

(19) $-(CH_2)_{0-4}-SO_2-(C_1-C_{12}$ alkyl),

(20) $-(CH_2)_{0-4}-SO_2-(C_3-C_7$ cycloalkyl),

(21) $-(CH_2)_{0-4}-N(H$ or $R_{N-5})-CO-O-R_{N-5}$ where R_{N-5} can be the same or different,

(22) $-(CH_2)_{0-4}-N(H$ or $R_{N-5})-CO-N(R_{N-5})_2$, where R_{N-5} can be the same or different,

(23) $-(CH_2)_{0-4}-N-CS-N(R_{N-5})_2$, where R_{N-5} can be the same or different,

(24) $-(CH_2)_{0-4}-N(-H$ or $R_{N-5})-CO-R_{N-2}$ where R_{N-5} and R_{N-2} can be the same or different,

(25) $-(CH_2)_{0-4}-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} can be the same or different,

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

(27) $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ 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) $-(CH_2)_{0-4}-O-CS-N(R_{N-5})_2$,

(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) $-(CH_2)_{0-4}-O-(C_1-C_6$ alkyl optionally substituted with one, two, three, four, or five of –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, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, or $-NR_{1-a}R_{1-b}$,

(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≡N, $-CF_3$, C_1-C_3 alkoxy, or $-NR_{1-a}R_{1-b}$,

(38) -$(CH_2)_{0-4}$–N(-H or R_{N-5})-SO_2-R_{N-2} where R_{N-5} and R_{N-2} can be the same of different, or

(39) -$(CH_2)_{0-4}$- C_3-C_7 cycloalkyl,

(B) -$R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is selected from the group consisting of: pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pryidazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, coumarinyl, isocoumarinyl, chromonyl, chromanonyl, pyridinyl-N-oxide,

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

(1) 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≡N, -CF_3, C_1-C_3 alkoxy, and -$NR_{1-a}R_{1-b}$,

(2) –OH,

(3) –NO_2,

(4) –F, -Cl, -Br, or -I,

(5) -CO-OH,

(6) -C≡N,

(7) –$(CH_2)_{0-4}$-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 consisting of:

(a) -H,

(b) -C_1-C_6 alkyl optionally substituted with one substitutent selected from the group consisting of:

(i) -OH, and

(ii) $-NH_2$,

(c) $-C_1$-C_6 alkyl optionally substituted with one, two, or three –F, -Cl, -Br, or -I,

(d) $-C_3$-C_7 cycloalkyl,

(e) $-(C_1$-C_2 alkyl)-(C_3-C_7 cycloalkyl),

(f) $-(C_1$-C_6 alkyl)-O-(C_1-C_3 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,

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

(j) $-R_{1\text{-aryl}}$, and

(k) $-R_{1\text{-heteroaryl}}$,

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

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

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

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

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

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

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

(15) $-(CH_2)_{0\text{-}4}$-CO-$R_{N\text{-}4}$ where $R_{N\text{-}4}$ is selected from the group consisting of morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homomorpholinyl 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) $-(CH_2)_{0\text{-}4}$-CO-O-$R_{N\text{-}5}$ where $R_{N\text{-}5}$ is selected from the group consisting of:

(a) C_1-C_6 alkyl,

(b) $-(CH_2)_{0\text{-}2}$-($R_{1\text{-aryl}}$),

(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

(f) $-(CH_2)_{0\text{-}2}$-($R_{1\text{-heteroaryl}}$),

(17) $-(CH_2)_{0-4}-SO_2-NR_{N-2}R_{N-3}$,

(18) $-(CH_2)_{0-4}-SO-(C_1-C_8$ alkyl),

(19) $-(CH_2)_{0-4}-SO_2-(C_1-C_{12}$ alkyl),

(20) $-(CH_2)_{0-4}-SO_2-(C_3-C_7$ cycloalkyl),

(21) $-(CH_2)_{0-4}-N(H$ or $R_{N-5})-CO-O-R_{N-5}$ where R_{N-5} can be the same or different,

(22) $-(CH_2)_{0-4}-N(H$ or $R_{N-5})-CO-N(R_{N-5})_2$, where R_{N-5} can be the same or different,

(23) $-(CH_2)_{0-4}-N-CS-N(R_{N-5})_2$, where R_{N-5} can be the same or different,

