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COMPOUNDS TO TREAT ALZHEIMER'S DISEASE

This application is being filed as a PCT International Patent Application in the name of Elan Pharmaceuticals, Inc., a U.S. national corporation and resident, (Applicant for all countries) and Pharmacia & Upjohn Company, a U.S. national corporation (Applicant for all countries), on 29 June 2001, designating all countries except US.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to the following provisional applications: United States provisional application Serial No. 60/215, 323, filed June 30, 2000; United States provisional application Serial No. 60/252,736, filed November 22, 2000; United States provisional application Serial No. 60/255,956, filed December 15, 2000; United States provisional application Serial No. 60/268,497, filed February 13, 2001; United States provisional application Serial No. 60/279,779, filed March 29, 2001; and United States provisional application Serial No. 60/295,589, filed June 4, 2001.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is directed to compounds useful in treatment of Alzheimer's disease and similar diseases.

2. 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, judgement, 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



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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 the 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, and Memapsin. See, for example, Sinha 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.

5 It has been proposed that A beta peptide accumulates as a result of APP processing by beta-secretase, thus inhibition of this enzyme's activity is desirable for the treatment of AD. *In vivo* processing of APP at the beta-secretase cleavage site is 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.,
10 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
15 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
20 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
25 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.

US Patents 4,616,088 and 4,665,193 discloses hydroxyethylamine compounds as anti-hypertensive agents due to their ability to inhibit renin.

30 US Patent 4,636,491 discloses various tetrapeptides which are useful as renin inhibitors.

US Patent 4,749,792 discloses amino compounds useful as analgesics because of their ability to inhibit an enkephalin-degrading aminopeptidase.

US Patent 5,142,056 discloses peptide derivatives with a C₂-symmetric dihydroxyethylene core as retroviral protease inhibitors.

US Patents 5,461,067 and 5,753,652 disclose the synthesis of retroviral protease inhibitors.

5 US Patent 5,475,138 and 5,631,405 disclose processes and various intermediates useful in the synthesis of selected protease inhibitors.

US Patent 5,502,061 discloses HIV protease inhibitors containing an unsaturated carbocycle or heterocycle at the C-terminus.

10 US Patent 5,545,640 discloses compounds which inhibit HIV protease activity.

US Patent 5,516,784 discloses compounds active against retroviruses, including HIV.

US Patent 5,602,175 discloses hydroxyethylamine compounds as retroviral protease inhibitors.

15 US Patent 5,631,405 discloses a process for the formation of intermediates useful in the synthesis of selected protease inhibitors.

US Patent 5,733,882 and International Publications WO 93/02057 and WO 93/17003 disclose dipeptide analogs as retroviral protease inhibitors.

20 US Patent 5,760,076 discloses hydroxyethylamino sulfonamide compounds as retrovirus protease inhibitors.

US Patent 5,807,870 discloses hydroxyethylamine compounds for the inhibition of HIV protease.

US Patent 5,827,891 discloses HIV protease inhibitors.

25 US Patent 5,830,897 discloses hydroxyethylamino sulfonamide compounds as retrovirus protease inhibitors.

US Patent 5,831,117 discloses a process and intermediates useful in retroviral protease inhibitor intermediates.

US Patent 5,847,169 discloses a process for preparing aminoepoxides involving the activation of the terminal hydroxyl of an aminodiol.

30 US Patent 5,849,911 discloses hydroxyethylamine HIV protease inhibitors which form hydrazines with one of the amino groups; this amino group must also be alkylated.

US Patent 5,922,770 discloses peptide derivatives which are useful in treating disorders resulting from a deficiency in growth hormone.

US Patent 6,013,658 discloses peptide derivatives which are useful in treating disorders resulting from a deficiency in growth hormone.

US Patent 6,022,872 discloses hydroxyethylamino sulfonyl urea compounds as HIV protease inhibitors.

5 US Patent 6,060,476 discloses hydroxyethylamino sulfonamide compounds as HIV protease inhibitors.

International Publication WO 89/01488 discloses renin inhibiting peptides with a hydroxyethylene or dihydroxyethylene isostere in the 10,11-position of the renin substrate angiotensinogen.

10 International Publication WO92/00750 discloses retroviral protease inhibitors.

International Publication WO 94/04492 discloses hydroxyethylamine intermediates useful for the treatment of retroviral diseases such as HIV. This disclosure also presents epoxides as intermediates for the retroviral inhibitors.

15 International Publication WO 95/06030 discloses epoxides, chloromethyl ketones, and alcohols prepared as intermediates for HIV protease inhibitors, with a single protecting group on the amine and arylalkyl side chain substituted with alkyl, nitro, nitrile, alkoxy, and thioalkoxy; a preferred side chain is 4-fluorophenylmethyl.

International Publication WO98/29401 discloses a method for the
20 preparation of aminoepoxides from aminoaldehydes by which the aminoaldehyde continuously flows into a mixing zone containing an *in situ* generated halomethyl organometallic reagent.

International Publication WO98/33795 discloses non-peptide inhibitors of cathepsin D.

25 International Publication WO98/50342 discloses bis aminomethyl carbonyl compounds as inhibitors of cysteine and serine proteases.

International Publication WO00/056335 discloses non-peptide inhibitors of aspartyl proteases. These compounds influence processing of the amyloid precursor protein APP.

30 EP 0 609 625 discloses HIV protease inhibitors with only one noncyclized nitrogen atom.

Bioorganic & Medicinal Chemistry Letters, 5, 721-726 (1995) describes the synthesis of compounds useful for the inhibition of HIV protease in which the C-terminal nitrogen of the hydroxyethylamine compound is incorporated into a ring

system such that a piperidine ring, with an amide substituent next to the nitrogen, is formed.

The hydroxyethylamine "nucleus" or isostere, which is present in the compounds of the present invention has been employed with success in the area of HIV protease inhibition. Many of these hydroxyethylamine compounds are known as well as how to make them. See for example, *J. Am. Chem. Soc.*, 93, 288-291 (1993), *Tetrahedron Letters*, 28(45) 5569-5572 (1987), *J. Med. Chem.*, 38(4), 581-584 (1994), *Tetrahedron Letters*, 38(4), 619-620 (1997).

US Patent 5,648,511 discloses a diprotected aralkyl epoxide.

US Patents 5,482,947; 5,508,294; 5,510,349; 5,510,388; 5,521,219; 5,610,190; 5,639,769; 5,760,064; and 5,965,588 disclose monoprotected (substituted) aralkyl epoxides.

Tetrahedron Lett., 30(40),5425-5428 (1989) discloses a process in which doubly protected alpha-amino aldehydes are transformed into the corresponding aminoalkyl epoxides.

J. Med. Chem., 36, 2300 (1993) discloses an azide substituted benzyl epoxide.

Tetrahedron Lett., 38, 3175 (1997) discloses a process for the preparation of N-BOC protected epoxides from protected amino acid esters.

J. Med. Chem., 35, 2525 (1992) discloses hydroxyethylamine inhibitors of HIV protease.

US Patent 5,481,011 discloses arylalkyl amino epoxides in which the amino group is protected by a carbamate functionality.

Synlett, 6, 902 (2000) discloses the preparation of alpha-chloroketones of aminoprotected-(substituted)benzyl esters.

US Patent 5,648,511 discloses a diprotected aralkyl alcohol.

US Patents 5,482,947; 5,508,294; 5,510,349; 5,510,388; 5,521,219; 5,610,190; 5,639,769; 5,760,064; and 5,965,588 disclose monoprotected (substituted) aralkyl alcohols.

US Patents 5,482,947; 5,508,294; 5,510,349; 5,510,388; 5,521,219; 5,610,190; 5,639,769; 5,760,064; and 5,965,588 disclose a process for removing the protecting group of the monoprotected (substituted) aralkyl alcohols to give the free amino alcohol product as the amine salt.

US Patent 5,648,511 discloses the removal of the amino protecting group of the protected amino-alcohol (VIII) to give the free amino-alcohol (IX).

US Patent 6,150,344 discloses phosphate containing compounds useful in treating Alzheimer's disease.

5 EP 652 009 A1 discloses inhibitors of aspartyl protease which inhibit beta-amyloid peptide production in cell culture and *in vivo*. The compounds which inhibit intracellular beta-amyloid peptide production are useful in treating Alzheimer's Disease.

10 WO00/69262 discloses a new beta-secretase and its use in assays to screen for potential drug candidates against Alzheimer's disease.

WO01/00663 discloses memapsin 2 (human beta-secretase) as well as catalytically active recombinant enzyme. In addition, a method of identifying inhibitors of memapsin 2, as well as two inhibitors are disclosed. Both inhibitors that are disclosed are peptides.

15 WO01/00665 discloses inhibitors of memapsin 2 that are useful in treating Alzheimer's disease.

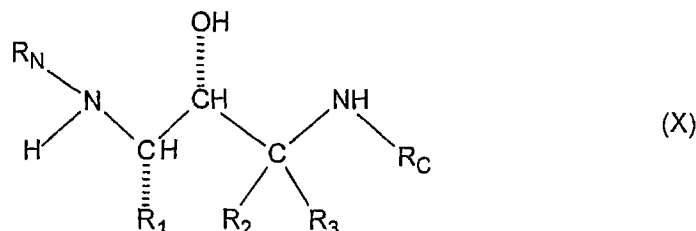
WO01/19797 discloses lactams of the formula -C-C-CO-N-lactam-W-X-Y-Z which are useful in treating Alzheimer's disease.

20 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.

25 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 INVENTION

Disclosed is a substituted amine of formula (X)



5

where R_1 is:

(I) $\text{C}_1\text{-C}_6$ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_1\text{-C}_7$ alkyl (optionally substituted with $\text{C}_1\text{-C}_3$ alkyl and $\text{C}_1\text{-C}_3$ alkoxy), -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF₃, $\text{C}_1\text{-C}_3$ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or $\text{C}_1\text{-C}_6$ alkyl, -OC=O NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

10

(II) -CH₂-S(O)₀₋₂-($\text{C}_1\text{-C}_6$ alkyl),

(III) -CH₂-CH₂-S(O)₀₋₂-($\text{C}_1\text{-C}_6$ alkyl),

15

(IV) $\text{C}_2\text{-C}_6$ 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 $\equiv$ N, -CF₃, $\text{C}_1\text{-C}_3$ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or $\text{C}_1\text{-C}_6$ alkyl,

(V) $\text{C}_2\text{-C}_6$ 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 $\equiv$ N, -CF₃, $\text{C}_1\text{-C}_3$ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or $\text{C}_1\text{-C}_6$ alkyl,

20

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

25

(A) $\text{C}_1\text{-C}_6$ alkyl optionally substituted with one, two or three substituents selected from the group consisting of $\text{C}_1\text{-C}_3$ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above, -C $\equiv$ N, -CF₃, $\text{C}_1\text{-C}_3$ alkoxy,

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

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

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

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

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

(H) -OH,

(I) -C≡N,

15 (J) C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

(K) -CO-(C₁-C₄ alkyl),

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

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

(N) -SO₂-(C₁-C₄ alkyl),

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

pyridinyl,

25 pyrimidinyl,

quinolinyl,

benzothienyl,

indolyl,

indolinyl,

30 pyridazinyl,

pyrazinyl,

isoindolyl,

isoquinolyl,

5 quinazolinyI,
 quinoxalinyI,
 phthalazinyI,
 imidazolyl,
 isoxazolyl,
 pyrazolyl,
 oxazolyl,
 thiazolyl,
 indolizinyI,
10 indazolyl,
 benzothiazolyl,
 benzimidazolyl,
 benzofuranyl,
 furanyl,
15 thienyl,
 pyrrolyl,
 oxadiazolyl,
 thiadiazolyl,
 triazolyl,
20 tetrazolyl,
 oxazolopyridinyI,
 imidazopyridinyI,
 isothiazolyl,
 naphthyridinyI,
25 cinnolinyI,
 carbazolyl,
 beta-carbolinyI,
 isochromanyl,
 chromanyl,
30 tetrahydroisoquinolinyI,
 isoindolinyI,
 isobenzotetrahydrofuranyl,
 isobenzotetrahydrothienyl,
 isobenzothienyl,

5 benzoxazolyl,
 pyridopyridinyl,
 benzotetrahydrofuranyl,
 benzotetrahydrothienyl,
 purinyl,
 benzodioxolyl,
 triazinyl,
 phenoxazinyl,
 phenothiazinyl,
10 pteridinyl,
 benzothiazolyl,
 imidazopyridinyl,
 imidazothiazolyl,
 dihydrobenzisoquinazolinyl,
15 benzisoquinazolinyl,
 benzoxazinyl,
 dihydrobenzothiazinyl,
 benzopyranyl,
 benzothiopyranyl,
20 coumarinyl,
 isocoumarinyl,
 chromonyl,
 chromanonyl,
 pyridinyl-N-oxide
25 tetrahydroquinolinyl
 dihydroquinolinyl
 dihydroquinolinonyl
 dihydroisoquinolinonyl
 dihydrocoumarinyl
30 dihydroisocoumarinyl
 isoindolinonyl
 benzodioxanyl
 benzoxazolinonyl
 pyrrolyl N-oxide,

5 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,
 10 phthalazinyl N-oxide,
 imidazolyl N-oxide,
 isoxazolyl N-oxide,
 oxazolyl N-oxide,
 thiazolyl N-oxide,
 15 indoliziny N-oxide,
 indazolyl N-oxide,
 benzothiazolyl N-oxide,
 benzimidazolyl N-oxide,
 pyrrolyl N-oxide,
 20 oxadiazolyl N-oxide,
 thiadiazolyl N-oxide,
 triazolyl N-oxide,
 tetrazolyl N-oxide,
 benzothiopyranyl S-oxide,
 25 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:

30 (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, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy,

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

5 (3) C₂-C₆ alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

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

10 (6) -C₁-C₆ 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,

15 (10) C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

(11) -CO-(C₁-C₄ alkyl),

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

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

(14) -SO₂-(C₁-C₄ alkyl), with the proviso that when n₁ is zero

R_{1-heteroaryl} is not bonded to the carbon chain by nitrogen,

(VIII) -(CH₂)_{n1}-(R_{1-heterocycle}) where n₁ is as defined above and

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

25 morpholinyl,
thiomorpholinyl,
thiomorpholinyl S-oxide,
thiomorpholinyl S,S-dioxide,
piperazinyl,
30 homopiperazinyl,
pyrrolidinyl,
pyrrolinyl,
tetrahydropyranyl,

piperidinyl,
 tetrahydrofuranyl,
 tetrahydrothienyl,
 homopiperidinyl,
 5 homomorpholinyl,
 homothiomorpholinyl,
 homothiomorpholinyl S,S-dioxide, and
 oxazolidinonyl,
 dihydropyrazolyl
 10 dihydropyrrolyl
 dihydropyrazinyl
 dihydropyridinyl
 dihydropyrimidinyl
 dihydrofuryl
 15 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
 20 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) $C_1\text{-}C_6$ alkyl optionally substituted with one, two or
 three substituents selected from the group consisting of $C_1\text{-}C_3$ alkyl, -F, -Cl, -Br, -I, -
 25 OH, -SH, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, $-C\equiv N$, $-CF_3$, $C_1\text{-}C_3$
 alkoxy,

(2) $C_2\text{-}C_6$ 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, $-C\equiv N$, $-CF_3$, $C_1\text{-}C_3$ alkoxy, $-NR_{1-a}R_{1-b}$ where R_{1-a}
 30 and R_{1-b} are -H or $C_1\text{-}C_6$ alkyl,

(3) $C_2\text{-}C_6$ 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, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

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

(5) C₁-C₆ alkoxy,

5 (6) -C₁-C₆ 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,

10 (9) -C≡N,

(10) C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

(11) -CO-(C₁-C₄ alkyl),

15 (12) -SO₂-NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

(13) -CO-NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined

above,

(14) -SO₂-(C₁-C₄ alkyl),

20 (15) =O, with the proviso that when n₁ is zero R₁₋

heterocycle is not bonded to the carbon chain by nitrogen;

where R₂ is selected from the group consisting of:

(I)-H,

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

(III) -(CH₂)₀₋₄-R₂₋₁ where R₂₋₁ is R_{1-aryl} or R_{1-heteroaryl} where R_{1-aryl} and R_{1-heteroaryl} are as defined above;

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

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

5 (VI) -(CH₂)₀₋₄- C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

where R₃ is selected from the group consisting of:

(I)-H,

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

(III) -(CH₂)₀₋₄-R₂₋₁ where R₂₋₁ is R_{1-aryl} or R_{1-heteroaryl} where R_{1-aryl} and R_{1-heteroaryl} are as defined above;

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

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

(VI) -(CH₂)₀₋₄- C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

20 and where R₂ and R₃ are taken together with the carbon to which they are attached to form a carbocycle of three, four, five, six, and seven carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of -O-, -S-, -SO₂-, -NR_{N-2}-, where R_{N-2} is as defined below;

where R_N is:

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

(A) -CO-,

(B) -SO₂-,

(C) -(CR'R'')₁₋₆ where R' and R'' are the same or different and are -H and C₁-C₄ alkyl,

30 (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,

(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, dihydronaphthyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl, optionally substituted with one, two or three of the following substituents which can be the same or different and are:

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

(2) -OH,

10 (3) $-NO_2$,

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

(5) $-CO-OH$,

(6) $-C\equiv N$,

15 (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) $-C_1\text{-}C_6$ alkyl optionally substituted with one substituent selected from the group consisting of:

(i) -OH,

20 (ii) $-NH_2$,

(c) $-C_1\text{-}C_6$ alkyl optionally substituted with one to three -F, -Cl, -Br, -I,

(d) $-C_3\text{-}C_7$ cycloalkyl,

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

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

(g) $-C_2\text{-}C_6$ alkenyl with one or two double bonds,

(h) $-C_2\text{-}C_6$ alkynyl with one or two triple bonds,

30 (i) $-C_1\text{-}C_6$ alkyl chain with one double bond and one triple bond,

(j) $-R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined above,

(k) $-R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined

above,

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

5 three double bonds),

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

three triple bonds),

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

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

10 above,

(12) $-(CH_2)_{0-4}-CO-R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined

defined above,

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

defined above,

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

15 (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, homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl where each group is optionally substituted with one, two, three, or four of C_1-C_6 alkyl,

20 (16) $-(CH_2)_{0-4}-CO-O-R_{N-5}$ where R_{N-5} is selected from the group consisting of:

(a) C_1-C_6 alkyl,

above,

(b) $-(CH_2)_{0-2}-(R_{1\text{-aryl}})$ where $R_{1\text{-aryl}}$ is as defined

25 bonds,

(c) C_2-C_6 alkenyl containing one or two double

bonds,

(d) C_2-C_6 alkynyl containing one or two triple

(e) C_3-C_7 cycloalkyl,

30 defined above,

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

as defined above,

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

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

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

(37) C₂-C₆ alkynyl with one or two triple bonds
optionally substituted with C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-
C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

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

(39) -(CH₂)₀₋₄-C₃-C₇ cycloalkyl,

(B) -R_{N-heteroaryl} where R_{N-heteroaryl} is selected from the group
consisting of:

10 pyridinyl,
pyrimidinyl,
quinolinyl,
benzothienyl,
indolyl,
indolinyl,
15 pyridazinyl,
pyrazinyl,
isoindolyl,
isoquinolyl,
quinazolinyl,
20 quinoxalinyl,
phthalazinyl,
imidazolyl,
isoxazolyl,
pyrazolyl,
25 oxazolyl,
thiazolyl,
indolizinyl,
indazolyl,
benzothiazolyl,
30 benzimidazolyl,
benzofuranyl,
furanyl,
thienyl,

pyrrolyl,
oxadiazolyl,
thiadiazolyl,
triazolyl,
5 tetrazolyl,
oxazolopyridinyl,
imidazopyridinyl,
isothiazolyl,
naphthyridinyl,
10 cinnolinyl,
carbazolyl,
beta-carbolinyl,
isochromanyl,
chromanyl,
15 tetrahydroisoquinolinyl,
isoindolinyl,
isobenzotetrahydrofuranyl,
isobenzotetrahydrothienyl,
isobenzothieryl,
20 benzoxazolyl,
pyridopyridinyl,
benzotetrahydrofuranyl,
benzotetrahydrothienyl,
purinyl,
25 benzodioxolyl,
triazinyl,
henoxazinyl,
phenothiazinyl,
pteridinyl,
30 benzothiazolyl,
imidazopyridinyl,
imidazothiazolyl,
dihydrobenzisoaxazinyl,
benzisoaxazinyl,

benzoxazinyl,
dihydrobenziso-thiazinyl,
benzopyranyl,
benzothiopyranyl,
5 coumarinyl,
isocoumarinyl,
chromonyl,
chromanonyl,
pyridinyl-N-oxide,
10 tetrahydroquinolinyl
dihydroquinolinyl
dihydroquinolinonyl
dihydroisoquinolinonyl
dihydrocoumarinyl
15 dihydroisocoumarinyl
isoindolinonyl
benzodioxanyl
benzoxazolinonyl
pyrrolyl N-oxide,
20 pyrimidinyl N-oxide,
pyridazinyl N-oxide,
pyrazinyl N-oxide,
quinolinyl N-oxide,
indolyl N-oxide,
25 indolinyl N-oxide,
isoquinolyl N-oxide,
quinazolinyl N-oxide,
quinoxalinyl N-oxide,
phthalazinyl N-oxide,
30 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,
 5 oxadiazolyl N-oxide,
 thiadiazolyl N-oxide,
 triazolyl N-oxide,
 tetrazolyl N-oxide,
 benzothiopyranyl S-oxide,
 10 benzothiopyranyl S,S-dioxide,

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:

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

- (2) -OH,
 20 (3) $-NO_2$,
 (4) -F, -Cl, -Br, -I,
 (5) $-CO-OH$,
 (6) $-C\equiv N$,
 (7) $-(CH_2)_{0-4}-CO-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are

25 the same or different and are selected from the group consisting of:

- (a) -H,
 (b) $-C_1\text{-}C_6$ alkyl optionally substituted with one substituent selected from the group consisting of:

- (i) -OH,
 30 (ii) $-NH_2$,
 (c) $-C_1\text{-}C_6$ alkyl optionally substituted with one to three -F, -Cl, -Br, -I,
 (d) $-C_3\text{-}C_7$ cycloalkyl,

- (e) $-(C_1-C_2 \text{ alkyl})-(C_3-C_7 \text{ cycloalkyl})$,
 (f) $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_3 \text{ alkyl})$,
 (g) $-C_2-C_6 \text{ alkenyl}$ with one or two double bonds,
 5 (h) $-C_2-C_6 \text{ alkynyl}$ with one or two triple bonds,
 (i) $-C_1-C_6 \text{ alkyl chain}$ with one double bond and one triple bond,
 (j) $-R_{1-aryl}$ where R_{1-aryl} is as defined above,
 10 (k) $-R_{1-heteroaryl}$ where $R_{1-heteroaryl}$ is as defined above,
 (8) $-(CH_2)_{0-4}-CO-(C_1-C_{12} \text{ alkyl})$,
 (9) $-(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkenyl}$ with one, two or three double bonds),
 15 (10) $-(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkynyl}$ with one, two or three triple bonds),
 (11) $-(CH_2)_{0-4}-CO-(C_3-C_7 \text{ cycloalkyl})$,
 (12) $-(CH_2)_{0-4}-CO-R_{1-aryl}$ where R_{1-aryl} is as defined above,
 20 (13) $-(CH_2)_{0-4}-CO-R_{1-heteroaryl}$ where $R_{1-heteroaryl}$ is as defined above,
 (14) $-(CH_2)_{0-4}-CO-R_{1-heterocycle}$ where $R_{1-heterocycle}$ is as defined above,
 (15) $-(CH_2)_{0-4}-CO-R_{N-4}$ where R_{N-4} is selected from the
 25 group consisting of morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl where each group is optionally substituted with one, two, three, or four of $C_1-C_6 \text{ alkyl}$,
 (16) $-(CH_2)_{0-4}-CO-O-R_{N-5}$ where R_{N-5} is selected from
 30 the group consisting of:
 (a) $C_1-C_6 \text{ alkyl}$,
 (b) $-(CH_2)_{0-2}-(R_{1-aryl})$ where R_{1-aryl} is as defined above,

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

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

5 (e) C₃-C₇ cycloalkyl,

(f) -(CH₂)₀₋₂-(R_{1-heteroaryl}) where R_{1-heteroaryl} is as defined above,

(17) -(CH₂)₀₋₄-SO₂-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} are as defined above,

10 (18) -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl),

(19) -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl),

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

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

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

(23) -(CH₂)₀₋₄-N-CS-N(R_{N-5})₂, where R_{N-5} can be the same or different and is as defined above,

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

(25) -(CH₂)₀₋₄-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} can be the same or different and are as defined above,

(26) -(CH₂)₀₋₄-R_{N-4} where R_{N-4} is as defined above,

(27) -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl),

25 (28) -(CH₂)₀₋₄-O-P(O)-(OR_{N-aryl-1})₂ where R_{N-aryl-1} is -H or C₁-C₄ alkyl,

(29) -(CH₂)₀₋₄-O-CO-N(R_{N-5})₂ where R_{N-5} is as defined above,

(30) -(CH₂)₀₋₄-O-CS-N(R_{N-5})₂ where R_{N-5} is as defined above,

(31) -(CH₂)₀₋₄-O-(R_{N-5})₂ where R_{N-5} is as defined above,

(32) -(CH₂)₀₋₄-O-(R_{N-5})₂-COOH where R_{N-5} is as defined above,

(33) $-(\text{CH}_2)_{0-4}-\text{S}-(\text{R}_{\text{N}-5})_2$ where $\text{R}_{\text{N}-5}$ is as defined

above,

(34) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{C}_1-\text{C}_6 \text{ alkyl optionally substituted}$

with one, two, three, four, or five of -F),

5 (35) $\text{C}_3-\text{C}_7 \text{ cycloalkyl}$,

(36) $\text{C}_2-\text{C}_6 \text{ alkenyl}$ with one or two double bonds

optionally substituted with $\text{C}_1-\text{C}_3 \text{ alkyl}$, -F, -Cl, -Br, -I, -OH, -SH, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1-\text{C}_3 \text{ alkoxy}$, $-\text{NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

(37) $\text{C}_2-\text{C}_6 \text{ alkynyl}$ with one or two triple bonds

10 optionally substituted with $\text{C}_1-\text{C}_3 \text{ alkyl}$, -F, -Cl, -Br, -I, -OH, -SH, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1-\text{C}_3 \text{ alkoxy}$, $-\text{NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

(38) $-(\text{CH}_2)_{0-4}-\text{N}(\text{H or } \text{R}_{\text{N}-5})-\text{SO}_2-\text{R}_{\text{N}-2}$ where $\text{R}_{\text{N}-5}$ and $\text{R}_{\text{N}-2}$ can be the same or different and are as described above,

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

15 (C) $\text{R}_{\text{N-aryl}}-\text{W}-\text{R}_{\text{N-aryl}}$,

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

(E) $\text{R}_{\text{N-aryl}}-\text{W}-\text{R}_{\text{N-1-heterocycle}}$, where $\text{R}_{\text{N-heterocycle}}$ is defined as R_{1-}

heterocycle is defined above,

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

20 (G) $\text{R}_{\text{N-heteroaryl}}-\text{W}-\text{R}_{\text{N-heteroaryl}}$,

(H) $\text{R}_{\text{N-heteroaryl}}-\text{W}-\text{R}_{\text{N-1-heterocycle}}$, where $\text{R}_{\text{N-1-heterocycle}}$ is defined

as R_{1-} heterocycle is defined above,

(I) $\text{R}_{\text{N-heterocycle}}-\text{W}-\text{R}_{\text{N-aryl}}$,

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

25 (K) $\text{R}_{\text{N-heterocycle}}-\text{W}-\text{R}_{\text{N-1-heterocycle}}$,

where W is

(1) $-(\text{CH}_2)_{0-4}-$,

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

(3) $-\text{S}(\text{O})_{0-2}-$,

30 (4) $-\text{N}(\text{R}_{\text{N}-5})-$ where $\text{R}_{\text{N}-5}$ is as defined above, or

(5) $-\text{CO}-$;

(II) $-\text{CO}-(\text{C}_1-\text{C}_{10} \text{ alkyl})$ where alkyl is optionally substituted with one

two or three substituents selected from the group consisting of:

- (A) -OH,
 (B) -C₁-C₆ alkoxy,
 (C) -C₁-C₆ thioalkoxy,
 (D) -CO-O-R_{N-8} where R_{N-8} is -H, C₁-C₆ alkyl or -phenyl,
 5 (E) -CO-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} are the same or different and are as defined above,
 (F) -CO-R_{N-4} where R_{N-4} is as defined above,
 (G) -SO₂-(C₁-C₈ alkyl),
 (H) -SO₂-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} are the same or
 10 different and are as defined above,
 (I) -NH-CO-(C₁-C₆ 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 and are as defined above,
 15 (L) -R_{N-4} where R_{N-4} is as defined above,
 (M) -O-CO-(C₁-C₆ alkyl),
 (N) -O-CO-NR_{N-8}R_{N-8} where R_{N-8} are the same or different and are as defined above,
 (O) -O-(C₁-C₅ alkyl)-COOH,
 20 (P) -O-(C₁-C₆ alkyl optionally substituted with one, two, or three of -F, -Cl, -Br, -I),
 (Q) -NH-SO₂-(C₁-C₆ alkyl),
 (R) -F, -Cl,
 (III) -CO-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl) where alkyl is optionally
 25 substituted with one, two, or three substituents selected from the group consisting of
 (A) -OH,
 (B) -C₁-C₆ alkoxy,
 (C) -C₁-C₆ thioalkoxy,
 30 (D) -CO-O-R_{N-8} where R_{N-8} is -H, C₁-C₆ alkyl or -phenyl,
 (E) -CO-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} are the same or different and are as defined above,
 (F) -CO-R_{N-4} where R_{N-4} is as defined above,

(G) $-\text{SO}_2-(\text{C}_1-\text{C}_8 \text{ alkyl})$,

(H) $-\text{SO}_2-\text{NR}_{\text{N-2}}\text{R}_{\text{N-3}}$ where $\text{R}_{\text{N-2}}$ and $\text{R}_{\text{N-3}}$ are the same or different and are as defined above,

(I) $-\text{NH}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$,

5 (J) $-\text{NH}-\text{CO}-\text{O}-\text{R}_{\text{N-8}}$ where $\text{R}_{\text{N-8}}$ is as defined above,

(K) $-\text{NR}_{\text{N-2}}\text{R}_{\text{N-3}}$ where $\text{R}_{\text{N-2}}$ and $\text{R}_{\text{N-3}}$ are the same or different and are as defined above,

(L) $-\text{R}_{\text{N-4}}$ where $\text{R}_{\text{N-4}}$ is as defined above,

(M) $-\text{O}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$,

10 (N) $-\text{O}-\text{CO}-\text{NR}_{\text{N-8}}\text{R}_{\text{N-8}}$ where $\text{R}_{\text{N-8}}$ are the same or different and are as defined above,

(O) $-\text{O}-(\text{C}_1-\text{C}_5 \text{ alkyl})-\text{COOH}$,

(P) $-\text{O}-(\text{C}_1-\text{C}_6 \text{ alkyl})$ optionally substituted with one, two, or three of $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$),

15 (Q) $-\text{NH}-\text{SO}_2-(\text{C}_1-\text{C}_6 \text{ alkyl})$,

(R) $-\text{F}$, $-\text{Cl}$,

(IV) $-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{S}-(\text{C}_1-\text{C}_6 \text{ alkyl})$ where alkyl is optionally substituted with one, two, or three of substituents selected from the group consisting of :

20 (A) $-\text{OH}$,

(B) $-\text{C}_1-\text{C}_6 \text{ alkoxy}$,

(C) $-\text{C}_1-\text{C}_6 \text{ thioalkoxy}$,

(D) $-\text{CO}-\text{O}-\text{R}_{\text{N-8}}$ where $\text{R}_{\text{N-8}}$ is as defined above,

25 (E) $-\text{CO}-\text{NR}_{\text{N-2}}\text{R}_{\text{N-3}}$ where $\text{R}_{\text{N-2}}$ and $\text{R}_{\text{N-3}}$ are the same or different and are as defined above,

(F) $-\text{CO}-\text{R}_{\text{N-4}}$ where $\text{R}_{\text{N-4}}$ is as defined above,

(G) $-\text{SO}_2-(\text{C}_1-\text{C}_8 \text{ alkyl})$,

(H) $-\text{SO}_2-\text{NR}_{\text{N-2}}\text{R}_{\text{N-3}}$ where $\text{R}_{\text{N-2}}$ and $\text{R}_{\text{N-3}}$ are the same or different and are as defined above,

30 (I) $-\text{NH}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$,

(J) $-\text{NH}-\text{CO}-\text{O}-\text{R}_{\text{N-8}}$ where $\text{R}_{\text{N-8}}$ is as defined above,

(K) $-\text{NR}_{\text{N-2}}\text{R}_{\text{N-3}}$ where $\text{R}_{\text{N-2}}$ and $\text{R}_{\text{N-3}}$ are the same or different and are as defined above,

- (L) $-R_{N-4}$ where R_{N-4} is as defined above,
 (M) $-O-CO-(C_1-C_6 \text{ alkyl})$,
 (N) $-O-CO-NR_{N-8}R_{N-8}$ where the R_{N-8} s are the same or different and are as defined above,
 5 (O) $-O-(C_1-C_5 \text{ alkyl})-COOH$,
 (P) $-O-(C_1-C_6 \text{ alkyl})$ optionally substituted with one, two, or three of $-F$, $-Cl$, $-Br$, $-I$,
 (Q) $-NH-SO_2-(C_1-C_6 \text{ alkyl})$,
 (R) $-F$, $-Cl$,
 10 (V) $-CO-CH(-(CH_2)_{0-2}-O-R_{N-10})-(CH_2)_{0-2}-R_{N-aryl}/R_{N-heteroaryl})$ where R_{N-aryl} and $R_{N-heteroaryl}$ are as defined above, where R_{N-10} is selected from the group consisting of:
 (A) $-H$,
 (B) $C_1-C_6 \text{ alkyl}$,
 15 (C) $C_3-C_7 \text{ cycloalkyl}$,
 (D) $C_2-C_6 \text{ alkenyl}$ with one double bond,
 (E) $C_2-C_6 \text{ alkynyl}$ with one triple bond,
 (F) R_{1-aryl} where R_{1-aryl} is as defined above,
 (G) $R_{N-heteroaryl}$ where $R_{N-heteroaryl}$ is as defined above,
 20 (VI) $-CO-(C_3-C_8 \text{ cycloalkyl})$ where alkyl is optionally substituted with one or two substituents selected from the group consisting of:
 (A) $-(CH_2)_{0-4}-OH$,
 (B) $-(CH_2)_{0-4}-C_1-C_6 \text{ alkoxy}$,
 (C) $-(CH_2)_{0-4}-C_1-C_6 \text{ thioalkoxy}$,
 25 (D) $-(CH_2)_{0-4}-CO-O-R_{N-8}$ where R_{N-8} is $-H$, $C_1-C_6 \text{ alkyl}$ 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 and are as defined above,
 (F) $-(CH_2)_{0-4}-CO-R_{N-4}$ where R_{N-4} is as defined above,
 30 (G) $-(CH_2)_{0-4}-SO_2-(C_1-C_8 \text{ alkyl})$,
 (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 and are as defined above,

(I) $-(\text{CH}_2)_{0-4}-\text{NH}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$,

(J) $-\text{NH}-\text{CO}-\text{O}-\text{R}_{\text{N}-8}$ where $\text{R}_{\text{N}-8}$ is as defined above,

(K) $-(\text{CH}_2)_{0-4}-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$ where $\text{R}_{\text{N}-2}$ and $\text{R}_{\text{N}-3}$ are the same or different and are as defined above,

5 (L) $-(\text{CH}_2)_{0-4}-\text{R}_{\text{N}-4}$ where $\text{R}_{\text{N}-4}$ is as defined above,

(M) $-\text{O}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$,

(N) $-\text{O}-\text{CO}-\text{NR}_{\text{N}-8}\text{R}_{\text{N}-8}$ where the $\text{R}_{\text{N}-8}$ s are the same or different and are as defined above,

(O) $-\text{O}-(\text{C}_1-\text{C}_5 \text{ alkyl})-\text{COOH}$,

10 (P) $-\text{O}-(\text{C}_1-\text{C}_6 \text{ alkyl})$ optionally substituted with one, two, or three of $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,

(Q) $-\text{NH}-\text{SO}_2-(\text{C}_1-\text{C}_6 \text{ alkyl})$,

(R) $-\text{F}$, $-\text{Cl}$,

where R_C is:

15 (I) $-\text{C}_1-\text{C}_{10}$ alkyl optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_6 alkoxy, $-\text{O}$ -phenyl, $-\text{NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, $-\text{OC}=\text{O NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, $-\text{S}(=\text{O})_{0-2}$ R_{1-a} where R_{1-a} is as defined above, $-\text{NR}_{1-a}\text{C}=\text{O NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, $-\text{C}=\text{O NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, and $-\text{S}(=\text{O})_2 \text{NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

(II) $-(\text{CH}_2)_{0-3}-(\text{C}_3-\text{C}_8)$ cycloalkyl where cycloalkyl can be optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_6 alkoxy, $-\text{O}$ -phenyl, $-\text{CO}-$
 25 OH , $-\text{CO}-\text{O}-(\text{C}_1-\text{C}_4 \text{ alkyl})$, $-\text{NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

(III) $-(\text{CR}_{\text{C}-x}\text{R}_{\text{C}-y})_{0-4}-\text{R}_{\text{C}-\text{aryl}}$ where $\text{R}_{\text{C}-x}$ and $\text{R}_{\text{C}-y}$ are

$-\text{H}$,

C_1-C_4 alkyl optionally substituted with one or two $-\text{OH}$,

C_1-C_4 alkoxy optionally substituted with one, two, or three of

30 $-\text{F}$,

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

C_2-C_6 alkenyl containing one or two double bonds,

C_2-C_6 alkynyl containing one or two triple bonds,

phenyl,

and where 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 and seven carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of -O-, -S-, -SO₂-, -NR_{N-2}- and R_{C-aryl} is defined as R_{N-aryl} is defined above;

(IV) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}$ where $R_{C-heteroaryl}$ is defined as $R_{N-heteroaryl}$ is defined above and R_{C-x} and R_{C-y} are as defined above,

(V) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}-R_{C-aryl}$ where R_{C-aryl} , R_{C-x} and R_{C-y} are as defined above,

(VI) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}-R_{C-heteroaryl}$ where R_{C-aryl} , $R_{C-heteroaryl}$, R_{C-x} and R_{C-y} are as defined above,

(VII) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}-R_{C-aryl}$ where $R_{C-heteroaryl}$, R_{C-aryl} , R_{C-x} and R_{C-y} are as defined above,

(VIII) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}-R_{C-heteroaryl}$ where $R_{C-heteroaryl}$, R_{C-x} and R_{C-y} are as defined above,

(IX) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}-R_{C-heterocycle}$ where R_{C-aryl} , R_{C-x} and R_{C-y} are as defined above, and $R_{C-heterocycle}$ is defined as $R_{N-heterocycle}$ is defined above,

(X) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}-R_{C-heterocycle}$ where $R_{C-heteroaryl}$, $R_{C-heterocycle}$, R_{C-x} and R_{C-y} are as defined above,

(XI) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heterocycle}-R_{C-aryl}$ where $R_{C-heterocycle}$, R_{C-aryl} , R_{C-x} and R_{C-y} are as defined above,

(XII) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heterocycle}-R_{C-heteroaryl}$ where $R_{C-heterocycle}$, $R_{C-heteroaryl}$, R_{C-x} and R_{C-y} are as defined above,

(XIII) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heterocycle}-R_{C-heterocycle}$ where $R_{C-heterocycle}$, R_{C-x} and R_{C-y} are as defined above,

(XIV) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heterocycle}$ where $R_{C-heterocycle}$, R_{C-x} and R_{C-y} are as defined above,

(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) -C₁-C₆ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH,

-SH, -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

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

(D) C₂-C₆ alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of
 10 C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

(E) -(CH₂)₁₋₂-S(O)₀₋₂-(C₁-C₆ alkyl),

(F) -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, -NR_{1-a}R_{1-b} where R_{1-a} and
 15 R_{1-b} are as defined above,