(24) $-(CH_2)_{0-4}-N(-H$ or $R_{N-5})-CO-R_{N-2}$ where R_{N-5} and R_{N-2} can be the same or different,

(25) $-(CH_2)_{0-4}-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} can be the same or different,

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

(27) $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ 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) $-(CH_2)_{0-4}-O-CS-N(R_{N-5})_2$,

(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) $-(CH_2)_{0-4}-O-(C_1-C_6$ alkyl optionally substituted with one, two, three, four, or five of –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, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, or $-NR_{1-a}R_{1-b}$,

(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≡N, $-CF_3$, C_1-C_3 alkoxy, or $-NR_{1-a}R_{1-b}$,

(38) -$(CH_2)_{0-4}$–N(-H or R_{N-5})-SO_2-R_{N-2} where R_{N-5} and R_{N-2} can be the same of different,,

(39) -$(CH_2)_{0-4}$- C_3-C_7 cycloalkyl,

(C) $R_{N\text{-}aryl}$-W-$R_{N\text{-}aryl}$,

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

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

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

(G) $R_{N\text{-}heteroaryl}$-W-$R_{N\text{-}heteroaryl}$,

(H) $R_{N\text{-}heteroaryl}$-W-$R_{N\text{-}1\text{-}heterocycle}$,

(I) $R_{N\text{-}heterocycle}$-W-$R_{N\text{-}aryl}$, where $R_{N\text{-}heterocycle}$ is the same as $R_{1\text{-}heterocycle}$,

(J) $R_{N\text{-}heterocycle}$-W-$R_{N\text{-}heteroaryl}$,

(K) $R_{N\text{-}heterocycle}$-W-$R_{N\text{-}1\text{-}heterocycle}$,

where W is

(6) –$(CH_2)_{0-4}$-,

(7) –O-,

(8) –$S(O)_{0-2}$-,

(9) –$N(R_{N-5})$- where R_{N-5} is as defined above, or

(10) –CO-;

(II) –CO-(C_1-C_{10} alkyl) where alkyl is optionally substituted with one three substitutents selected from the group consisting of:

(A) -OH,

(B)-C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or –phenyl,

(E) –CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(F) -CO-R_{N-4} where R_{N-4},

(G) -SO_2-(C_1-C_8 alkyl),

(H) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8},

(K) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(L) -R_{N-4},

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where the R_{N-8}s are the same or different,

(O) -O-(C_1-C_5 alkyl)-COOH,

(P) –O-(C_1-C_6 alkyl optionally substitued with one, two, or three of -F, -Cl, -Br, or -I),

(Q) -NH-SO_2-(C_1-C_6 alkyl), and

(R) -F, -Cl,

(III) –CO-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl) where alkyl is optionally substituted with one, two, or three substitutents selected from the group consisting of

(A) -OH,

(B)-C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -φ,

(E) –CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) -SO_2-(C_1-C_8 alkyl),

(H) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8},

(K) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(L) -R_{N-4},

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where R_{N-8} are the same or different,

(O) -O-(C_1-C_5 alkyl)-COOH,

(P) –O-(C_1-C_6 alkyl optionally substitued with one, two, or three of -F, -Cl, -Br, or -I),

(Q) -NH-SO_2-(C_1-C_6 alkyl), and

(R) -F, or -Cl,

(IV) –CO-(C_1-C_6 alkyl)-S-(C_1-C_6 alkyl) where alkyl is optionally substituted with one, two, or three of substitutents selected from the group consisting of

(A) -OH,

(B) -C_1-C_6 alkoxy,

(C) -C_1-C_6 thioalkoxy,

(D) –CO-O-R_{N-8},

(E) –CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) -SO_2-(C_1-C_8 alkyl),

(H) -SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(I) -NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,

(K) -$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(L) -R_{N-4} where R_{N-4} is as defined above,

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where the R_{N-8}s are the same or different,

(O) -O-(C_1-C_5 alkyl)-COOH,

(P) –O-(C_1-C_6 alkyl optionally substitued with one, two, or three of –F, -Cl, -Br, or -I),

(Q) -NH-SO_2-(C_1-C_6 alkyl), and

(R) -F, or -Cl,

(V) –CO-CH(-$(CH_2)_{0-2}$-O-R_{N-10})-$(CH_2)_{0-2}$-R_{N-aryl}/$R_{N-heteroaryl}$), where R_{N-10} is selected from the group consisting of:

(A) –H,

(B) C_1-C_6 alkyl,

(C) C_3-C_7 cycloalkyl,

(D) C_2-C_6 alkenyl with one double bond,

(E) C_2-C_6 alkynyl with one triple bond,

(F) R_{1-aryl}, and

(G) $R_{N-heteroaryl}$, or

(VI) –CO-(C_3-C_8 cycloalkyl) where alkyl is optionally substituted with one or two substitutents selected from the group consisting of:

(A) -$(CH_2)_{0-4}$-OH,

(B) -$(CH_2)_{0-4}$-C_1-C_6 alkoxy,

(C) -$(CH_2)_{0-4}$-C_1-C_6 thioalkoxy,

(D) -$(CH_2)_{0-4}$-CO-O-R_{N-8} where R_{N-8} is –H, C_1-C_6 alkyl or -phenyl,

(E) -$(CH_2)_{0-4}$-CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

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

(G) -$(CH_2)_{0-4}$-SO_2-(C_1-C_8 alkyl),

(H) -$(CH_2)_{0-4}$-SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

(I) -$(CH_2)_{0-4}$-NH-CO-(C_1-C_6 alkyl),

(J) -NH-CO-O-R_{N-8},

(K) -$(CH_2)_{0-4}$-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different,

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

(M) -O-CO-(C_1-C_6 alkyl),

(N) -O-CO-$NR_{N-8}R_{N-8}$ where R_{N-8} are the same or different,

(O) -O-(C_1-C_5 alkyl)-COOH,

(P) –O-(C_1-C_6 alkyl optionally substitued with one, two, or three of –F, -Cl, -Br, or -I),

(Q) -NH-SO_2-(C_1-C_6 alkyl), and

(R) -F, or -Cl,

wherein R_C is:

(I)-C_1-C_{10} 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≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, -$NR_{1-a}R_{1-b}$, -OC=O $NR_{1-a}R_{1-b}$, -$S(=O)_{0-2}$, - NR_{1-a}C=O $NR_{1-a}R_{1-b}$, -C=O $NR_{1-a}R_{1-b}$, and -$S(=O)_2$ $NR_{1-a}R_{1-b}$,

(II) -$(CH_2)_{0-3}$-(C_3-C_8) cycloalkyl where cycloalkyl can be 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≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, -CO-OH, -CO-O-(C_1-C_4 alkyl), and -$NR_{1-a}R_{1-b}$,

(III) -$(CR_{C-x}R_{C-y})_{0-4}$-R_{C-aryl} where R_{C-x} and R_{C-y} are

(A) –H,

(B) C_1-C_4 alkyl optionally substituted with one or two –OH,

(C) C_1-C_4 alkoxy optionally substituted with one, two, or three -F,

(D) -$(CH_2)_{0-4}$-C_3-C_7 cycloalkyl,

(E) C_2-C_6 alkenyl containing one or two double bonds,

(F) C_2-C_6 alkynyl contianing one or two triple bonds,

(G) phenyl,

and where R_{C-x} and R_{C-y} are taken together with the carbon to which they are attached to form a carbocycle of three, four, five, six or seven carbon atoms, optionally where

one carbon atom is replaced by a heteroatom selected from the group consisting of –O-, -S-, -SO_2-, and -$NR_{N\text{-}2}$- and $R_{C\text{-}aryl}$ is the same as $R_{N\text{-}aryl}$;

(IV) -$(CR_{C\text{-}x}R_{C\text{-}y})_{0\text{-}4}$-$R_{C\text{-}heteroaryl}$ where $R_{C\text{-}heteroaryl}$ is the same as $R_{N\text{-}heteroaryl}$,

(V) -$(CR_{C\text{-}x}R_{C\text{-}y})_{0\text{-}4}$-$R_{C\text{-}aryl}$-$R_{C\text{-}aryl}$,

(VI) -$(CR_{C\text{-}x}R_{C\text{-}y})_{0\text{-}4}$-$R_{C\text{-}aryl}$-$R_{C\text{-}heteroaryl}$,

(VII) -$(CR_{C\text{-}x}R_{C\text{-}y})_{0\text{-}4}$-$R_{C\text{-}heteroaryl}$-$R_{C\text{-}aryl}$,