(G) -(C₁-C₄ alkyl)-R_{C'-aryl} where R_{C'-aryl} is as defined for R_{1-aryl},

(H) -(C₁-C₄ alkyl)-R_{C-heteroaryl} where R_{C-heteroaryl} is as defined above,

(I) -(C₁-C₄ alkyl)-R_{C-heterocycle} where R_{C-heterocycle} is as defined above,

(J) -R_{C-heteroaryl} where R_{C-heteroaryl} is as defined above,

(K) -R_{C-heterocycle} where R_{C-heterocycle} is as defined above,

(M) -(CH₂)₁₋₄-R_{C-4}-(CH₂)₀₋₄-R_{C'-aryl} where R_{C-4} is -O-, -S- or
 25 -NR_{C-5}- where R_{C-5} is C₁-C₆ alkyl, and where R_{C'-aryl} is defined above,

(N) -(CH₂)₁₋₄-R_{C-4}-(CH₂)₀₋₄-R_{C-heteroaryl} where R_{C-4} and R_{C-heteroaryl} are as defined above,

(O) -R_{C'-aryl} where R_{C'-aryl} is as defined above,

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

30 (A) -H,

(B) -C₁-C₆ alkyl optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH,

-SH, -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

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

(D) C₂-C₆ alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of
 10 C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

(E) -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl,
 -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, -NR_{1-a}R_{1-b} where R_{1-a} and
 15 R_{1-b} are as defined above,

(F) -R_{C'-aryl} where R_{C'-aryl} is as defined above,

(G) -R_{C-heteroaryl} where R_{C-heteroaryl} is as defined above,

(H) -R_{C-heterocycle} where R_{C-heterocycle} is as defined above,

(I) -(C₁-C₄ alkyl)-R_{C'-aryl} where R_{C'-aryl} is as defined above,

(J) -(C₁-C₄ alkyl)-R_{C-heteroaryl} where R_{C-heteroaryl} is as defined
 20 above,

(K) -(C₁-C₄ alkyl)-R_{C-heterocycle} where R_{C-heterocycle} is as defined
 above,

(XVI) -CH(R_{C-aryl})₂ where R_{C-aryl} are the same or different and are as
 25 defined above,

(XVII) -CH(R_{C-heteroaryl})₂ where R_{C-heteroaryl} are the same or different
 and are as defined above,

(XVIII) -CH(R_{C-aryl})(R_{C-heteroaryl}) where R_{C-aryl} and R_{C-heteroaryl} are as
 defined above,

(XIX) -cyclopentyl, -cyclohexyl, or -cycloheptyl ring fused to R_{C-aryl}
 30 or R_{C-heteroaryl} or R_{C-heterocycle} where R_{C-aryl} or R_{C-heteroaryl} or R_{C-heterocycle} are as defined
 above where one carbon of cyclopentyl, cyclohexyl, or -cycloheptyl is optionally
 replaced with NH, NR_{N-5}, O, S(=O)₀₋₂, and where cyclopentyl, cyclohexyl, or -

cycloheptyl can be optionally substituted with one or two -C₁-C₃ alkyl, -F, -OH, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, =O, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

(XX) C₂-C₁₀ alkenyl containing one or two double bonds optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

(XXI) C₂-C₁₀ alkynyl containing one or two triple bonds optionally substituted with one, two or three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, -O-phenyl, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

(XXI) -(CH₂)₀₋₁-CHR_{C-6}-(CH₂)₀₋₁-R_{C-aryl} where R_{C-aryl} is as defined above and R_{C-6} is -(CH₂)₀₋₆-OH,

(XXII) -(CH₂)₀₋₁-CHR_{C-6}-(CH₂)₀₋₁-R_{C-heteroaryl} where R_{C-heteroaryl} and R_{C-6} is as defined above,

(XXIII) -CH(-R_{C-aryl} or R_{C-heteroaryl})-CO-O(C₁-C₄ alkyl) where R_{C-aryl} and R_{C-heteroaryl} are as defined above,

(XXIV) -CH(-CH₂-OH)-CH(-OH)-micro-NO₂,

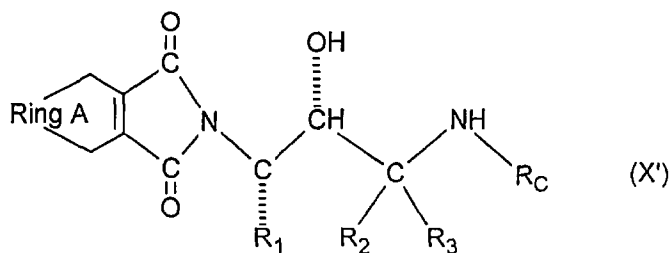
(XXV) (C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-OH,

(XXVII) -CH₂-NH-CH₂-CH(-O-CH₂-CH₃)₂,

(XXVIII) -H,

(XXIX) -(CH₂)₀₋₆-C(=NR_{1-a})(NR_{1-a}R_{1-b}) where R_{1-a} and R_{1-b} are as defined above, and pharmaceutically acceptable salts thereof.

Also disclosed is a substituted amine of the formula (X')



where R₁, R₂, R₃ and R_C are as defined above;

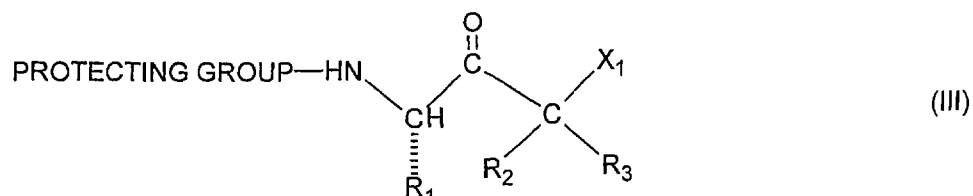
where Ring A is phenyl, 1-naphthyl and 2-naphthyl optionally substituted with one, two or three of the following substituents which can be the same or different and are:

- 5
- (1) C₁-C₆ alkyl,
 - (2) -F, -Cl, -Br, I,
 - (3) -OH,
 - (4) -NO₂,
 - (5) -CO-OH,
 - (6) -C≡N,
 - (7) -CO-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} are as defined above,
 - (8) -CO-(C₃-C₁₂ alkyl),
 - 10 (9) -CO-(C₃-C₆ cycloalkyl),
 - (10) -CO-R_{1-heteroaryl} where R_{1-heteroaryl} is as defined in above,
 - (11) -CO-R_{1-heterocycle} where R_{1-heterocycle} is as defined in above,
 - 15 (12) -CO-R_{N-4} where R_{N-4} is as defined in above,
 - (13) -CO-O-R_{N-5} where R_{N-5} is as defined in above,
 - (14) -SO₂-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} are as defined above,
 - (15) -SO-(C₁-C₈ alkyl),
 - 20 (16) -SO₂-(C₃-C₁₂ alkyl) with the proviso that the alkyl group not be straight chained,
 - (17) -NH-CO-O-R_{N-5} where R_{N-5} is as defined above,
 - (18) -NH-CO-N(C₁-C₃ alkyl)₂,
 - (19) -N-CS-N(C₁-C₃ alkyl)₂,
 - 25 (20) -N(-H or C₁-C₃ alkyl)-CO-R_{N-5} where R_{N-5} is as defined above,
 - (21) -NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} can be the same or different and are as defined above,
 - (22) -R_{N-4} where R_{N-4} is as defined above,
 - 30 (23) -O-CO-(C₁-C₆ alkyl),
 - (24) -O-CO-N(C₁-C₃ alkyl)₂,
 - (25) -O-CS-N(C₁-C₃ alkyl)₂,
 - (26) -O-(C₁-C₆ alkyl),

(27) -O-(C₂-C₅ alkyl)-COOH,(28) -S-(C₁-C₆ alkyl) and pharmaceutically acceptable

salts thereof.

Additionally disclosed is a protected compound of the formula (III)

where R₁, R₂ and R₃ are as defined above;where X₁ is -Cl, -Br, -I, -O-tosylate, -O-mesylate, -O-nosylate;where PROTECTING GROUP is selected from the group consisting of *t*-

butoxycarbonyl, benzyloxycarbonyl, formyl, trityl, acetyl, trichloroacetyl,

10 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-

15 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-methylcyclohexanyloxycarbonyl, 2-

20 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-

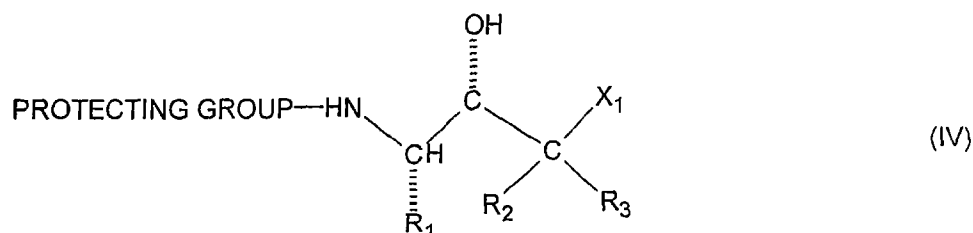
25 propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl,

isobornyloxycarbonyl and 1-piperidyloxycarbonyl, 9-fluorenylmethyl carbonate,

-CH-CH=CH₂ and phenyl-C(=N-)-H.

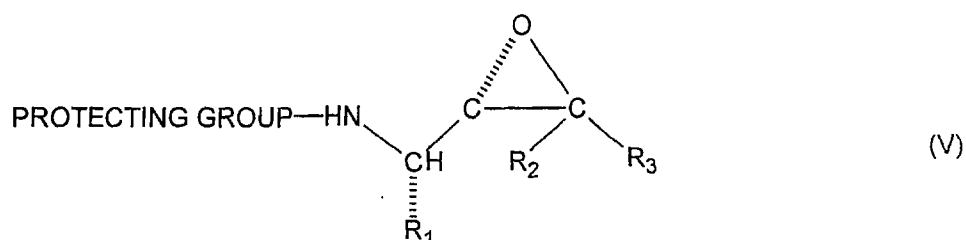
Further disclosed is an alcohol of the formula (IV)

37



where R₁, R₂, R₃, X₁ and PROTECTING GROUP are as defined above.

Additionally disclosed is an epoxide of the formula (V)



5

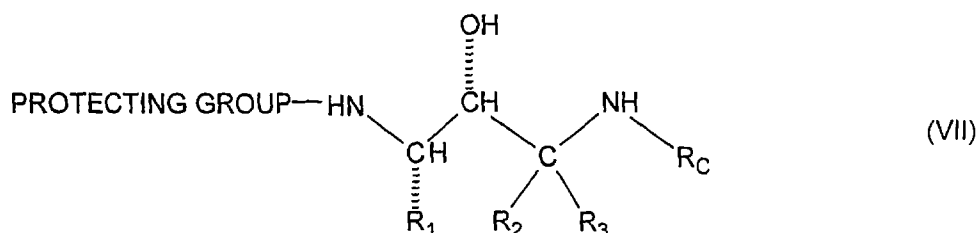
where R₂, R₃ and PROTECTING GROUP are as defined above and where R₁ is:

-CH₂-phenyl where -phenyl is substituted with two -F,

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

10 -(CH₂)_{n1}-R_{1-heterocycle} where R_{1-heterocycle} is as defined above.

Further disclosed is a protected alcohol of the formula (VII)



where R₂, R₃, R_C and PROTECTING GROUP are as defined above, and

15 where R₁ is:

-CH₂-phenyl where -phenyl is substituted with two -F,

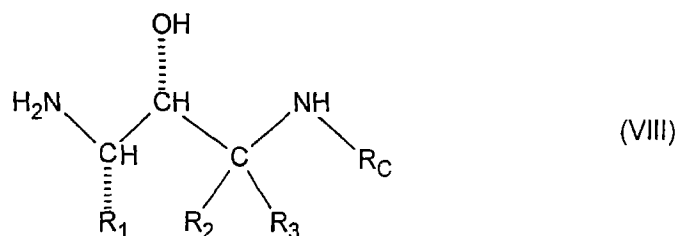
-(CH₂)_{n1}-R_{1-heteroaryl} where R_{1-heteroaryl} is as defined above and

-(CH₂)_{n1}-R_{1-heterocycle} where R_{1-heterocycle} is as defined above and

chemically acceptable salts thereof.

20

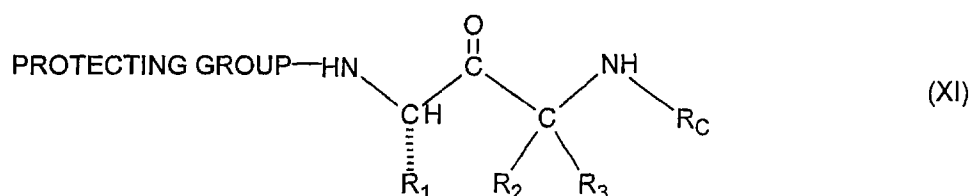
Also disclosed is an amine of the formula (VIII)



where R_2 , R_3 and R_C are as defined above and where R_1 is:

- 5 $-\text{CH}_2\text{-phenyl}$ where -phenyl is substituted with two -F,
 $-(\text{CH}_2)_{n1}\text{-R}_1\text{-heteroaryl}$ where $\text{R}_1\text{-heteroaryl}$ is as defined above and
 $-(\text{CH}_2)_{n1}\text{-R}_1\text{-heterocycle}$ where $\text{R}_1\text{-heterocycle}$ is as defined above and
 chemically acceptable salts thereof.

Disclosed is a protected ketone of formula (XI)



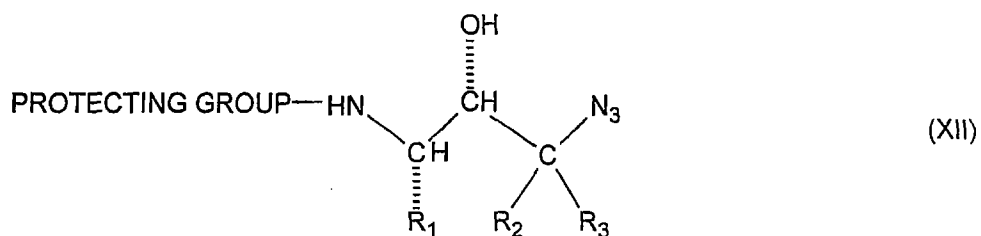
10

where R_2 , R_3 , R_C and PROTECTING GROUP are as defined above and

where R_1 is:

- 15 $-\text{CH}_2\text{-phenyl}$ where -phenyl is substituted with two -F,
 $-(\text{CH}_2)_{n1}\text{-R}_1\text{-heteroaryl}$ where $\text{R}_1\text{-heteroaryl}$ is as defined above and
 $-(\text{CH}_2)_{n1}\text{-R}_1\text{-heterocycle}$ where $\text{R}_1\text{-heterocycle}$ is as defined above.

Also disclosed is a protected azide of formula (XII)

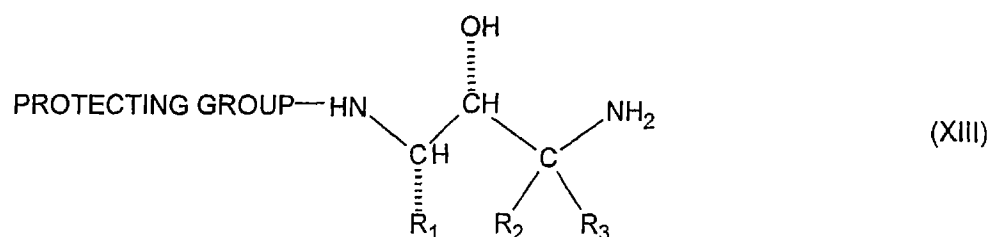


20

where R_2 , R_3 and PROTECTING GROUP are as defined above and where R_1 is:

- $-\text{CH}_2\text{-phenyl}$ where -phenyl is substituted with two -F,
 $-(\text{CH}_2)_{n1}\text{-R}_1\text{-heteroaryl}$ where $\text{R}_1\text{-heteroaryl}$ is as defined above and
 $-(\text{CH}_2)_{n1}\text{-R}_1\text{-heterocycle}$ where $\text{R}_1\text{-heterocycle}$ is as defined above.

Further disclosed is a protected amine of formula (XIII)



5

where R_2 , R_3 and PROTECTING GROUP are as defined above and where R_1 is:

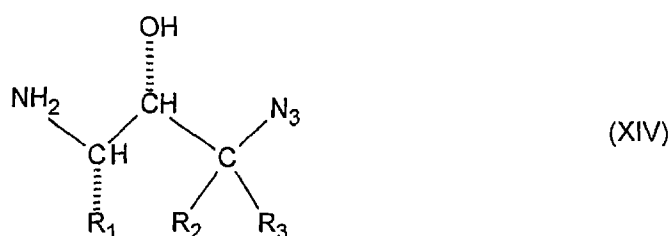
$-\text{CH}_2$ -phenyl where -phenyl is substituted with two -F,

$-(\text{CH}_2)_n$ - R_1 -heteroaryl where R_1 -heteroaryl is as defined above and

$-(\text{CH}_2)_n$ - R_1 -heterocycle where R_1 -heterocycle is as defined above.

10

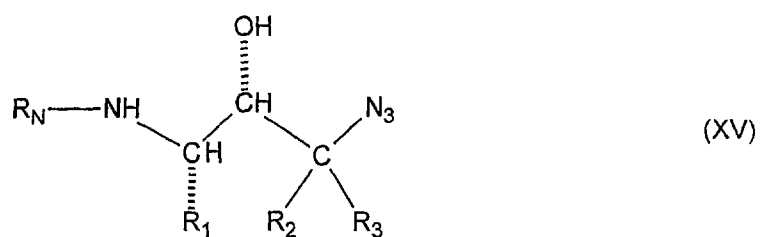
Additionally disclosed is an unprotected azide of formula (XIV)



15

where R_1 , R_2 , R_3 and PROTECTING GROUP are as defined above for the substituted amine (X).

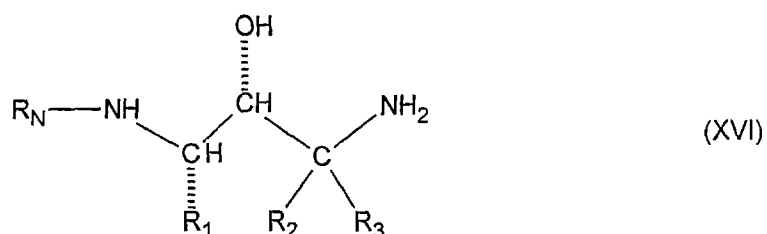
Further disclosed is an azide of formula (XV)



20

where R_1 , R_2 , R_3 and R_N are as defined above for the substituted amine (X).

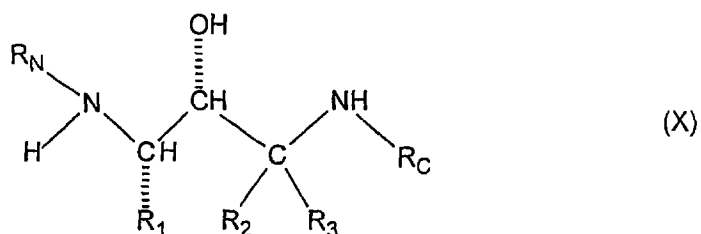
Also disclosed is a free amine of formula (XVI)



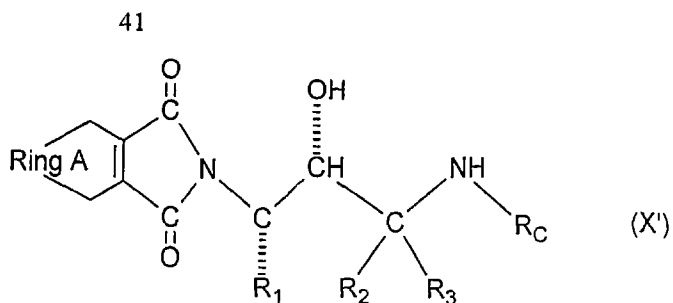
where R_2 , R_3 and R_N are as defined above and where R_1 is:

- (A) $-\text{CH}_2\text{-phenyl}$ where $-\text{phenyl}$ is substituted with two $-\text{F}$,
- (B) $-(\text{CH}_2)_{n1}\text{-}R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above and
- (C) $-(\text{CH}_2)_{n1}\text{-}R_{1\text{-heterocycle}}$ where $R_{1\text{-heterocycle}}$ is as defined above.