(VIII) -$(CR_{C\text{-}x}R_{C\text{-}y})_{0\text{-}4}$-$R_{C\text{-}heteroaryl}$-$R_{C\text{-}heteroaryl}$,

(IX) -$(CR_{C\text{-}x}R_{C\text{-}y})_{0\text{-}4}$-$R_{C\text{-}aryl}$-$R_{C\text{-}heterocycle}$ and where $R_{C\text{-}heterocycle}$ is the same as $R_{1\text{-}heterocycle}$,

(X) -$(CR_{C\text{-}x}R_{C\text{-}y})_{0\text{-}4}$-$R_{C\text{-}heteroaryl}$-$R_{C\text{-}heterocycle}$,

(XI) -$(CR_{C\text{-}x}R_{C\text{-}y})_{0\text{-}4}$-$R_{C\text{-}heterocycle}$-$R_{C\text{-}aryl}$,

(XII) -$(CR_{C\text{-}x}R_{C\text{-}y})_{0\text{-}4}$-$R_{C\text{-}heterocycle}$-$R_{C\text{-}heteroaryl}$,

(XIII) -$(CR_{C\text{-}x}R_{C\text{-}y})_{0\text{-}4}$-$R_{C\text{-}heterocycle}$-$R_{C\text{-}heterocycle}$,

(XIV) -$(CR_{C\text{-}x}R_{C\text{-}y})_{0\text{-}4}$-$R_{C\text{-}heterocycle}$,

(XV) -$[C(R_{C\text{-}1})(R_{C\text{-}2})]_{1\text{-}3}$-CO-N-$(R_{C\text{-}3})_2$ where $R_{C\text{-}1}$ and $R_{C\text{-}2}$ are the same or different and are selected from the group consisting of:

(A) -H,

(B) -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≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(C) 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 C_1-C_3 alkyl, –F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(D) 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 C_1-C_3 alkyl, –F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(E) –$(CH_2)_{1\text{-}2}$-$S(O)_{0\text{-}2}$-(C_1-C_6 alkyl),

(F) –$(CH_2)_{0\text{-}4}$-C_3-C_7 cycloalkyl, 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≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, and -$NR_{1\text{-}a}R_{1\text{-}b}$,

(G) -(C_1-C_4 alkyl)-$R_{C'\text{-}aryl}$ where $R_{C'\text{-}aryl}$ is as defined for $R_{1\text{-}aryl}$,

(H) -(C_1-C_4 alkyl)-$R_{C\text{-}heteroaryl}$,

(I) -(C_1-C_4 alkyl)-$R_{C\text{-}heterocycle}$,

(J) $-R_{C\text{-heteroaryl}}$,

(K) $-R_{C\text{-heterocycle}}$,

(M) $-(CH_2)_{1-4}-R_{C-4}-(CH_2)_{0-4}-R_{C'\text{-aryl}}$ where R_{C-4} is –O-, -S- or $-NR_{C-5}-$ where R_{C-5} is C_1-C_6 alkyl,

(N) $-(CH_2)_{1-4}-R_{C-4}-(CH_2)_{0-4}-R_{C\text{-heteroaryl}}$, and

(O) $-R_{C'\text{-aryl}}$,

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

(A) -H,

(B) -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≡N, $-CF_3$, C_1-C_6 alkoxy, -O-phenyl, and $-NR_{1-a}R_{1-b}$,

(C) 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 C_1-C_3 alkyl, –F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_6 alkoxy, -O-phenyl, and $-NR_{1-a}R_{1-b}$,

(D) 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 C_1-C_3 alkyl, –F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_6 alkoxy, -O-phenyl, and $-NR_{1-a}R_{1-b}$,

(E) $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl, 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≡N, $-CF_3$, C_1-C_6 alkoxy, -O-phenyl, and $-NR_{1-a}R_{1-b}$,

(F) $-R_{C'\text{-aryl}}$,

(G) $-R_{C\text{-heteroaryl}}$,

(H) $-R_{C\text{-heterocycle}}$,

(I) -(C_1-C_4 alkyl)-$R_{C'\text{-aryl}}$,

(J) -(C_1-C_4 alkyl)-$R_{C\text{-heteroaryl}}$, or

(K) -(C_1-C_4 alkyl)-$R_{C\text{-heterocycle}}$,

(XVI) $-CH(R_{C\text{-aryl}})_2$ where $R_{C\text{-aryl}}$ are the same or different and are as defined above,