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 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 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 amine of formula (X)

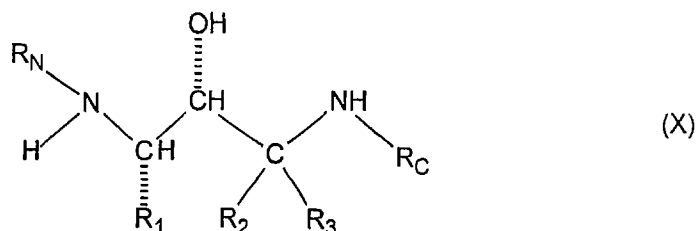


where R_1 , R_2 , R_3 , R_C , and R_N are as defined above for the substituted amine (X), and pharmaceutically acceptable salts thereof, and a substituted amine with R_N cyclized of formula (X')



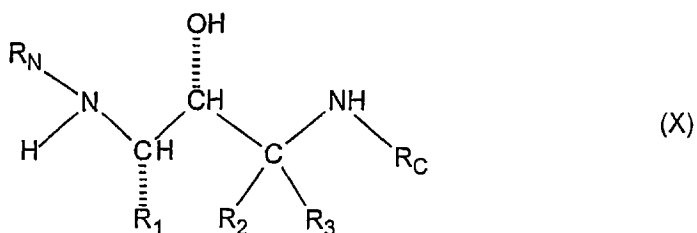
where R_1 , R_2 , R_3 , R_C , and Ring A, are as defined above for the amine (X'), and pharmaceutically acceptable salts thereof.

- 5 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
- 10 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 amine of formula (X)

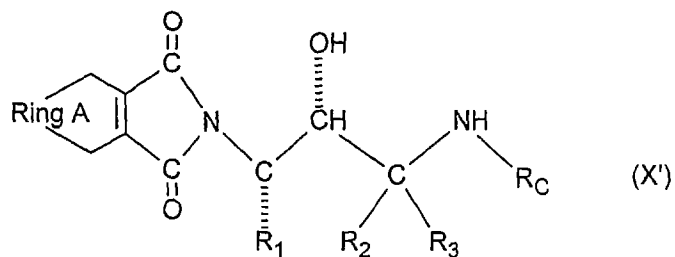


- 15 where R_1 , R_2 , R_3 , R_C , and R_N are as defined above for the substituted amine (X), and pharmaceutically acceptable salts thereof.

Disclosed is a pharmaceutical composition which comprises a substituted amine of formula (X)

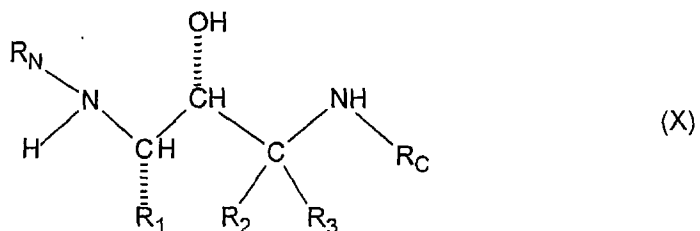


where R_1 , R_2 , R_3 , R_N and R_C are as defined above for the substituted amine (X), or a substituted amine with R_N cyclized of formula (X')

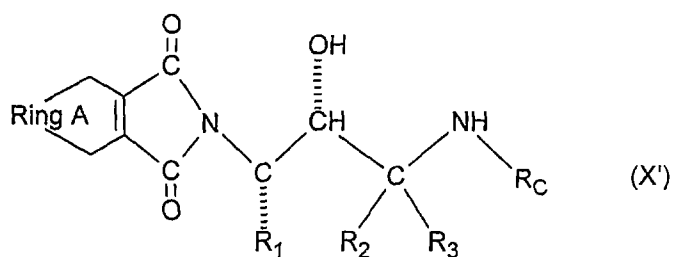


- 5 where R_1 is as defined above for compound (X') and where Ring A is as defined above, and pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable inert carriers.

Disclosed is the use of a substituted amine of formula (X)



- 10 where R_1 , R_2 , R_3 , R_N and R_C are as defined above for the substituted amine (X), or a substituted amine with R_N cyclized of formula (X')



- 15 where R_1 , R_2 , R_3 , R_C , and Ring A, are as defined above for compound (X'), and pharmaceutically acceptable salts 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 preventing or delaying the onset of Alzheimer's
- 20 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 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
5 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 present invention provides compounds, compositions, kits, and methods for inhibiting beta-secretase-mediated cleavage of amyloid precursor protein (APP).
10 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
15 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 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
20 cerebral beta-amyloid angiopathy and preventing its potential consequences such as single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, for treating dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse
25 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.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is the substituted amines (X) that are useful in treating and preventing Alzheimer's disease. The anti-Alzheimer's substituted amines (X) are made by methods well known to those skilled in the art from starting compounds known to those skilled in the art. The process chemistry is well known to those skilled in the art. The most general process to prepare the substituted amines (X) of the present invention is set forth in CHART A. The chemistry is straight forward and in summary involves the steps of N-protecting an amino acid (I) starting material to produce the corresponding protected amino acid (II), reaction of the protected amino acid (II) with diazomethane followed by work-up to add a carbon atom to produce the corresponding protected compound (III), reduction of the protected compound (III) to the corresponding alcohol (IV), formation of the corresponding epoxide (V), opening of the epoxide (V) with a C-terminal amine, R_C-NH_2 (VI) to produce the corresponding protected alcohol (VII) which then has the nitrogen protecting group removed to produce the corresponding amine (VIII), which is then reacted with an amide forming agent of the formula $(R_{N-1}-X_N)_2O$ or $R_{N-1}-X_N-X_2$ or $R_{N-1}-X_N-OH$ (IX) to produce the anti-Alzheimer substituted amine (X). 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 amine end product (X) of the invention would be able to prepare them by known methods from known starting materials without any additional information. The explanation below therefore is not necessary but is deemed helpful to those skilled in the art who desire to make the compounds of the present invention.

The backbone of the compounds of the present invention is a hydroxyethylamine moiety, $-NH-CH(R)-CH(OH)-$. It can be readily prepared by methods disclosed in the literature and known to those skilled in the art. For example, *J. Med. Chem.*, 36, 288-291 (1992), *Tetrahedron Letters*, 28, 5569-5572 (1987), *J. Med. Chem.*, 38, 581-584 (1994) and *Tetrahedron Letters*, 38, 619-620 (1997) all disclose processes to prepare hydroxyethylamine type compounds.

CHART A sets forth a general method used in the present invention to prepare the appropriately substituted amines (X). The anti-Alzheimer substituted

amines (X) of the present invention are prepared by starting with the corresponding amino acid (I). The amino acids (I) are well known to those skilled in the art or can be readily prepared from known compounds by methods well known to those skilled in the art. The substituted amines (X) of the present invention have at least two

5 enantiomeric centers which give four enantiomers. The first of these enantiomeric centers derives from the amino acid starting material (I). 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)-

10 amino acid (I) of the same configuration as that of the substituted amine (X) product. For the amino acids (I), 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 $\equiv$ N, -CF₃, C_1 - C_3 alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C_1 - C_6

15 alkyl, -OC=O NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

(II) -CH₂-S(O)₀₋₂-(C_1 - C_6 alkyl),

(III) -CH₂-CH₂-S(O)₀₋₂-(C_1 - C_6 alkyl),

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

20 substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C $\equiv$ N, -CF₃, C_1 - C_3 alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C_1 - C_6 alkyl,

(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, -

25 OH, -SH, -C $\equiv$ N, -CF₃, C_1 - C_3 alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C_1 - C_6 alkyl,

(VI) -(CH₂)_{n1}-(R_{1-aryl}) where n₁ is zero or one and where R_{1-aryl} is phenyl, 1-naphthyl, 2-naphthyl and indanyl, indenyl, dihydronaphthalyl, tetralinyl optionally substituted with one, two, three, or four of the following substituents on

30 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, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above, -C $\equiv$ N, -CF₃, C_1 - C_3 alkoxy,

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

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

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

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

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

(H) -OH,

(I) -C≡N,

15 (J) C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

(K) -CO-(C₁-C₄ alkyl),

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

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

(N) -SO₂-(C₁-C₄ alkyl),

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

pyridinyl,

25 pyrimidinyl,

quinolinyl,

benzothienyl,

indolyl,

indolinyl,

30 pyridazinyl,

pyrazinyl,

isoindolyl,

isoquinolyl,

	quinazoliny,
	quinoxaliny,
	phthalaziny,
	imidazolyl,
5	isoxazolyl,
	pyrazolyl,
	oxazolyl,
	thiazolyl,
	indoliziny,
10	indazolyl,
	benzothiazolyl,
	benzimidazolyl,
	benzofuranyl,
	furanyl,
15	thienyl,
	pyrrolyl,
	oxadiazolyl,
	thiadiazolyl,
	triazolyl,
20	tetrazolyl,
	oxazolopyridiny,
	imidazopyridiny,
	isothiazolyl,
	naphthyridiny,
25	cinnoliny,
	carbazolyl,
	beta-carboliny,
	isochromanyl,
	chromanyl,
30	tetrahydroisoquinoliny,
	isoindoliny,
	isobenzotetrahydrofuranyl,
	isobenzotetrahydrothienyl,
	isobenzothienyl,

	benzoxazolyl,
	pyridopyridinyl,
	benzotetrahydrofuranyl,
	benzotetrahydrothienyl,
5	purinyl,
	benzodioxolyl,
	triazinyl,
	phenoxazinyl,
	phenothiazinyl,
10	pteridinyl,
	benzothiazolyl,
	imidazopyridinyl,
	imidazothiazolyl,
	dihydrobenzisoxazinyl,
15	benzisoxazinyl,
	benzoxazinyl,
	dihydrobenziso-thiazinyl,
	benzopyranyl,
	benzothiopyranyl,
20	coumarinyl,
	isocoumarinyl,
	chromonyl,
	chromanonyl,
	pyridinyl-N-oxide
25	tetrahydroquinolinyl
	dihydroquinolinyl
	dihydroquinolinonyl
	dihydroisoquinolinonyl
	dihydrocoumarinyl
30	dihydroisocoumarinyl
	isoindolinonyl
	benzodioxanyl
	benzoxazolinonyl
	pyrrolyl N-oxide,

- 5 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,
 10 phthalazinyl N-oxide,
 imidazolyl N-oxide,
 isoxazolyl N-oxide,
 oxazolyl N-oxide,
 thiazolyl N-oxide,
 15 indoliziny N-oxide,
 indazolyl N-oxide,
 benzothiazolyl N-oxide,
 benzimidazolyl N-oxide,
 pyrrolyl N-oxide,
 20 oxadiazolyl N-oxide,
 thiadiazolyl N-oxide,
 triazolyl N-oxide,
 tetrazolyl N-oxide,
 benzothiopyranyl S-oxide,
 25 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:

- 30 (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, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy,

- (2) C₂-C₆ alkenyl with one or two double bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,
- 5 (3) C₂-C₆ alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,
- (4) -F, Cl, -Br and -I,
- 10 (6) -C₁-C₆ alkoxy optionally substituted with one, two, or three of -F,
- (7) -NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} are as defined below,
- (8) -OH,
- 15 (9) -C≡N,
- (10) C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,
- (11) -CO-(C₁-C₄ alkyl),
- 20 (12) -SO₂-NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,
- (13) -CO-NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,
- (14) -SO₂-(C₁-C₄ alkyl), with the proviso that when n₁ is zero R_{1-heteroaryl} is not bonded to the carbon chain by nitrogen,
- (VIII) -(CH₂)_{n1}-(R_{1-heterocycle}) where n₁ is as defined above and
- 25 R_{1-heterocycle} is selected from the group consisting of:
- morpholinyl,
- thiomorpholinyl,
- thiomorpholinyl S-oxide,
- thiomorpholinyl S,S-dioxide,
- 30 piperazinyl,
- homopiperazinyl,
- pyrrolidinyl,
- pyrrolinyl,

- tetrahydropyranyl,
 piperidinyI,
 tetrahydrofuranyl,
 tetrahydrothienyl,
 5 homopiperidinyI,
 homomorpholinyl,
 homothiomorpholinyl,
 homothiomorpholinyl S,S-dioxide, and
 oxazolidinonyl,
 10 dihydropyrazolyl
 dihydropyrrolyl
 dihydropyrazinyl
 dihydropyridinyl
 dihydropyrimidinyl
 15 dihydrofuryl
 dihydropyranyl
 tetrahydrothienyl S-oxide
 tetrahydrothienyl S,S-dioxide
 homothiomorpholinyl S-oxide
- 20 where the R_{1-heterocycle} group is bonded by any atom of the parent R_{1-heterocycle} group substituted by hydrogen such that the new bond to the R_{1-heterocycle} group replaces the hydrogen atom and its bond, where heterocycle is optionally substituted with one, two, three, or four of:
- (1) C₁-C₆ alkyl optionally substituted with one, two or
 25 three substituents selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above, -C≡N, -CF₃, C₁-C₃ alkoxy,
- (2) C₂-C₆ alkenyl with one or two double bonds,
 optionally substituted with one, two or three substituents selected from the group
 30 consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,
- (3) C₂-C₆ alkynyl with one or two triple bonds,
 optionally substituted with one, two or three substituents selected from the group

consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

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

(5) C₁-C₆ alkoxy,

5 (6) -C₁-C₆ 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,

10 (9) -C≡N,

(10) C₃-C₇ cycloalkyl, optionally substituted with one,

two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

(11) -CO-(C₁-C₄ alkyl),

15 (12) -SO₂-NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

(13) -CO-NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined

above,

(14) -SO₂-(C₁-C₄ alkyl),

20 (15) =O, with the proviso that when n₁ is zero

R_{1-heterocycle} is not bonded to the carbon chain by nitrogen. It is preferred that R₁ be -(CH₂)₀₋₁-(R_{1-aryl}) or -(CH₂)_{n1}-(R_{1-heteroaryl}). It is more preferred that R₁ is -(CH₂)-(R_{1-aryl}) or -(CH₂)-(R_{1-heteroaryl}). It is further preferred that R₁ is -(CH₂)-(R_{1-aryl}) where R_{1-aryl} is phenyl. It is even more preferred that R₁ is -(CH₂)-(R_{1-aryl}) where R_{1-aryl} is phenyl substituted with two -F. It is additionally preferred that the -F substitution is 3,5-difluorobenzyl.

When R₁ is R_{1-heteroaryl} or R_{1-heterocycle} the bond from the R_{1-heteroaryl} or R_{1-heterocycle} group to the -(CH₂)_{n1}- group can be from any ring atom which has an available valence provided that such bond does not result in formation of a charged species or unstable valence. This means that the R_{1-heteroaryl} or R_{1-heterocycle} group is

30 bonded to

$-(CH_2)_{n1}$ -by any ring atom of the parent $R_{1\text{-heteroaryl}}$ or $R_{1\text{-heterocycle}}$ group which was substituted by hydrogen such that the new bond to the $R_{1\text{-heteroaryl}}$ or $R_{1\text{-heterocycle}}$ group replaces the hydrogen atom and its bond.

The first step of the process is to protect the free amino group of the (S)-
5 amino acid (I) with an amino protecting group to produce the (S)-protected amino acid (II) 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,
10 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 (I) 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
15 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*-
20 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-
25 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,
30 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-(decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl and 1-piperidyloxycarbonyl, 9-fluorenylmethyl carbonate, -CH-CH=CH₂ and phenyl-C(=N)-H. It is preferred that the protecting group be *t*-butoxycarbonyl (BOC) and benzyloxycarbonyl (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.

10 The (S)-protected amino acid (II) is transformed to the corresponding (S)-protected compound (III) by two different methods depending on the nature of R₂ and R₃.

R₂ and R₃ are independently selected from the group consisting of:

(I)-H,

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

(III) -(CH₂)₀₋₄-R₂₋₁ where R₂₋₁ is R_{1-aryl} or R_{1-heteroaryl} where R_{1-aryl} and R_{1-heteroaryl} are as defined above;

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

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

(VI) -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl,

25 and where R₂ and R₃ are taken together with the carbon to which they are attached to form a carbocycle of three, four, five, six, and seven carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of -O-, -S-, -SO₂-, -NR_{N-2}-, where R_{N-2} is as defined below. It is preferred that R₂ and R₃ both be -H. If R₂ and R₃ are not the same, an additional enantiomeric center is added to the molecule. If it is desired that both R₂ and R₃ are -H, then the (S)-protected amino acid (II) is reacted with diazomethane, as is well known to those skilled in the art, followed by reaction with a compound of the formula H-X₁ to produce the (S)-protected compound (III). X₁ includes -Cl, -Br, -I, -O-tosylate, -O-mesylate, -O-nosylate.; it is preferred that -X₁ be -Br or -Cl. Suitable reaction conditions include running the reaction in inert solvents, such as but not limited to ether, tetrahydrofuran and the like. The reactions from the (S)-protected amino acid (II) to the (S)-protected compound (III) are carried out for a period of time between 10 minutes and 1 day and at temperatures ranging from -78 degrees to 20-25 degrees

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C. It is preferred to conduct the reactions for a period of time between 1-4 hours and at temperatures between -30 degrees to -10 degrees C. This process adds one methylene group.

Alternatively, the (S)-protected compounds of formula (III) can be prepared
5 by first converting the (S)-protected amino acid (II) to a corresponding methyl or ethyl ester, according to methods well established in the art, followed by treatment with a reagent of formula $X_1-C(R_2)(R_3)-X_1$ and a strong metal base. The base serves to affect a halogen-metal exchange, where the $-X_1$ undergoing exchange is a halogen selected from chlorine, bromine or iodine. The nucleophilic addition to the ester
10 derivative gives directly the (S)-protected compound (III). Suitable bases include, but are not limited to the alkylolithiums including, for example, *sec*-butyllithium, *n*-butyllithium, and *t*-butyllithium. The reactions are preferably conducted at low temperature, such as -78 degrees C. Suitable reaction conditions include running the reaction in inert solvents, such as but not limited to, ether, tetrahydrofuran and the
15 like. Where R_2 and R_3 are both hydrogen, then examples of $X_1-C(R_2)(R_3)-X_1$ include dibromomethane, diiodomethane, chloriodomethane, bromiodomethane and bromochloromethane. One skilled in the art knows the preferred conditions required to conduct this reaction. Furthermore, if R_2 and/or R_3 are not -H, then by the addition of $-C(R_2)(R_3)-X_1$ to esters of the (S)-protected amino acid (II) to
20 produce the (S)-protected compound (III), an additional chiral center will be incorporated into the product, provided that R_2 and R_3 are not the same.

The (S)-protected compound (III) is then reduced by means well known to those skilled in the art for reduction of a ketone to the corresponding secondary alcohol affording the corresponding alcohol (IV). The means and reaction
25 conditions for reducing the (S)-protected compound (III) to the corresponding alcohol (IV) include, for example, sodium borohydride, lithium borohydride, borane, diisobutylaluminum hydride, and lithium aluminium hydride. Sodium borohydride is the preferred reducing agent. The reductions are carried out for a period of time between 1 hour and 3 days at temperatures ranging from -78 degrees C to elevated
30 temperature up to the reflux point of the solvent employed. It is preferred to conduct the reduction between -78 degrees C and 0 degrees C. If borane is used, it may be employed as a complex, for example, borane-methyl sulfide complex, borane-piperidine complex, or borane-tetrahydrofuran complex. The preferred combination of reducing agents and reaction conditions needed are known to those skilled in the
35 art, see for example, Larock, R.C. in Comprehensive Organic Transformations,

VCH Publishers, 1989. The reduction of the (S)-protected compound (III) to the corresponding alcohol (IV) produces the second chiral center (third chiral center if R_2 and R_3 are not the same). The reduction of the (S)-protected compound (III) produces a mixture of enantiomers at the second center, (S, R/S)-alcohol (IV). This
 5 enantiomeric mixture is then separated by means known to those skilled in the art such as selective low-temperature recrystallization or chromatographic separation, for example by HPLC, employing commercially available chiral columns. The enantiomer that is used in the remainder of the process of CHART A is the (S,S)-alcohol (IV) since this enantiomer will give the desired biologically active anti-
 10 Alzheimer (S,R)-substituted amine (X).

The (S, S)-alcohol (IV) is transformed to the corresponding epoxide (V) by means known to those skilled in the art. The stereochemistry of the (S)-(IV) center is maintained in forming the epoxide (V). A preferred means is by reaction with base, for example, but not limited to, hydroxide ion generated from sodium
 15 hydroxide, potassium hydroxide, lithium hydroxide and the like. Reaction conditions include the use of C_1 - C_6 alcohol solvents; ethanol is preferred. A common co-solvent, such as for example, ethyl acetate may also be employed. Reactions are conducted at temperatures ranging from -45 degrees C up to the reflux temperature of the alcohol employed; preferred temperature ranges are between -20
 20 degrees C and 20-25 degrees C.

The epoxide (V) is then reacted with the appropriately substituted C-terminal amine, R_C -NH₂ (VI) by means known to those skilled in the art that opens the epoxide to produce the desired corresponding enantiomerically pure (S,R)-protected alcohol (VII). The substituted C-terminal amines, R_C -NH₂ (VI) of this invention are
 25 commercially available or are known to those skilled in the art and can be readily prepared from known compounds. R_C includes:

(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 $\equiv$ N, -CF₃, C_1 - C_6 alkoxy, -O-phenyl, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as
 30 defined above, -OC=O NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above, -S(=O)₀₋₂ R_{1-a} where R_{1-a} is as defined above, -NR_{1-a}C=O NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above, -C=O NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above, and -S(=O)₂ NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are as defined above,

(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, $-C\equiv N$, $-CF_3$, C_1-C_6 alkoxy, -O-phenyl, -CO-OH, -CO-O- (C_1-C_4) alkyl, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

5 (III) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}$ where R_{C-x} and R_{C-y} are
 -H,
 C_1-C_4 alkyl optionally substituted with one or two -OH,
 C_1-C_4 alkoxy optionally substituted with one, two, or three of
 -F,
 10 $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl,
 C_2-C_6 alkenyl containing one or two double bonds,
 C_2-C_6 alkynyl containing one or two triple bonds,
 phenyl-,

and where R_{C-x} and R_{C-y} are taken together with the carbon to which they are
 15 attached to form a carbocycle of three, four, five, six and seven carbon atoms,
 optionally where one carbon atom is replaced by a heteroatom selected from the
 group consisting of

-O-, -S-, $-SO_2$ -, $-NR_{N-2}$ - and R_{C-aryl} is defined as R_{N-aryl} is defined below;

(IV) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}$ where $R_{C-heteroaryl}$ is defined as R_{N-}
 20 $heteroaryl$ is defined above and R_{C-x} and R_{C-y} are as defined above,

(V) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}-R_{C-aryl}$ where R_{C-aryl} , R_{C-x} and R_{C-y} are as
 defined above,

(VI) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}-R_{C-heteroaryl}$ where R_{C-aryl} , $R_{C-heteroaryl}$, R_{C-x}
 and R_{C-y} are as defined above,

25 (VII) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}-R_{C-aryl}$ where $R_{C-heteroaryl}$, R_{C-aryl} , R_{C-x}
 and R_{C-y} are as defined above,

(VIII) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}-R_{C-heteroaryl}$ where $R_{C-heteroaryl}$, R_{C-x} and
 R_{C-y} are as defined above,

(IX) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}-R_{C-heterocycle}$ where R_{C-aryl} , R_{C-x} and R_{C-y} are
 30 as defined above, and $R_{C-heterocycle}$ is defined as $R_{N-heterocycle}$, is defined below,

(X) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}-R_{C-heterocycle}$ where $R_{C-heteroaryl}$, R_{C-}
 $heterocycle$, R_{C-x} and R_{C-y} are as defined above,

(XI) $-(\text{CR}_{\text{C-x}}\text{R}_{\text{C-y}})_{0-4}-\text{R}_{\text{C-heterocycle}}-\text{R}_{\text{C-aryl}}$ where $\text{R}_{\text{C-heterocycle}}$, $\text{R}_{\text{C-aryl}}$, $\text{R}_{\text{C-x}}$ and $\text{R}_{\text{C-y}}$ are as defined above,

(XII) $-(\text{CR}_{\text{C-x}}\text{R}_{\text{C-y}})_{0-4}-\text{R}_{\text{C-heterocycle}}-\text{R}_{\text{C-heteroaryl}}$ where $\text{R}_{\text{C-heterocycle}}$, $\text{R}_{\text{C-heteroaryl}}$, $\text{R}_{\text{C-x}}$ and $\text{R}_{\text{C-y}}$ are as defined above,

5 (XIII) $-(\text{CR}_{\text{C-x}}\text{R}_{\text{C-y}})_{0-4}-\text{R}_{\text{C-heterocycle}}-\text{R}_{\text{C-heterocycle}}$ where $\text{R}_{\text{C-heterocycle}}$, $\text{R}_{\text{C-x}}$ and $\text{R}_{\text{C-y}}$ are as defined above,

(XIV) $-(\text{CR}_{\text{C-x}}\text{R}_{\text{C-y}})_{0-4}-\text{R}_{\text{C-heterocycle}}$ where $\text{R}_{\text{C-heterocycle}}$ is defined as $\text{R}_{1\text{-heterocycle}}$ is defined above, and $\text{R}_{\text{C-x}}$ and $\text{R}_{\text{C-y}}$ are as defined above,

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

(A) -H,

(B) $\text{C}_1\text{-C}_6$ alkyl, optionally substituted with one, two or three substituents selected from the group consisting of $\text{C}_1\text{-C}_3$ alkyl, -F, -Cl, -Br, -I, -OH, -SH, $\text{-C}\equiv\text{N}$, -CF_3 , $\text{C}_1\text{-C}_6$ alkoxy, -O-phenyl, $\text{-NR}_{1\text{-a}}\text{R}_{1\text{-b}}$ where $\text{R}_{1\text{-a}}$ and $\text{R}_{1\text{-b}}$ are as defined above,

(C) $\text{C}_2\text{-C}_6$ alkenyl with one or two double bonds, optionally substituted with one, two or three substituents selected from the group consisting of $\text{C}_1\text{-C}_3$ alkyl, -F, -Cl, -Br, -I, -OH, -SH, $\text{-C}\equiv\text{N}$, -CF_3 , $\text{C}_1\text{-C}_6$ alkoxy, -O-phenyl, $\text{-NR}_{1\text{-a}}\text{R}_{1\text{-b}}$ where $\text{R}_{1\text{-a}}$ and $\text{R}_{1\text{-b}}$ are as defined above,

20 (D) $\text{C}_2\text{-C}_6$ alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of $\text{C}_1\text{-C}_3$ alkyl, -F, -Cl, -Br, -I, -OH, -SH, $\text{-C}\equiv\text{N}$, -CF_3 , $\text{C}_1\text{-C}_6$ alkoxy, -O-phenyl, $\text{-NR}_{1\text{-a}}\text{R}_{1\text{-b}}$ where $\text{R}_{1\text{-a}}$ and $\text{R}_{1\text{-b}}$ are as defined above,

(E) $-(\text{CH}_2)_{1-2}-\text{S(O)}_{0-2}-(\text{C}_1\text{-C}_6 \text{ alkyl})$,

25 (F) $-(\text{CH}_2)_{0-4}-\text{C}_3\text{-C}_7 \text{ cycloalkyl}$, optionally substituted with one, two or three substituents selected from the group consisting of $\text{C}_1\text{-C}_3$ alkyl, -F, -Cl, -Br, -I, -OH, -SH, $\text{-C}\equiv\text{N}$, -CF_3 , $\text{C}_1\text{-C}_6$ alkoxy, -O-phenyl, $\text{-NR}_{1\text{-a}}\text{R}_{1\text{-b}}$ where $\text{R}_{1\text{-a}}$ and $\text{R}_{1\text{-b}}$ are as defined above,

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

(H) $-(\text{C}_1\text{-C}_4 \text{ alkyl})-\text{R}_{\text{C-heteroaryl}}$ where $\text{R}_{\text{C-heteroaryl}}$ is as defined above,

- above,
- (I) $-(C_1-C_4 \text{ alkyl})-R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is as defined above,
- (J) $-R_{C\text{-heteroaryl}}$ where $R_{C\text{-heteroaryl}}$ is as defined above,
- (K) $-R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is as defined above,
- 5 (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, and where $R_{C'\text{-aryl}}$ is defined above,
- (N) $-(CH_2)_{1-4}-R_{C-4}-(CH_2)_{0-4}-R_{C\text{-heteroaryl}}$ where R_{C-4} and $R_{C\text{-heteroaryl}}$ are as defined above,
- (O) $-R_{C'\text{-aryl}}$ where $R_{C'\text{-aryl}}$ is as defined above,
- 10 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, $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_6 alkoxy, $-O$ -phenyl, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,
- 15 (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, $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_6 alkoxy, $-O$ -phenyl, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,
- 20 (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, $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_6 alkoxy, $-O$ -phenyl, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,
- (E) $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl, optionally substituted with
- 25 one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_6 alkoxy, $-O$ -phenyl, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,
- (F) $-R_{C'\text{-aryl}}$ where $R_{C'\text{-aryl}}$ is as defined above,
- 30 (G) $-R_{C\text{-heteroaryl}}$ where $R_{C\text{-heteroaryl}}$ is as defined above,
- (H) $-R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is as defined above,
- (I) $-(C_1-C_4 \text{ alkyl})-R_{C'\text{-aryl}}$ where $R_{C'\text{-aryl}}$ is as defined above,

(J) $-(C_1-C_4 \text{ alkyl})-R_{C\text{-heteroaryl}}$ where $R_{C\text{-heteroaryl}}$ is as defined

above,

(K) $-(C_1-C_4 \text{ alkyl})-R_{C\text{-heterocycle}}$ where $R_{C\text{-heterocycle}}$ is as defined

above,

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

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

10 (XVIII) $-\text{CH}(R_{C\text{-aryl}})(R_{C\text{-heteroaryl}})$ where $R_{C\text{-aryl}}$ and $R_{C\text{-heteroaryl}}$ are as defined above,

(XIX) $-\text{cyclopentyl}$, $-\text{cyclohexyl}$, or $-\text{cycloheptyl}$ ring fused to $R_{C\text{-aryl}}$ or $R_{C\text{-heteroaryl}}$ or $R_{C\text{-heterocycle}}$ where $R_{C\text{-aryl}}$ or $R_{C\text{-heteroaryl}}$ or $R_{C\text{-heterocycle}}$ are as defined above where one carbon of cyclopentyl, cyclohexyl, or $-\text{cycloheptyl}$ is optionally replaced with NH , NR_{N-5} , O , $\text{S}(=\text{O})_{0-2}$, and where cyclopentyl, cyclohexyl, or $-\text{cycloheptyl}$ can be optionally substituted with one or two $-C_1-C_3$ alkyl, $-\text{F}$, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_6 alkoxy, $=\text{O}$, $-\text{NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

(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, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_6 alkoxy, $-\text{O-phenyl}$, $-\text{NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

(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, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_6 alkoxy, $-\text{O-phenyl}$, $-\text{NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

(XXI) $-(\text{CH}_2)_{0-1}-\text{CHR}_{C-6}-(\text{CH}_2)_{0-1}-R_{C\text{-aryl}}$ where $R_{C\text{-aryl}}$ is as defined above and R_{C-6} is $-(\text{CH}_2)_{0-6}-\text{OH}$,

(XXII) $-(\text{CH}_2)_{0-1}-\text{CHR}_{C-6}-(\text{CH}_2)_{0-1}-R_{C\text{-heteroaryl}}$ where $R_{C\text{-heteroaryl}}$ and R_{C-6} is as defined above,

30 (XXIII) $-\text{CH}(-R_{C\text{-aryl}} \text{ or } R_{C\text{-heteroaryl}})-\text{CO}-\text{O}(C_1-C_4 \text{ alkyl})$ where $R_{C\text{-aryl}}$ and $R_{C\text{-heteroaryl}}$ are as defined above,

(XXIV) $-\text{CH}(-\text{CH}_2-\text{OH})-\text{CH}(-\text{OH})-\text{phenyl}-\text{NO}_2$,

(XXV) $(C_1-C_6 \text{ alkyl})-\text{O}-(C_1-C_6 \text{ alkyl})-\text{OH}$,

(XXVII) $-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}(-\text{O}-\text{CH}_2-\text{CH}_3)_2$,

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

(XXIX) $-(\text{CH}_2)_{0-6}-\text{C}(=\text{NR}_{1-a})(\text{NR}_{1-a}\text{R}_{1-b})$ where R_{1-a} and R_{1-b} are as defined above.

5 It is preferred that R_C is:

$-\text{C}_1-\text{C}_8$ alkyl,

$-(\text{CH}_2)_{0-3}-(\text{C}_3-\text{C}_7)$ cycloalkyl,

$-(\text{CR}_{C-x}\text{R}_{C-y})_{0-4}-\text{R}_{C-\text{aryl}}$,

$-(\text{CR}_{C-x}\text{R}_{C-y})_{0-4}-\text{R}_{C-\text{heteroaryl}}$,

10 $-(\text{CR}_{C-x}\text{R}_{C-y})_{0-4}-\text{R}_{C-\text{heterocycle}}$,

-cyclopentyl or -cyclohexyl ring fused to $\text{R}_{C-\text{aryl}}$ or $\text{R}_{C-\text{heteroaryl}}$ or

$\text{R}_{C-\text{heterocycle}}$.

It is more preferred that R_C is:

$-(\text{CH}_2)_{0-3}-(\text{C}_3-\text{C}_7)$ cycloalkyl,

15 $-(\text{CR}_{C-x}\text{R}_{C-y})_{0-4}-\text{R}_{C-\text{aryl}}$,

$-(\text{CR}_{C-x}\text{R}_{C-y})_{0-4}-\text{R}_{C-\text{heteroaryl}}$,

$-(\text{CR}_{C-x}\text{R}_{C-y})_{0-4}-\text{R}_{C-\text{heterocycle}}$,

-cyclopentyl or -cyclohexyl ring fused to a $\text{R}_{C-\text{aryl}}$ or $\text{R}_{C-\text{heteroaryl}}$ or

$\text{R}_{C-\text{heterocycle}}$.

20 It is even more preferred that R_C is:

$-(\text{CR}_{C-x}\text{R}_{C-y})_{0-4}-\text{R}_{C-\text{aryl}}$,

$-(\text{CR}_{C-x}\text{R}_{C-y})_{0-4}-\text{R}_{C-\text{heteroaryl}}$,

-cyclopentyl or -cyclohexyl ring fused to a $\text{R}_{C-\text{aryl}}$ or $\text{R}_{C-\text{heteroaryl}}$ or

$\text{R}_{C-\text{heterocycle}}$.

25 It is still more preferred that R_C is selected from the group consisting of:

$-(\text{CR}_{C-x}\text{R}_{C-y})_{0-4}-\text{R}_{C-\text{aryl}}$ where $\text{R}_{C-\text{aryl}}$ is phenyl,

$-(\text{CR}_{C-x}\text{R}_{C-y})_{0-4}-\text{R}_{C-\text{heteroaryl}}$,

-cyclopentyl or -cyclohexyl ring fused to a $\text{R}_{C-\text{aryl}}$ or $\text{R}_{C-\text{heteroaryl}}$ or R_{C-}

heterocycle. Further, it is preferred that when R_C is phenyl, it is substituted in the 3-

30 position or 3,5-positions.

Suitable reaction conditions for opening the epoxide (V) include running the reaction in a wide range of common and inert solvents. C_1-C_6 alcohol solvents are preferred and isopropyl alcohol most preferred. The reactions can be run at

temperatures ranging from 20-25 degrees C up to the reflux temperature of the alcohol employed. The preferred temperature range for conducting the reaction is between 50 degrees C up to the reflux temperature of the alcohol employed. When the substituted C-terminal amine (VI) is a 1-amino-3,5-cis-dimethyl cyclohexyldicarboxylate it is preferably prepared as follows. To dimethyl-5-aminoisophthalate in acetic acid and methanol, is added rhodium in alumina in a high-pressure bottle. The bottle is saturated with hydrogen at 55 psi and shaken for one week of time. The mixture is then filtered through a layer of diatomaceous earth and rinsed with methanol three times, the solvents are removed under reduced pressure (with heat) to give a concentrate. The concentrate is triturated with ether and filtered again to give the desired C-terminal amine (VI). When the substituted C-terminal amine (VI) is 1-amino-3,5-cis-dimethoxy cyclohexane it is prepared by following the general procedure above and making non-critical variations but starting with 3,5-dimethoxyaniline. When the substituted C-terminal amine (VI) is an aminomethyl group where the substituent on the methyl group is an aryl group, for example $\text{NH}_2\text{-CH}_2\text{-R}_{\text{C-aryl}}$, and $\text{NH}_2\text{-CH}_2\text{-R}_{\text{C-aryl}}$ is not commercially available it is preferably prepared as follows. A suitable starting material is the (appropriately substituted) aralkyl compound. The first step is bromination of the alkyl substituent via methods known to those skilled in the art, see for example R.C. Larock in Comprehensive Organic Transformations, VCH Publishers, 1989, p. 313. Next the alkyl halide is reacted with azide to produce the aryl-(alkyl)-azide. Last the azide is reduced to the corresponding amine by hydrogen/catalyst to give the C-terminal amine (VI) of formula $\text{NH}_2\text{-CH}_2\text{-R}_{\text{C-aryl}}$. The suitably functionalized C-terminal amines (VI) may readily be prepared by one skilled in the art via known methods in the literature, making non-significant modifications. Select literature references include 1) Calderwood, *et al.*, *Tet. Lett.*, 1997, 38, 1241, 2) Ciganek, *J. Org. Chem.*, 1992, 57, 4521, 3) Thurkauf, *et al.*, *J. Med. Chem.*, 1990, 33, 1452, 4) Werner, *et al.*, *Org. Syn., Coll. Vol. 5*, 273, 5) *J. Med. Chem.*, 1999, 42, 4193, 6) *Chem. Rev.* 1995, 95, 2457, 7) *J. Am. Chem. Soc.*, 1986, 3150, 8) Felman *et al.*, *J. Med. Chem.*, 1992, 35, 1183, 9) *J. Am. Chem. Soc.* 1970, 92, 3700, 10) *J. Med. Chem.*, 1997, 40, 2323.

CHART B discloses an alternative process for production of the enantiomerically pure (S,R)-protected alcohol (VII) from the (S)-protected compound (III). In the alternative process, the (S)-protected compound (III) is first reacted with the appropriately substituted C-terminal amine $\text{R}_{\text{C}}\text{-NH}_2$ (VI) using the

preferred conditions described above to produce the corresponding (S)-protected ketone (XI) which is then reduced using the preferred conditions described above to produce the corresponding (S,R)-protected alcohol (VII).

CHART C discloses another alternative process for production of
5 enantiomerically pure (S,R)-protected alcohol (VII) but this time from the epoxide (V). In the process of CHART C, the epoxide (V) is reacted with azide to produce the corresponding enantiomerically pure (S,R)-protected azide (XII). Conditions to conduct the azide mediated epoxide opening are known to those skilled in the art, see for example, J. March, Advanced Organic Chemistry, 3rd Edition, John Wiley &
10 Sons Publishers, 1985, p. 380. Next, the (S,R)-protected azide (XII) is reduced to the corresponding protected amine (XIII) by methods known to those skilled in the art. Preferred reducing conditions to reduce the (S,R)-protected azide (XII) in the presence of a *t*-butoxycarbonyl N-protecting group include catalytic hydrogenation, the conditions for which are known to those skilled in the art. Alternative reducing
15 conditions which may be used to avoid N-deprotection with protecting groups other than *t*-butoxycarbonyl are known to those skilled in the art, see for example, R.C. Larock in Comprehensive Organic Transformations, VCH Publishers, 1989, p. 409.

The (S,R)-protected alcohol (VII) is deprotected to the corresponding (S,R)-amine (VIII) by means known to those skilled in the art for removal of amine
20 protecting group. 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 (VII) in a trifluoroacetic
25 acid/dichloromethane mixture. When complete, the solvents are removed under reduced pressure to give the corresponding (S,R)-amine (as the corresponding salt.

Typical chemically suitable salts include trifluoroacetate, and the anion of mineral acids such as chloride, sulfate, phosphate; preferred is trifluoroacetate and chloride.