(XVII) $-CH(R_{C\text{-heteroaryl}})_2$ where $R_{C\text{-heteroaryl}}$ are the same or different and are as defined above,

(XVIII) $-CH(R_{C\text{-aryl}})(R_{C\text{-heteroaryl}})$,

(XIX) -cyclopentyl, -cyclohexyl, or -cycloheptyl ring fused to $R_{C\text{-aryl}}$ or $R_{C\text{-heteroaryl}}$ or $R_{C\text{-heterocycle}}$ where one carbon of cyclopentyl, cyclohexyl, or -cycloheptyl is optionally

replaced with NH, NR_{N-5}, O, or $S(=O)_{0-2}$, and where cyclopentyl, cyclohexyl, or -cycloheptyl can be optionally substituted with one or two -C_1-C_3 alkyl, –F, -OH, -SH, -C≡N, -CF_3, C_1-C_6 alkoxy, =O, or -$NR_{1-a}R_{1-b}$,

(XX) C_2-C_{10} alkenyl containing one or two double bonds 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≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, and -$NR_{1-a}R_{1-b}$,

(XXI) C_2-C_{10} alkynyl containing one or two triple bonds 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≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, and -$NR_{1-a}R_{1-b}$,

(XXI) –$(CH_2)_{0-1}$-CHR_{C-6}-$(CH_2)_{0-1}$-R_{C-aryl} and R_{C-6} is -$(CH_2)_{0-6}$-OH,

(XXII) –$(CH_2)_{0-1}$-CHR_{C-6}-$(CH_2)_{0-1}$-$R_{C-heteroaryl}$,

(XXIII) –CH(-R_{C-aryl} or $R_{C-heteroaryl}$)-CO-O(C_1-C_4 alkyl),

(XXIV) –CH(-CH_2-OH)-CH(-OH)-NO_2,

(XXV) (C_1-C_6 alkyl)-O-(C_1-C_6 alkyl)-OH,

(XXVII) –CH_2-NH-CH_2-CH(-O-CH_2-CH_3)$_2$,

(XXVIII) –H,

(XXIX) -$(CH_2)_{0-6}$-C(=NR_{1-a})($NR_{1-a}R_{1-b}$); and

wherein R_{20} is H or C_{1-6} alkyl or alkenyl.

2. A pharmaceutically acceptable salt or ester of a compound according to claim 1.

3. A compound according to claim 1, wherein X is CR_2R_3.

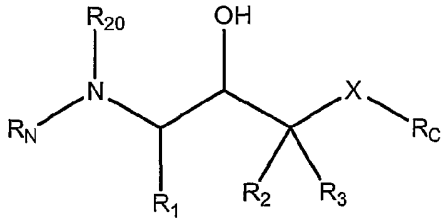
4. A compound according to claim 1, wherein X is O.

5. A compound according to claim 1, wherein X is S.

6. A compound according to claim 1, wherein X is SO.

7. A compound according to claim 1, wherein X is SO_2.

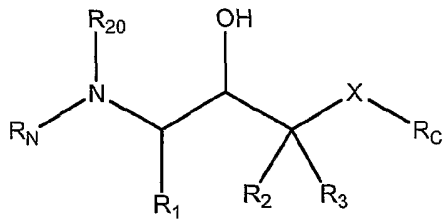
8. A method for making a compound of formula (I)



(I)

or a pharmaceutically acceptable salt or ester thereof, wherein R_1, R_2, R_3, X, R_N, R_{20} and R_C are as defined in claim 1.