The (S,R)-amine (VIII) is then reacted with an appropriately substituted amide forming agent (IX) such as anhydride, acyl halide, or acid of the formula
 5 $(R_{N-1}-X_N)_2O$ or $R_{N-1}-X_N-X_2$ or $R_{N-1}-X_N-OH$ (IX) by nitrogen-acylation means known to those skilled in the art to produce the corresponding (S,R)-substituted amine (X). Nitrogen acylation conditions for reaction of the (S,R)-amine (VIII) with an amide forming agent (IX) to produce the corresponding (S,R)-substituted amine (X) are known to those skilled in the art and can be found in R.C. Larock in
 10 Comprehensive Organic Transformations, VCH Publishers, 1989, p. 981, 979, and 972. R_N includes:

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

(A) $-CO-$,

(B) $-SO_2-$,

15 (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,

(E) a single bond;

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

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

25 (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, $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

(2) $-OH$,

30 (3) $-NO_2$,

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

(5) $-CO-OH$,

(6) $-C\equiv N$,

(7) $-(\text{CH}_2)_{0-4}-\text{CO}-\text{NR}_{\text{N}-2}\text{R}_{\text{N}-3}$ where $\text{R}_{\text{N}-2}$ and $\text{R}_{\text{N}-3}$ are the same or different and are selected from the group consisting of:

- (a) -H,
- (b) $-\text{C}_1-\text{C}_6$ alkyl optionally substituted with one substituent selected from the group consisting of:
 - (i) -OH,
 - (ii) $-\text{NH}_2$,
 - (c) $-\text{C}_1-\text{C}_6$ alkyl optionally substituted with one, two or three -F, -Cl, -Br, -I,
 - (d) $-\text{C}_3-\text{C}_7$ cycloalkyl,
 - (e) $-(\text{C}_1-\text{C}_2 \text{ alkyl})-(\text{C}_3-\text{C}_7 \text{ cycloalkyl})$,
 - (f) $-(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{O}-(\text{C}_1-\text{C}_3 \text{ alkyl})$,
 - (g) $-\text{C}_2-\text{C}_6$ alkenyl with one or two double bonds,
 - (h) $-\text{C}_2-\text{C}_6$ alkynyl with one or two triple bonds,
 - (i) $-\text{C}_1-\text{C}_6$ alkyl chain with one double bond and one triple bond,
 - (j) $-\text{R}_{1-\text{aryl}}$ where $\text{R}_{1-\text{aryl}}$ is as defined above,
 - (k) $-\text{R}_{1-\text{heteroaryl}}$ where $\text{R}_{1-\text{heteroaryl}}$ is as defined above,
- (8) $-(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_1-\text{C}_{12} \text{ alkyl})$,
- (9) $-(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_2-\text{C}_{12} \text{ alkenyl with one, two or three double bonds})$,
- (10) $-(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_2-\text{C}_{12} \text{ alkynyl with one, two or three triple bonds})$,
- (11) $-(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_3-\text{C}_7 \text{ cycloalkyl})$,
- (12) $-(\text{CH}_2)_{0-4}-\text{CO}-\text{R}_{1-\text{aryl}}$ where $\text{R}_{1-\text{aryl}}$ is as defined above,
- (13) $-(\text{CH}_2)_{0-4}-\text{CO}-\text{R}_{1-\text{heteroaryl}}$ where $\text{R}_{1-\text{heteroaryl}}$ is as defined above,
- (14) $-(\text{CH}_2)_{0-4}-\text{CO}-\text{R}_{1-\text{heterocycle}}$ where $\text{R}_{1-\text{heterocycle}}$ is as defined above,

(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, homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl where each group is optionally substituted with one, two, three, or four of C_1-C_6 alkyl,

(16) $-(CH_2)_{0-4}-CO-O-R_{N-5}$ where R_{N-5} is selected from the group consisting of:

(a) C_1-C_6 alkyl,

(b) $-(CH_2)_{0-2}-(R_{1-aryl})$ where R_{1-aryl} is as defined above,

(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,

(f) $-(CH_2)_{0-2}-(R_{1-heteroaryl})$ where $R_{1-heteroaryl}$ is as defined above,

(17) $-(CH_2)_{0-4}-SO_2-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are as defined above,

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

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

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

(21) $-(CH_2)_{0-4}-N(H \text{ or } R_{N-5})-CO-O-R_{N-5}$ where R_{N-5} can be the same or different and is as defined above,

(22) $-(CH_2)_{0-4}-N(H \text{ or } R_{N-5})-CO-N(R_{N-5})_2$, where R_{N-5} can be the same or different and is as defined above,

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

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

(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 and are as defined above,

(26) $-(CH_2)_{0-4}-R_{N-4}$ where R_{N-4} is as defined above,

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

- (28) $-(\text{CH}_2)_{0-4}-\text{O}-\text{P}(\text{O})-(\text{OR}_{\text{N-aryl-1}})_2$ where $\text{R}_{\text{N-aryl-1}}$ is -H or $\text{C}_1\text{-C}_4$ alkyl,
- (29) $-(\text{CH}_2)_{0-4}-\text{O}-\text{CO}-\text{N}(\text{R}_{\text{N-5}})_2$ where $\text{R}_{\text{N-5}}$ is as defined above,
- 5 (30) $-(\text{CH}_2)_{0-4}-\text{O}-\text{CS}-\text{N}(\text{R}_{\text{N-5}})_2$ where $\text{R}_{\text{N-5}}$ is as defined above,
- (31) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{\text{N-5}})_2$ where $\text{R}_{\text{N-5}}$ is as defined above,
- (32) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{R}_{\text{N-5}})_2-\text{COOH}$ where $\text{R}_{\text{N-5}}$ is as defined above,
- 10 (33) $-(\text{CH}_2)_{0-4}-\text{S}-(\text{R}_{\text{N-5}})_2$ where $\text{R}_{\text{N-5}}$ is as defined above,
- (34) $-(\text{CH}_2)_{0-4}-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl optionally substituted with one, two, three, four or five of -F}),$
- 15 (35) $\text{C}_3\text{-C}_7$ cycloalkyl,
- (36) $\text{C}_2\text{-C}_6$ alkenyl with one or two double bonds optionally substituted with $\text{C}_1\text{-C}_3$ alkyl, -F, -Cl, -Br, -I, -OH, -SH, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1\text{-C}_3$ alkoxy, $-\text{NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,
- (37) $\text{C}_2\text{-C}_6$ alkynyl with one or two triple bonds
- 20 optionally substituted with $\text{C}_1\text{-C}_3$ alkyl, -F, -Cl, -Br, -I, -OH, -SH, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1\text{-C}_3$ alkoxy, $-\text{NR}_{1-a}\text{R}_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,
- (38) $-(\text{CH}_2)_{0-4}-\text{N}(-\text{H or } \text{R}_{\text{N-5}})-\text{SO}_2-\text{R}_{\text{N-2}}$ where $\text{R}_{\text{N-5}}$ and $\text{R}_{\text{N-2}}$ can be the same or different and are as described above,
- (39) $-(\text{CH}_2)_{0-4}-\text{C}_3\text{-C}_7$ cycloalkyl,
- 25 (B) $-\text{R}_{\text{N-heteroaryl}}$ where $\text{R}_{\text{N-heteroaryl}}$ is selected from the group consisting of:
- pyridinyl,
- pyrimidinyl,
- quinolinyl,
- 30 benzothienyl,
- indolyl,
- indolinyl,
- pyridazinyl,

	pyrazinyl,
	isoindolyl,
	isoquinolyl,
	quinazolinyl,
5	quinoxalyl,
	phthalazyl,
	imidazolyl,
	isoxazolyl,
	pyrazolyl,
10	oxazolyl,
	thiazolyl,
	indolizyl,
	indazolyl,
	benzothiazolyl,
15	benzimidazolyl,
	benzofuranyl,
	furanyl,
	thienyl,
	pyrrolyl,
20	oxadiazolyl,
	thiadiazolyl,
	triazolyl,
	tetrazolyl,
	oxazolopyridinyl,
25	imidazopyridinyl,
	isothiazolyl,
	naphthyridinyl,
	cinnolyl,
	carbazolyl,
30	beta-carbolyl,
	isochromanyl,
	chromanyl,
	tetrahydroisoquinolyl,
	isoindolyl,

	isobenzotetrahydrofuranyl,
	isobenzotetrahydrothienyl,
	isobenzothienyl,
	benzoxazolyl,
5	pyridopyridinyl,
	benzotetrahydrofuranyl,
	benzotetrahydrothienyl,
	purinyl,
	benzodioxolyl,
10	triazinyl,
	phenoxazinyl,
	phenothiazinyl,
	pteridinyl,
	benzothiazolyl,
15	imidazopyridinyl,
	imidazothiazolyl,
	dihydrobenzisoxazinyl,
	benzisoxazinyl,
	benzoxazinyl,
20	dihydrobenziso-thiazinyl,
	benzopyranyl,
	benzothiopyranyl,
	coumarinyl,
	isocoumarinyl,
25	chromonyl,
	chromanonyl,
	pyridinyl-N-oxide,
	tetrahydroquinolinyl
	dihydroquinolinyl
30	dihydroquinolinonyl
	dihydroisoquinolinonyl
	dihydrocoumarinyl
	dihydroisocoumarinyl
	isoindolinonyl

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

where the $R_{N\text{-heteroaryl}}$ group is bonded by any atom of the parent $R_{N\text{-heteroaryl}}$ group
30 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, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

(2) -OH,

(3) $-NO_2$,

5

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

(5) $-CO-OH$,

(6) $-C\equiv N$,

(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:

10

(a) -H,

(b) C_1-C_6 alkyl optionally substituted with one

substituent selected from the group consisting of:

(i) -OH,

(ii) $-NH_2$,

15

(c) C_1-C_6 alkyl optionally substituted with one

to three -F, -Cl, -Br, -I,

(d) C_3-C_7 cycloalkyl,

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

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

20

(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

25

and one triple bond,

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

(k) $-R_{1-heteroaryl}$ where $R_{1-heteroaryl}$ is as defined

above,

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

30

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

three double bonds),

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

three triple bonds),

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

(12) $-(\text{CH}_2)_{0-4}-\text{CO}-\text{R}_{1-\text{aryl}}$ where $\text{R}_{1-\text{aryl}}$ is as defined

above,

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

5 defined above,

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

defined above,

(15) $-(\text{CH}_2)_{0-4}-\text{CO}-\text{R}_{\text{N-4}}$ where $\text{R}_{\text{N-4}}$ is selected from the

group consisting of morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl,

10 homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S-oxide,

homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl where each group is

optionally substituted with one, two, three, or four of C_1-C_6 alkyl,

(16) $-(\text{CH}_2)_{0-4}-\text{CO}-\text{O}-\text{R}_{\text{N-5}}$ where $\text{R}_{\text{N-5}}$ is selected from

the group consisting of:

15

(a) C_1-C_6 alkyl,

(b) $-(\text{CH}_2)_{0-2}-(\text{R}_{1-\text{aryl}})$ where $\text{R}_{1-\text{aryl}}$ is as defined

above,

(c) C_2-C_6 alkenyl containing one or two double

bonds,

20

(d) C_2-C_6 alkynyl containing one or two triple

bonds,

(e) C_3-C_7 cycloalkyl,

(f) $-(\text{CH}_2)_{0-2}-(\text{R}_{1-\text{heteroaryl}})$ where $\text{R}_{1-\text{heteroaryl}}$ is as

defined above,

25

(17) $-(\text{CH}_2)_{0-4}-\text{SO}_2-\text{NR}_{\text{N-2}}\text{R}_{\text{N-3}}$ where $\text{R}_{\text{N-2}}$ and $\text{R}_{\text{N-3}}$ are

as defined above,

(18) $-(\text{CH}_2)_{0-4}-\text{SO}-(\text{C}_1-\text{C}_8 \text{ alkyl})$,

(19) $-(\text{CH}_2)_{0-4}-\text{SO}_2-(\text{C}_1-\text{C}_{12} \text{ alkyl})$,

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

30

(21) $-(\text{CH}_2)_{0-4}-\text{N}(\text{H or } \text{R}_{\text{N-5}})-\text{CO}-\text{O}-\text{R}_{\text{N-5}}$ where $\text{R}_{\text{N-5}}$

can be the same or different and is as defined above,

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

can be the same or different and is as defined above,

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

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

5 (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 and are as defined above,

(26) $-(CH_2)_{0-4}-R_{N-4}$ where R_{N-4} is as defined above,

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

(28) $-(CH_2)_{0-4}-O-P(O)-(OR_{N-aryl-1})_2$ where $R_{N-aryl-1}$ is -H
10 or C_1-C_4 alkyl,

(29) $-(CH_2)_{0-4}-O-CO-N(R_{N-5})_2$ where R_{N-5} is as defined above,

(30) $-(CH_2)_{0-4}-O-CS-N(R_{N-5})_2$ where R_{N-5} is as defined above,

15 (31) $-(CH_2)_{0-4}-O-(R_{N-5})_2$ where R_{N-5} is as defined above,

(32) $-(CH_2)_{0-4}-O-(R_{N-5})_2-COOH$ where R_{N-5} is as defined above,

(33) $-(CH_2)_{0-4}-S-(R_{N-5})_2$ where R_{N-5} is as defined
20 above,

(34) $-(CH_2)_{0-4}-O-(C_1-C_6 \text{ alkyl optionally substituted with one, two, three, four, or five of -F})$,

(35) C_3-C_7 cycloalkyl,

(36) C_2-C_6 alkenyl with one or two double bonds
25 optionally substituted with C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

(37) C_2-C_6 alkynyl with one or two triple bonds
optionally substituted with C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

30 (38) $-(CH_2)_{0-4}-N(-H \text{ or } R_{N-5})-SO_2-R_{N-2}$ where R_{N-5} and R_{N-2} can be the same or different and are as described above,

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

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

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

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

$R_{1-heterocycle}$ is defined above,

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

5

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

(H) $R_{N-heteroaryl}-W-R_{N-1-heterocycle}$, where $R_{N-1-heterocycle}$ is defined

as $R_{1-heterocycle}$ is defined above,

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

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

10

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

where W is

(1) $-(CH_2)_{0-4}-$,

(2) $-O-$,

(3) $-S(O)_{0-2}-$,

15

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

(5) $-CO-$;

(II) $-CO-(C_1-C_{10} \text{ alkyl})$ where alkyl is optionally substituted with one two, or three substituents selected from the group consisting of:

(A) $-OH$,

20

(B) $-C_1-C_6 \text{ alkoxy}$,

(C) $-C_1-C_6 \text{ thioalkoxy}$,

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

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

different and are as defined above,

25

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

(G) $-SO_2-(C_1-C_8 \text{ alkyl})$,

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

different and are as defined above,

(I) $-NH-CO-(C_1-C_6 \text{ alkyl})$,

30

(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

and are as defined above,

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

(M) $-O-CO-(C_1-C_6 \text{ alkyl})$,

(N) -O-CO-NR_{N-8}R_{N-8} where the R_{N-8}s are the same or different and are as defined above,

(O) -O-(C₁-C₅ alkyl)-COOH,

(P) -O-(C₁-C₆ alkyl optionally substituted with one, two, or three of: -F, -Cl, -Br, -I),

(Q) -NH-SO₂-(C₁-C₆ alkyl),

(R) -F, -Cl,

(III) -CO-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl) where alkyl is optionally substituted with one, two, or three substituents selected from the group consisting of:

(A) -OH,

(B) -C₁-C₆ alkoxy,

(C) -C₁-C₆ thioalkoxy,

(D) -CO-O-R_{N-8} where R_{N-8} is -H, C₁-C₆ alkyl or -phenyl,

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

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

(G) -SO₂-(C₁-C₈ alkyl),

(H) -SO₂-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} are the same or different and are as defined above,

(I) -NH-CO-(C₁-C₆ 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 and are as defined above,

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

(M) -O-CO-(C₁-C₆ alkyl),

(N) -O-CO-NR_{N-8}R_{N-8} where the R_{N-8}s are the same or different and are as defined above,

(O) -O-(C₁-C₅ alkyl)-COOH,

(P) -O-(C₁-C₆ alkyl optionally substituted with one, two, or three of: -F, -Cl, -Br, -I),

(Q) -NH-SO₂-(C₁-C₆ alkyl),

(R) -F, -Cl,

(IV) $-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{S}-(\text{C}_1-\text{C}_6 \text{ alkyl})$ where alkyl is optionally substituted with one, two, or three substituents selected from the group consisting of:

- (A) $-\text{OH}$,
 - (B) $-\text{C}_1-\text{C}_6 \text{ alkoxy}$,
 - (C) $-\text{C}_1-\text{C}_6 \text{ thioalkoxy}$,
 - (D) $-\text{CO}-\text{O}-\text{R}_{\text{N-8}}$ where $\text{R}_{\text{N-8}}$ is as defined above,
 - (E) $-\text{CO}-\text{NR}_{\text{N-2}}\text{R}_{\text{N-3}}$ where $\text{R}_{\text{N-2}}$ and $\text{R}_{\text{N-3}}$ are the same or different and are as defined above,
 - (F) $-\text{CO}-\text{R}_{\text{N-4}}$ where $\text{R}_{\text{N-4}}$ is as defined above,
 - (G) $-\text{SO}_2-(\text{C}_1-\text{C}_8 \text{ alkyl})$,
 - (H) $-\text{SO}_2-\text{NR}_{\text{N-2}}\text{R}_{\text{N-3}}$ where $\text{R}_{\text{N-2}}$ and $\text{R}_{\text{N-3}}$ are the same or different and are as defined above,
 - (I) $-\text{NH}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$,
 - (J) $-\text{NH}-\text{CO}-\text{O}-\text{R}_{\text{N-8}}$ where $\text{R}_{\text{N-8}}$ is as defined above,
 - (K) $-\text{NR}_{\text{N-2}}\text{R}_{\text{N-3}}$ where $\text{R}_{\text{N-2}}$ and $\text{R}_{\text{N-3}}$ are the same or different and are as defined above,
 - (L) $-\text{R}_{\text{N-4}}$ where $\text{R}_{\text{N-4}}$ is as defined above,
 - (M) $-\text{O}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$,
 - (N) $-\text{O}-\text{CO}-\text{NR}_{\text{N-8}}\text{R}_{\text{N-8}}$ where the $\text{R}_{\text{N-8}}$ s are the same or different and are as defined above,
 - (O) $-\text{O}-(\text{C}_1-\text{C}_5 \text{ alkyl})-\text{COOH}$,
 - (P) $-\text{O}-(\text{C}_1-\text{C}_6 \text{ alkyl})$ optionally substituted with one, two, or three of: $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,
 - (Q) $-\text{NH}-\text{SO}_2-(\text{C}_1-\text{C}_6 \text{ alkyl})$,
 - (R) $-\text{F}$, $-\text{Cl}$,
- (V) $-\text{CO}-\text{CH}(-(\text{CH}_2)_{0-2}-\text{O}-\text{R}_{\text{N-10}})-(\text{CH}_2)_{0-2}-\text{R}_{\text{N-aryl}}/\text{R}_{\text{N-heteroaryl}}$ where $\text{R}_{\text{N-aryl}}$ and $\text{R}_{\text{N-heteroaryl}}$ are as defined above, where $\text{R}_{\text{N-10}}$ is selected from the group consisting of:
- (A) $-\text{H}$,
 - (B) $\text{C}_1-\text{C}_6 \text{ alkyl}$,
 - (C) $\text{C}_3-\text{C}_7 \text{ cycloalkyl}$,
 - (D) $\text{C}_2-\text{C}_6 \text{ alkenyl}$ with one double bond,

- (E) C₂-C₆ alkynyl with one triple bond,
 (F) R_{1-aryl} where R_{1-aryl} is as defined above,
 (G) R_{N-heteroaryl} where R_{N-heteroaryl} is as defined above,
 (VI) -CO-(C₃-C₈ cycloalkyl) where alkyl is optionally substituted
- 5 with one or two substituents selected from the group consisting of:
- (A) -(CH₂)₀₋₄-OH,
 (B) -(CH₂)₀₋₄-C₁-C₆ alkoxy,
 (C) -(CH₂)₀₋₄-C₁-C₆ thioalkoxy,
 (D) -(CH₂)₀₋₄-CO-O-R_{N-8} where R_{N-8} is -H, C₁-C₆ alkyl or -
- 10 phenyl,
- (E) -(CH₂)₀₋₄-CO-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} are the same or different and are as defined above,
 (F) -(CH₂)₀₋₄-CO-R_{N-4} where R_{N-4} is as defined above,
 (G) -(CH₂)₀₋₄-SO₂-(C₁-C₈ alkyl),
- 15 (H) -(CH₂)₀₋₄-SO₂-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} are the same or different and are as defined above,
 (I) -(CH₂)₀₋₄-NH-CO-(C₁-C₆ alkyl),
 (J) -NH-CO-O-R_{N-8} where R_{N-8} is as defined above,
 (K) -(CH₂)₀₋₄-NR_{N-2}R_{N-3} where R_{N-2} and R_{N-3} are the same or
- 20 different and are as defined above,
- (L) -(CH₂)₀₋₄-R_{N-4} where R_{N-4} is as defined above,
 (M) -O-CO-(C₁-C₆ alkyl),
 (N) -O-CO-NR_{N-8}R_{N-8} where the R_{N-8}s are the same or different and are as defined above,
- 25 (O) -O-(C₁-C₅ alkyl)-COOH,
 (P) -O-(C₁-C₆ alkyl optionally substituted with one, two, or three of: -F, -Cl, -Br, -I),
 (Q) -NH-SO₂-(C₁-C₆ alkyl),
 (R) -F, -Cl.
- 30 It is preferred that R_N is selected from the group consisting of:

$R_{N-1}-X_N$ - where X_N is -CO-, where R_{N-1} is R_{N-aryl} or $R_{N-heteroaryl}$ where R_{N-aryl} is phenyl where the substitution on phenyl is 1,3-, and where R_{N-aryl} or $R_{N-heteroaryl}$ are substituted with one -CO-NR_{N-2}R_{N-3},

5 $R_{N-1}-X_N$ - where X_N is -CO-, where R_{N-1} is R_{N-aryl} or $R_{N-heteroaryl}$ where R_{N-aryl} is phenyl substituted with one C₁ alkyl where the substitution on the phenyl is 1,3,5-, and where R_{N-aryl} or $R_{N-heteroaryl}$ are substituted with one -CO-NR_{N-2}R_{N-3},

$R_{N-1}-X_N$ - where X_N is -CO-, where R_{N-1} is $R_{N-heteroaryl}$ where $R_{N-heteroaryl}$ is substituted with one -CO-NR_{N-2}R_{N-3}. It is further preferred that R_{N-2} and R_{N-3} are the same and are C₃ alkyl. It is further preferred that:

10 $R_{N-1}-X_N$ - where X_N is -CO-, where R_{N-1} is R_{N-aryl} where R_{N-aryl} is phenyl substituted with one -CO-NR_{N-2}R_{N-3} where the substitution on phenyl is 1,3-,

$R_{N-1}-X_N$ - where X_N is -CO-, where R_{N-1} is R_{N-aryl} where R_{N-aryl} is phenyl substituted with one C₁ alkyl and with one -CO-NR_{N-2}R_{N-3} where the substitution on the phenyl is 1,3,5-. It is preferred that X_N is (A) -CO- and (B) -SO₂-; it is more
15 preferred that X_N be -CO-. X_2 includes -Cl, -Br; it is preferred that X_2 is -Cl.

The nitrogen-acylation of primary amines to produce secondary amides is one of the oldest known reactions. The amide forming agents, $(R_{N-1}-X_N)_2O$ or $R_{N-1}-X_N-X_2$ or $R_{N-1}-X_N-OH$ (IX) are known to those skilled in the art and are commercially available or can be readily prepared from known starting materials by
20 methods known in the literature. It is preferred to use an isophthalic acid acylating agent (IX) of the formula $R_{N-2}R_{N-3}N-CO-phenyl-CO-$ or a methylisophthalic acid acylating agent (IX) of the formula

$R_{N-2}R_{N-3}N-CO-(CH_3-phenyl-CO-$ where the substitution is 5-methyl-1,3-isophthalic acid. The more preferred 5-methyl-1,3-isophthalic acid is 3-[(N,N-
25 dipropylamino)carbonyl]-5-methylbenzoic acid (IX). These compounds are preferably prepared 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. Next the desired amine ($H-NR_{N-2}R_{N-3}$) is added. After 3-24 hr of stirring at 20 degrees C to the reflux
30 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 organic extracts are combined and then washed with

saturated aqueous solutions of bicarbonate and saline and dried over anhydrous sodium sulfate or magnesium sulfate. Filtration of the drying agent and removal of solvents by reduced pressure gives the methyl ester of the desired $R_{N-2}R_{N-3}N$ -CO-phenyl-CO-O-CH₃ or a methylisophthalic acid acylating agent (IX) $R_{N-2}R_{N-3}N$ -CO-(CH₃-)phenyl-CO-O-CH₃. Purification of the (methyl) ester can be achieved via chromatography on silica gel eluting with ethyl acetate in hexanes. The isophthalate ester or methylisophthalate ester of the mono-alkyl or di-alkyl amide is then treated with an aqueous solution of base such as lithium hydroxide in a minimum amount of THF/methanol/water and stirred 3-24 hours at 20 degrees C to the reflux temperature of the solvent. The solvents are then removed under reduced pressure and subsequently partitioned between water and a water immiscible solvent such as ethyl acetate, for example. If emulsions prohibit separation of the two phases, a small amount of saline is added to aid in separation. The aqueous phase is separated and extracted once more with a water immiscible solvent such as ethyl acetate, for example. The aqueous phase is then acidified with concentrated acid, preferably hydrochloric until pH ≤ 3 . The mixture obtained is then extracted three times with a water immiscible solvent such as ethyl acetate, for example. These combined organic extracts are dried over anhydrous sodium or magnesium sulfate. The drying agent is removed by filtration and the organic solvent is removed under reduced pressure to give product. The mono- or di-alkyl amide isophthalate/methylisophthalate is used as such in the next reaction with the (S,R)-amine (VIII) to produce the (S,R)-substituted amine (X).

When it is desired to produce a primary amide, R_{N-2} and R_{N-3} are both -H, the following procedure is preferred. An ester, preferably the methyl ester of isophthalate or methyl 5-methyl-1,3-isophthalate is dissolved in a THF/DMF mixture. CDI is added at 20-25 degrees C. After five to thirty minutes, ammonia gas is bubbled into the mixture through a syringe needle for 1 hr. The mixture is cooled to 0 degrees C for the duration of the hour. The reaction is left stirring under a balloon of ammonia overnight at 20-25 degrees C, after which time the reaction mixture is partitioned between saturated aqueous ammonium chloride and a water immiscible solvent such as ethyl acetate, for example. The phases are separated and the aqueous phase is extracted twice more with ethyl acetate. The organic extracts are washed with saturated aqueous solutions of bicarbonate and saline and dried over anhydrous sodium or magnesium sulfate. Filtration of the drying agent and

removal of solvents under reduced pressure gives the ester of the desired isophthalic acid or the isophthalic acid acylating agent (IX). Purification of the (methyl) ester can be achieved via chromatography on silica gel eluting with isopropanol/chloroform. The isophthalate ester or methylisophthalate ester of the primary amide is then treated with an aqueous solution of base such as lithium hydroxide in a minimum amount of THF/methanol/water and stirred overnight at 20-25 degrees C after which time the solvents are removed under reduced pressure and subsequently partitioned between water and a water immiscible solvent such as ethyl acetate, for example. If emulsions prohibit separation of the two phases, a small amount of saline is added to aid in separation. The aqueous phase is separated and extracted once more with a water immiscible solvent such as ethyl acetate, for example. The aqueous phase is then acidified with concentrated acid, preferably hydrochloric until $\text{pH} \leq 3$. The mixture obtained is then extracted three times with ethyl acetate. These combined organic extracts are dried over anhydrous sodium or magnesium sulfate. The drying agent is removed by filtration and the organic solvent removed under reduced pressure to give product. The amide isophthalic acid is used as such in the next reaction with (VIII) to produce (X).

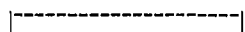
When it is desired that the amine be cyclized to be a group such as morpholinyl, piperazinyl, piperidinyl and pyrrolidinyl, etc the following procedure is preferably followed. An ester, preferably the methyl ester of isophthalic acid or methyl 5-methyl-1,3-isophthalate is dissolved in dry methylene chloride and three drops of DMF are added. The mixture is cooled to 0 degrees C and then oxalyl chloride is added. The mixture is stirred at 0 degrees C for 30 minutes to two hours after which the solvents are removed under reduced pressure. The acid chloride is left under vacuum overnight. The crude acid chloride is dissolved in dry methylene and cooled to 0 degrees C before the addition of the cyclic amine and a tertiary amine base such as N-methyl piperidine, for example. The reaction mixture is stirred at 0 degrees C for 1 to 6 hr before the solvents are removed under reduced pressure. The residue is diluted with water and a water immiscible solvent such as ethyl acetate, for example, and the phases are separated. The aqueous phase is extracted twice more with a water immiscible solvent such as ethyl acetate, for example, and the combined organic extracts are washed with saturated aqueous bicarbonate and dried over anhydrous sodium or magnesium sulfate. Filtration of the drying agent and removal of solvents under reduced pressure gives the product

cyclic amide. The cyclic amide is then treated with an aqueous base such as lithium hydroxide in a minimum amount of THF/methanol/water and stirred overnight at 20-25 degrees C, after which time the solvents are removed under reduced pressure and the residue is subsequently partitioned between water and a water immiscible solvent such as ethyl acetate, for example. The aqueous phase is extracted once more with ethyl acetate. Removal of water from the aqueous phase under reduced pressure gives the desired cyclic amide product (IX).

When it is desired that R_{N-1} is carbocycle, for example but not limited to, cyclohexane, one may then start with a suitably functionalized dimethyl isophthalate and via methods taught in the literature (Meyers, A.I., *Org. Syn.*, 1971, 51, 103) one may reduce the six-membered ring with reducing agents such as rhodium (5%) on alumina in the presence of acetic acid and methanol under a hydrogen atmosphere to afford the corresponding dimethyl cyclohexane dicarboxylate.

CHART D sets forth an alternative process for production of the (S,R)-substituted amine (X) from the (S,R)-protected azide (XII), which is produced from the corresponding epoxide (V) in CHART C. The amino protecting group is removed to produce the corresponding unprotected azide (XIV) by methods previously described in CHART A for the conversion of (S,R)-protected alcohol (VII) to the corresponding (S,R)-amine (VIII). The (S,R)-unprotected azide (XIV) is then acylated on nitrogen to produce the corresponding (S,R)-azide (XV). Next, the azide functionality is reduced as previously discussed for the conversion of the (S,R)-protected azide (XII) to the corresponding (S,R)-protected amine (XIII) to give the (S,R)-free amine (XVI). Last, the (S,R)-free amine (XVI) is transformed to the corresponding (S,R)-substituted amine (X) by nitrogen alkylation with a compound of the formula R_C-X_3 to give the corresponding (S,R)-substituted amine (X). X_3 is an appropriate leaving group, such as but not limited to, -Cl, -Br, -I, -O-mesylate, -O-tosylate, O-triflate, etc. X_3 may also be an aldehyde; the corresponding coupling with (XVI) via the well known reductive amination procedure gives the (S,R)-substituted amine (X).

Carbocyclic amide forming agents (IX) are also provided for by the invention. For example, the carbocyclic amide forming agents of the formula



R'-CH-C(R'')(R''')-CH-X_N-OH (IX) are readily prepared from known starting materials by methods disclosed in the literature and known to those skilled in the art, for example, *J. Med. Chem.* **1998**, *41*, 1581, *J. Org. Chem.* **2000**, *65*, 1305. It is also understood that instead of the carboxylic acid, one may readily employ an acyl halide, where the halide is preferably chloride, or a suitable group to produce a mixed anhydride; these methods are taught by CHART A. For additional guidance on the formation of carbocycles and preferably cyclopropanes, one may consult M.P. Doyle; M.A. McKerverly; T. Ye in *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds From Cyclopropanes to Ylides*, Wiley-Interscience, **1998**, pp. 163-279.

CHARTS E, F, G, and H disclose various methods to produce the R_N portion of the substituted amine (X) where the phenyl ring of the R_N 1,3-disubstituted moiety, -CO-phenyl-CO-, is further substituted in the 5-position with various groups such as amides, nitriles, halides, and amines. These compounds are prepared by methods known to those skilled in the art. The process chemistry of each reaction is known to those skilled in the art. What is novel here is the order of each process step and/or the specific reactants used. One skilled in the art knowing the desired product would know at least one method to prepare the desired product by using known starting materials. Hence, the following discussion is not necessary but is set forth to further aid those interested in preparing the compounds of the invention.

CHART E discloses alternate processes for the transformation of the aniline (XVII) or acid ester (XVIII) to the corresponding acid (IX-XXIII). One process begins with the commercially available aniline (XVII) where R_{N-a} is preferably -H, C₁-C₄ alkyl or benzyl. The aniline (XVII) is treated with a diazotizing reagent such as sodium or potassium nitrite in mineral acid, followed by a halogen source such as copper (II) halide or alkali metal halide, or by an organic diazotizing reagent such as an alkyl nitrite in a strong acid such as acetic acid or trifluoroacetic acid, followed by a halide source such as copper (II) halide or alkali metal halide to give the halo acid ester (XIX) where R_{N-b} is -Cl, -Br or -I. Alternatively, the acid ester (XVIII) is

treated with N-halosuccinimide and trifluoromethanesulfonic acid to give the halo acid ester (XIX). The halo acid ester (XIX) is then converted to the ester amide (XXI) using a primary or secondary amine of the formula $H-NR_{N\alpha}R_{N\beta}$ (AMINE) where $R_{N\alpha}$ and $R_{N\beta}$ are the same or different or can be cyclized.

- 5 These groups, $R_{N\alpha}$ and $R_{N\beta}$, become part of the substituted amine (X) and are included in the definition of R_N . R_N includes $R_{N-1}-X_N$ where the linker, $-X_N$, includes $-CO-$ and R_{N-1} includes R_{N-aryl} . R_{N-aryl} is defined to include phenyl (-phenyl) optionally substituted with two amides:

$-CO-NR_{N-2}R_{N-3}$ and

- 10 $-CO-R_{N-4}$. $R_{N\alpha}$ and $R_{N\beta}$ include both the non-cyclic amides, $-CO-NR_{N-2}R_{N-3}$ and the cyclic amides $-CO-R_{N-4}$ where R_{N-2} , R_{N-3} and R_{N-4} are as defined in the claims. Alternatively, the halo acid ester (XIX) is converted to the dihalo ester (XX) by methods known to those skilled in the art. R_{N-c} includes $-Cl$ and $-F$. The dihalo ester (XX) is treated with a primary or secondary amine of the formula $H-$
- 15 $NR_{N\alpha}R_{N\beta}$ (AMINE) to give the ester amide (XXI). The ester amide (XXI) is then reacted with an AMINE in a carbon monoxide atmosphere in the presence of a palladium catalyst using methods such as those reviewed by Heck, (Palladium Reagents in Organic Synthesis, 1985 pp. 342-365). to give the diamide (XXII). Hydrolysis of the ester portion of the diamide (XXII) using methods well known to
- 20 those skilled in the art gives the diamide acid (XXIII).

- In CHART F, an alternate route to intermediate diamide (XXII) is shown starting from commercially available phenol (XXIV). The phenol (XXIV) is treated with a trifluoromethanesulfonating reagent such as trifluoromethanesulfonic anhydride to give triflate (XXV). The triflate (XXV) is reacted under the conditions
- 25 of palladium catalysis in the presence of carbon monoxide and an amine of the formula $H-NR_{N\alpha}R_{N\beta}$ (AMINE) as for the conversion of the ester amide (XXI) to the corresponding diamide (XXII) in CHART E to give the diester (XXVI). The diester (XXVI) is hydrolyzed using methods known to those skilled in the art to give the monoacid (XXVII). The monoacid (XXVII) is then converted to the diamide
- 30 (XXII) using conditions such as for the conversion of the halo acid ester (XIX) to the ester amide (XXI) in CHART E.

CHART G discloses another route to prepare the ester amide (XXI). The reaction starts with commercially available nitro compound (XXVIII) which is condensed with an (AMINE) using coupling methods known to those skilled in the

art to give the nitro amide (XXX). The nitro amide (XXX) can also be prepared by first treating the nitro compound (XXVIII) with reagents such as thionyl chloride, or DMF and oxalyl chloride, or other methods known to those skilled in the art to give the acid chloride (XXIX), which upon treatment with the (AMINE) gives the nitro
5 amide (XXX). Reduction of the nitro amide (XXX) using methods known to those skilled in the art (see, for example, Smith and March, *Advanced Organic Chemistry*, 5th ed.) gives amide aniline (XXXI). The amide aniline (XXXI) is then treated with diazotizing reagents such as sodium or potassium nitrite in mineral acid, followed by a halogen source such as copper (II) halide or alkali metal halide, or by an organic
10 diazotizing reagent such as an alkyl nitrite in a strong acid such as acetic acid or trifluoroacetic acid, followed by a halide source such as copper (II) halide or alkali metal halide to give the ester amide (XXI).

CHART H discloses a process to prepare the diamide acid (IX-XXIII) from the ester amide (XXI), where one of the amides is unsubstituted and is -CO-NH₂.
15 This process starts from either the ester or the acid, for example the ester amide (XXI) is treated with copper (I) cyanide (CuCN) in N-methylpyrrolidinone or DMF, preferably N-methylpyrrolidinone, to give the nitrile (XXXII). The nitrile (XXXII) is converted to the primary amide (XXXIII) using urea-hydrogen peroxide complex (see *Synth. Commun.* (1993) 3149) or the methods of *Synth. Commun.* (1990) 1445,
20 *Synth. Commun.* (1997) 3119, *J. Org. Chem.* (1992) 2521, *Tet. Lett.* (1996) 6555, *Ind. J. Chem., Sect. B*, (1999) 974, *Tet. Lett.* (1995) 3469, *Tet. Lett.* (1998) 3005, or others. When the ester amide (XXI) is in the form of an ester, an additional hydrolysis step using lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide, or other hydrolysis methods known to those skilled in the art is
25 used to convert the diamide ester (XXXIII) to the diamide acid (IX-XXIII).

CHART I discloses an alternate synthetic route from the protected alcohol (VII) to the substituted amine (X) which uses a diprotected intermediate (XXXIV) whereby the nitrogen atom attached to the R_C substituent is protected. Using the process of CHART I, the mono protected alcohol (VII) is reacted with a new
30 protecting group to form the orthogonally protected (XXXIV). This is a common strategy employed in traditional peptide chemistry by those skilled in the art, see M. Bodansky, *Principles of Peptide Chemistry*. When the mono protected alcohol (VII) is protected with CBZ one skilled in the art could react it with either (BOC)₂O in

methylene chloride or similar organic solvent or Fmoc-Cl in methylene chloride or similar organic solvent to prepare orthogonally protected (XXXIV). Then the CBZ group is removed by hydrogenation in the presence of a catalytic amount of palladium on carbon in an alcoholic solvent, such as methanol, or ethyl acetate, or with catalytic palladium on carbon in alcoholic solvents in the presence of ammonium formate as is known to those skilled in the art. This gives the R_C -N protected (XXXV). Similarly, when the mono protected alcohol (VII) is protected as a BOC it can be reacted with CBZ-Cl under Schotten-Bauman conditions or CBZ-OSu in THF to prepare the reversed (XXXIV). Then the BOC group can be cleaved with hydrochloric acid (4 N) in methanol, ethanol or dioxane or with trifluoroacetic acid in methylene chloride or by other methods such as those described in *The Peptides, Analysis, Synthesis, Biology*, Vol. 3, Ed. E. Gross and J. Meienhofer (1981) to liberate the CBZ R_C -N protected (XXXV). This functional group manipulation gives various permutations in the sequence (VII) to (XXXIV) to (XXXV) as is apparent to one skilled in the art. When the appropriately R_C -N protected compound (XXXV) is reacted with the amide forming agent (IX), in acid form, under standard peptide coupling conditions, for example, EDC/HOBt in methylene chloride or DMF or a previously activated acid, $(R_N)_2O$ gives the corresponding R_N -substituted R_C -N protected (XXXVI). Simple de-protection of the R_N -substituted R_C -N protected (XXXVI) then gives the desired substituted amine (X). Thus when the R_N -substituted R_C -N protected (XXXVI) is protected with BOC, treatment with hydrochloric acid (4N) in dioxane or the other reagents discussed above gives the substituted amine (X). When the R_N -substituted R_C -N protected (XXXVI) is protected with CBZ, treatment with hydrogen from 10 - 50 psi in alcoholic solvents, such as methanol with a catalytic amount of palladium on carbon will give, after work-up, the desired substituted amine (X). Similarly when the R_N -substituted R_C -N protected (XXXVI) is protected with Fmoc, treatment with a secondary amine, preferably either piperidine (10 %) or diethylamine (10 %) in an inert solvent such as, for example, methylene chloride will give after work up the desired substituted amine (X).