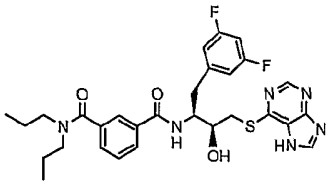
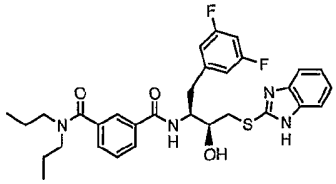
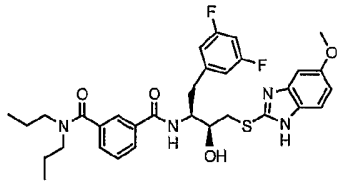
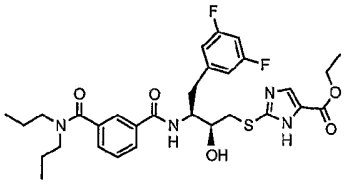
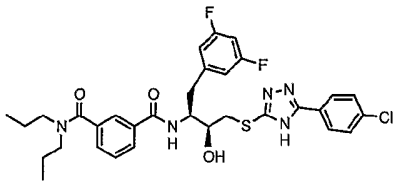
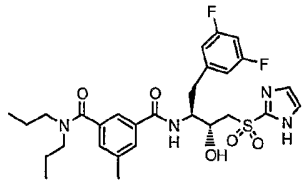
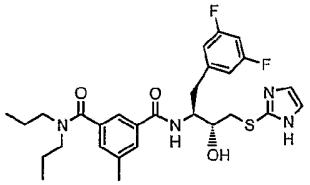
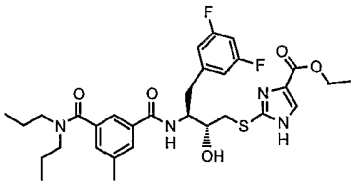
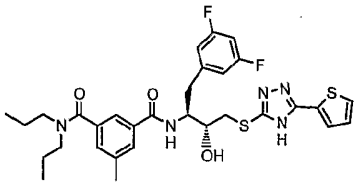
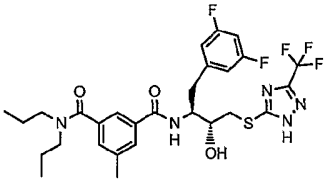
9. A method of treating a patient who has, or in preventing a patient from getting, a disease or condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI) and/or preventing 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 angiopathy and/or 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 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 comprises administration of a therapeutically effective amount of a compound selected from the group consisting of a substituted alcohol of formula (I)



(I)

where R_1, R_2, R_3, X, R_N, R_{20} and R_C are as defined in claim 1, or pharmaceutically acceptable salt or ester thereof.

10. A compound selected from the group consisting of:

SEQUENCE LISTING

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Hom, Roy
Tucker, John

<120> Substituted Alcohols Useful in Treatment of Alzheimer's Disease

<130> 01-1704-D

<160> 9

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Lys Lys

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Lys

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Lys Thr Glu Glu Ile Ser Glu Val Asn Leu Asp Ala Glu Phe
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INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/US 02/20754

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/52 A61K31/4184 A61K31/4164 A61K31/4196 A61P25/28
C07D473/38 C07D235/28 C07D233/90 C07D249/12 C07D409/04

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 70672 A (ELAN PHARM INC) 27 September 2001 (2001-09-27) Formula (XII), examples 40, 41, 59	1-3,9
X	WO 98 38167 A (BROWN MATTHEW FRANK ;KATH JOHN CHARLES (US); PFIZER (US); POSS CHR) 3 September 1998 (1998-09-03) Formula (I), examples, e.g. ex. 26, 46	1-3
A	US 5 703 129 A (CHATURVEDULA PRASAD ET AL) 30 December 1997 (1997-12-30) claims 1,8	1-7,9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
20 November 2002	27/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Johnson, C

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Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1 (part), 8

Claim 8 concerns a method for making a compound of claim 1, however no information about the method is given. In the absence of any technical features pertaining to the method claimed, the scope of the claim is unclear and it does not fulfil the requirements of Article 6 PCT to such an extent that no meaningful search can be performed.

Claim 1 is over 17 pages long and covers a vast array of widely varying possibilities, only a fraction of which have been exemplified. So many possibilities are covered that it is extremely difficult to ascertain the scope of this claim, hence the requirements of Article 6 PCT are not fulfilled. Furthermore, the extremely limited scope of the examples (which all vary only in the XRc group) compared with that of the claims leads to a lack of support and disclosure under Article 5 PCT. This lack of clarity and support means that a meaningful search over the entire scope of the claims is not possible. For this reason, the full search has only been performed for the preferred embodiments, i.e. for the compounds of claim 1 wherein R1 is a CH2 group substituted by any of the groups defined in claim 1; RN is a C(O)-phenyl group which may be substituted as defined in claim 1; X is O, S, SO or SO2; Rc is an aryl or heteroaryl group.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/20754

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

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

Although claim 9 isdirected to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1 (part), 8
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/20754

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