CHART J discloses a process to prepare compounds where the phenyl ring of the R_N substituent of -CO-phenyl-CO- is substituted with a sulfonamide group in the 5-position. The process starts with the halo amide ester (XXI, CHART E) which

is reacted with sodium nitrite, sulfur dioxide, copper chloride (II) and acetic acid by the method disclosed in *J. Med. Chem.*, 42, 3797 (1999) to prepare the sulfonyl chloride (XXXVII). The sulfonyl chloride (XXXVII) is then reacted with AMINE, as defined above, by methods known to those skilled in the art to produce the
5 corresponding sulfonamide (XXXVIII). Last the sulfonamide (XXXVIII) is transformed to the corresponding sulfonamide acid (XXXIX) by methods known to those skilled in the art such as using lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide, or other hydrolysis methods known to those skilled in the art.

10 CHART K discloses how to prepare the R_N substituents where R_N is $R_{N-1}-X_{N-}$, where X_{N-} is $-CO-$ and R_{N-1} is R_{N-aryl} where R_{N-aryl} is phenyl substituted with one alkyl group and one $-CO-NR_{N-2}R_{N-3}$ or $-CO-R_{N-4}$. See the discussion above for CHART E regarding the amine, $H-NR_{N-alpha}R_{N-beta}$ (AMINE), used to form the amide R_N substituents. The process starts with the halo amide ester (XXI) which is then
15 reacted with an alkyl boronic acid having the desired alkyl group in the presence of a palladium catalyst such as $Pd(PPh_3)Cl_2$ using the general method described in *J. Med. Chem.*, 4288 (2000). The alkyl boronic acids are commercially available or can be prepared by the process described in *J. Am. Chem. Soc.*, 60, 105 (1938). It is preferred that R_{N-b} is bromo. This step produces the alkyl ester (XL) which is then
20 hydrolyzed by means known to those skilled in the art to produce the desired alkyl acid (XLI).

CHART L discloses a process to prepare the amide forming agent (IX - XLVII) where the R_N substituent is $R_{N-1}-X_{N-}$, where the linker, $-X_{N-}$ is $-CO-$, where R_{N-1} is R_{N-aryl} and where R_{N-aryl} is phenyl (-phenyl) substituted with groups:

25 C_1-C_6 alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, and $-N(-H$ and C_1-C_3 alkyl)- $CO-R_{N-5}$. This specific amide forming agent, (IX - XLVII) is prepared by starting with the phenyl nitro compound (XLII) which is reduced to the
30 corresponding phenyl nitro hydroxy compound (XLIII) using borane-methyl sulfide or borane in THF. The phenyl nitro hydroxy compound (XLIII) is reduced to the corresponding phenyl amino hydroxy compound (XLIV) using hydrogen and palladium catalyst as is known to those skilled in the art. The phenyl amino hydroxy

compound (XLIV) is reacted with an aldehyde in the presence of a reducing agent such as sodium cyanoborohydride or sodium triacetoxyborohydride to give the phenyl substituted amino hydroxy compound (XLV). The phenyl substituted amino hydroxy compound (XLV) is acylated with an acid chloride or acid anhydride by methods known to those skilled in the art to give the phenyl disubstituted amino hydroxy compound (XLVI). The phenyl disubstituted amino hydroxy compound (XLVI) is hydrolyzed using an alkali hydroxide, followed by acidification, to give the amide forming agent (IX - XLVII). The amide forming agent (XLVII) is then coupled with amine (VIII) using methods known to those skilled in the art and methods previously discussed, such as with diethyl cyanophosphonate, to give the substituted amine (X). Further treatment of the substituted amine (X) with diethyl cyanophosphonate gives the substituted amine where the hydroxyalkyl substituent on the phenyl ring has a phosphate substituent.

CHART M discloses a process to prepare amide forming agents (IX- L) where the R_N substituent is $R_{N-1}-X_N-$, where the linker, $-X_N-$ is $-CO-$, where R_{N-1} is R_{N-aryl} and where R_{N-aryl} is phenyl (-phenyl) substituted with two groups. The first substituent at what is usually identified as position "5-" can be either:

$-R_{N-aryl}$ or

$-R_{N-heteroaryl}$. The second substituent at what is usually identified as position "3-" can be either:

$-CO-NR_{N-2}R_{N-3}$ or

$-CO-R_{N-4}$. $R_{N\alpha}$ and $R_{N\beta}$ include both the non-cyclic amides, $-CO-NR_{N-2}R_{N-3}$ and the cyclic amides $-CO-R_{N-4}$ where R_{N-2} , R_{N-3} and R_{N-4} are as defined in the claims. The process starts with the trisubstituted phenyl compound (XLVIII) where R_{N-d} is $-Cl$, $-Br$, $-I$ or $-O$ -triflate. Treatment with an aryl or heteroaryl boronic acid or heteroaryl or aryl boronic acid ester such as (aryl or heteroaryl)- $B(OH)_2$ or (aryl or heteroaryl)- $B(OR^a)(OR^b)$ (where R^a and R^b are lower alkyl, ie. C_1-C_6 , or taken together, R^a and R^b are lower alkylene, ie. C_2-C_{12}) in the presence of a metal catalyst with or without a base in an inert solvent yields (XLIX). Metal catalysts in these transformations include, but are not limited to, salts or phosphine complexes of Cu, Pd, or Ni (eg. $Cu(OAc)_2$, $PdCl_2(PPh_3)_2$, $NiCl_2(PPh_3)_2$). Bases may include, but are not limited to, alkaline earth metal carbonates, alkaline earth

metal bicarbonates, alkaline earth metal hydroxides, alkali metal carbonates, alkali metal bicarbonates, alkali metal hydroxides, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably diisopropylethylamine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, acetonitrile, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylacetamides (preferably dimethylacetamide), N,N-dialkylformamides (preferably dimethylformamide), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes (preferably methylene chloride). Preferred reaction temperatures range from room temperature up to the boiling point of the solvent employed. The reactions may be run in conventional glassware or in one of many commercially available parallel synthesizer units. Non-commercially available boronic acids or boronic acid esters may be obtained from the corresponding optionally substituted aryl halide as described in *Tetrahedron*, 50, 979-988 (1994). Intermediate (XLIX) is then hydrolyzed using alkali metal hydroxide, for example lithium, sodium or potassium hydroxide, followed by acidification, to give aryl or heteroaryl coupled acids (IX-L). Alternatively, as described in *Tetrahedron*, 50, 979-988 (1994), one may convert the R_{N-d} to the corresponding boronic acid or boronic acid ester $(OH)_2B-$ or $(OR^a)(OR^b)B-$ and obtain the same products set forth above by treating with a suitable aryl or heteroaryl halide or triflate.

CHART N discloses a process to prepare amide forming agents (IX - LII) where the R_N substituent is $R_{N-1}-X_N-$ where the linker, $-X_N-$ is $-CO-$, where R_{N-1} is R_{N-aryl} and where R_{N-aryl} is phenyl (-phenyl) substituted with two groups. The first substituent at what is usually identified as position "5-" is $-C\equiv C-R$. The second substituent at what is usually identified as position "3-" can be either $-CO-NR_{N-2}R_{N-3}$ or $-CO-R_{N-4}$. The halo ester (XXI) is treated with a mixture of $PdCl_2(Pphenyl)_2$ and trimethylsilyl acetylene, using methods known to those skilled in the art, to give

acetylene ester (LI). Acetylene ester (LI) is then hydrolyzed using alkali metal hydroxide, followed by acidification, to give acetylene acid (IX - LII).

CHARTs O and O' disclose processes to prepare amide forming agents (IX - LX) and (IX - LXIII) with an extended methylene group where the R_N substituent is $R_{N-1}-X_N-$ where the linker, $-X_N-$ is $-CO-$, where R_{N-1} is R_{N-aryl} and where R_{N-aryl} is phenyl (-phenyl) substituted with two groups. The substituent at what is usually identified as position "3-" can be either $-CO-NR_{N-2}R_{N-3}$ or $-CO-R_{N-4}$. In the process of CHART O, the substituent at the 5-position is $-CH_2CO-NH_2$ and in the process of CHART O', the substituent at the 5-position is $-CH_2C\equiv N$. The starting diester acid (LIII) is reduced with borane in solvents such as THF to give the corresponding diester alcohol (LIV). The diester alcohol (LIV) is converted to the corresponding diester bromo compound (LV) using a brominating agent such as PBr_3 , CBr_4 , or other halogenating agent such as are known to those skilled in the art. The bromine of the diester bromo compound (LV) is then displaced with cyanide to give the corresponding nitrile (LVI). In CHART O', the nitrile (LVI) is then hydrolyzed to the corresponding cyano ester (LXI). The cyano ester (LXI) is then coupled with $H-NR_{N\alpha}R_{N\beta}$ (AMINE), as previously described using methods known to those skilled in the art to give the corresponding cyano amide (LXII). The cyano amide (LXII) is then hydrolyzed to the corresponding cyano acid (IX-LXIII) which is in turn coupled with amine (VIII) to give the substituted amine (X). When the substituent on the extended methyl group is $-CO-NH_2$, the process of CHART O is used. There the nitrile (LVI) is converted to the corresponding diester amine (LVII) by methods known to those skilled in the art. The next steps are the same as for CHART O' where the diester amide (LVII) is hydrolyzed to the corresponding ester amine (LVIII) which is then converted to the corresponding diamide ester (LIX) which is hydrolyzed to the corresponding diamide acid (IX - LX). The diamide acid (IX - XL) is then coupled with the appropriate amine (VIII) to produce the desired substituted amide (X).

CHART P discloses a process to prepare amide forming agents (IX - LXVII) with an extended hydroxymethylene group where the R_N substituent is $R_{N-1}-X_N-$ where the linker, $-X_N-$ is $-CO-$, where the R_{N-1} is R_{N-aryl} , where R_{N-aryl} is phenyl (-phenyl) substituted with two groups. The substituent at what is usually identified as position "3-" can be either $-CO-NR_{N-2}R_{N-3}$ or $-CO-R_{N-4}$. The process begins with a

halo amide (LXIV), preferably iodo, which is converted to the corresponding aldehyde (LXV) and then to the corresponding alcohol (LXVI) by the method described in *Synth. Commun.* 28, 4270 (1998), optionally with variations known to those skilled in the art. Hydrolysis of the alcohol (LXVI) using alkali hydroxides, followed by acidification, gives the desired hydroxy acid (IX - LXVII). The hydroxy acid (IX - LXVII) is then coupled with the appropriate amine (VIII) to give the desired substituted amine (X).

CHART Q discloses a process to prepare amide forming agents (IX - LXXII) with an alkyl group or a halogen atom or an amino group at the 5-position where the R_N substituent is $R_{N-1}-X_N$ - where the linker, $-X_N$ - is $-CO-$, where the R_{N-1} is R_{N-aryl} , where R_{N-aryl} is phenyl (-phenyl) substituted with two groups. The substituent at what is usually identified as position "3-" can be either $-CO-NR_{N-2}R_{N-3}$ or $-CO-R_{N-4}$. The process begins with an appropriately 5-substituted diacid (LXVIII) which is esterified by methods known to those skilled in the art to give the corresponding diester (LXIX). The diester (LXIX) is then hydrolyzed using alkali hydroxides, followed by acidification, to give the corresponding monoacid (LXX). Alternatively, the monoacid (LXX) can be produced directly from the diacid (LXVIII) by known methods. The monoacid (LXX) is then coupled with $H-NR_{N\alpha}R_{N\beta}$ (AMINE) to give the corresponding amide ester (LXXI). The amide ester (LXXI) is then hydrolyzed using alkali hydroxides, followed by acidification, to give the corresponding acid amide (IX - LXXII).

CHART R discloses a general process to prepare the amide forming agents (IX - LXXVII) which, for example, have an alkyl group at what is known as the 5-position and a ketone at the 3-position. These acids (IX- LXXVII) are formed by starting with the acid (LXXIII) which is converted to the corresponding acid halide (LXXIV) using methods known to those skilled in the art. The acid halide (LXXIV) is preferably the acid chloride. The acid halide (LXXIV) in the presence of copper (I) bromide and tetrahydrofuran and at temperatures ranging from -78 degrees C to 0 degrees C is treated with a Grignard reagent (aryl-Mg-X, or alkyl-Mg-X, where X is -Cl or -Br) to give the ketone esters (LXXVI and LXXVI'). Many Grignard reagents are available for purchase; others are prepared by methods known to those skilled in the art. An alternative method for preparing the ketone esters (LXXVI, LXXVI') is to prepare the Weinreb amide (LXXV), either from the acid (LXXIII) directly or by

way of acid halide (LXXIV) followed by treatment with N,O-dimethylhydroxylamine to give Weinreb amide (LXXV) and then treating the Weinreb amide (LXXV) with a Grignard reagent, by methods known to those skilled in the art. The ketone esters (LXXVI, LXXVI') are then hydrolyzed using alkali hydroxides, followed by acidification, to give the ketone acids (LXXVII, LXXVII').

CHART S discloses various methods to modify the R_N portion of the substituted amine (X) where the phenyl ring of the R_N moiety is further substituted in the 3-position with various groups such as aryl and heteroaryl. These compounds are prepared by methods known to those skilled in the art. The process chemistry of each reaction is known to those skilled in the art. What is novel here is the order of each process step and/or the specific reactants used. One skilled in the art knowing the desired product would know at least one method to prepare the desired product by using known starting materials. Hence, the following discussion is not necessary but is set forth to further aid those interested in preparing the compounds of the invention.

CHART S sets forth a general method used in the present invention to prepare the substituted amines (X) where $R_N = R_N\text{-aryl-}R_N\text{-aryl-X}_N$ or $R_N\text{-heteroaryl-}R_N\text{-aryl-X}_N$. Treatment of the (S,R)-amine (VIII) with amide forming agents (IX) according to the methods set forth above where for CHART S, R_{N-1} is $\text{Br-}R_N\text{-aryl}$ generates the corresponding (S,R)-substituted amine (X) where R_N is $\text{Br-N}_R\text{-aryl-X}_N$. Further treatment with an aryl boronic acid or aryl boronic acid ester such as (aryl or heteroaryl)- B(OH)_2 or (aryl or heteroaryl)- $\text{B(OR}^a\text{)(OR}^b\text{)}$ (where R^a and R^b are lower alkyl, ie. $\text{C}_1\text{-C}_6$, or taken together, R^a and R^b are lower alkylene, ie. $\text{C}_2\text{-C}_{12}$) in the presence of a metal catalyst with or without a base in an inert solvent yields the (S,R)-substituted amine (X) where R_N is $\text{N}_R\text{-aryl-N}_R\text{-aryl-X}_N$ or $R_N\text{-heteroaryl-}R_N\text{-aryl-X}_N$. Metal catalysts in these transformations include, but are not limited to, salts or phosphine complexes of Cu, Pd, or Ni (eg. Cu(OAc)_2 , $\text{PdCl}_2(\text{PPh}_3)_2$, $\text{NiCl}_2(\text{PPh}_3)_2$). Bases may include, but are not limited to, alkaline earth metal carbonates, alkaline earth metal bicarbonates, alkaline earth metal hydroxides, alkali metal carbonates, alkali metal bicarbonates, alkali metal hydroxides, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides,

alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably diisopropylethylamine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, acetonitrile, dialkyl
5 ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylacetamides (preferably dimethylacetamide), N,N-dialkylformamides (preferably dimethylformamide), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes (preferably methylene chloride). Preferred reaction temperatures range
10 from room temperature up to the boiling point of the solvent employed. The reactions may be run in conventional glassware or in one of many commercially available parallel synthesizer units. Non-commercially available boronic acids or boronic acid esters may be obtained from the corresponding optionally substituted aryl halide as described in *Tetrahedron*, 50, 979-988 (1994).

15 Where the above chemistry is incompatible with other functionality present in the (S,R)-substituted amine (X) where R_N is $Br-N_{R-aryl}-X_N$, then one skilled in the art will readily understand that an alternative sequence of coupling steps is required. For example, treatment of an appropriately substituted amide forming agent (IX) $R_{N-1}-X_N-OH$ where R_{N-1} is $Br-R_{N-aryl}$ with a boronic acid or boronic acid ester under
20 the conditions described above will afford the appropriately substituted amide forming agent (IX) where R_{N-1} is $N_{R-aryl}-N_{R-aryl}$ or $R_N-heteroaryl-R_{N-aryl}$. When the amide forming agent (IX) where R_{N-1} is $N_{R-aryl}-N_{R-aryl}$ or $R_N-heteroaryl-R_{N-aryl}$ is treated with the (S,R)-amine (VIII), one then obtains the same substituted amines (X) set forth in CHART S.

25 The above examples for CHART S are not meant to limit the scope of the chemistry. In addition to bromine, a suitable group may include iodine or triflate. Alternatively, as described in *Tetrahedron*, 50, 979-988 (1994), one may convert the $Br-R_{N-aryl}$ to the corresponding boronic acid or boronic acid ester $(OH)_2B-R_{N-aryl}$ or $(OR^a)(OR^b)B-R_{N-aryl}$ and obtain the same products set forth above by treating
30 with a suitable aryl or heteroaryl halide or triflate. Additionally, each $-R_{N-aryl}$ and $-R_N-heteroaryl$ are interchangeable at each occurrence in the chemistry described above.

CHART T discloses a process to prepare amide forming agents (IX - LXXIX) where the R_N substituent is $R_{N-1}-X_N-$, where the linker, $-X_N-$ is $-CO-$, where R_{N-1} is R_{N-aryl} and where R_{N-aryl} is phenyl substituted with $-CO-NR_{N\alpha}R_{N\beta}$ (AMINE) and with an amide of the formulas:

- 5 $-(CH_2)_{0-4}-N(-H \text{ and } R_{N-5})-CO-R_{N-2}$
 $-(CH_2)_{0-4}-N(-H \text{ or } R_{N-5})-SO_2-R_{N-2}.$

The process begins with the amide aniline (XXXI) which is reacted with the corresponding acid halide or sulfonyl halide, or acid anhydride or sulfonyl anhydride to produce the corresponding amide ester (LXXVIII). Suitable solvents include
 10 THF or dichloromethane at temperatures ranging from -78 degrees to 100 degrees C. The amide ester (LXXVIII) is then hydrolyzed to the corresponding amide acid (IX - LXXIX) by methods known to those skilled in the art. When the amide forming agent (IX - LXXIX) is reacted with the appropriate amine (VIII), the desired substituted amine (X) is obtained.

15 CHART U discloses a general method for preparing various C-terminal amines (VI) as represented by the preparation of C-terminal amine (LXXXIV). Methods to prepare amines of this type are well understood using methods known to those skilled in the art, or one may consult the references: 1) *JACS*, 1970, 92, 3700, and 2) US patent 4,351,842.

20 CHART V further discloses general methods for preparing various C-terminal amines (VI) as represented by the preparation of C-terminal amines (LXXXIX). Multiple examples of the heterocyclic carboxylic acids or acid chlorides are commercially available. Optionally, the carboxylic acid (LXXXV) may be converted to the acid chloride (LXXXVI) with reagents such as, but not
 25 limited to, thionyl chloride. Displacement with ammonia generates the common intermediate amides (LXXXVII) which are readily reduced to amines (VI - LXXXIX) using a variety of methods detailed previously. Alternatively, other heteroaryls are commercially available as the methyl halide (LXXXVIII) which are treated with ammonia to yield the title C-terminal amines (VI - LXXXVIII).

30 CHART W discloses general methods for preparing thiazolyl containing C-terminal amines as represented by the preparation of C-terminal amines (LXXXIX). The synthesis of the thiazoles is outlined in CHART W; these procedures are amply taught in the literature and are modified from the procedures outlined in: Mashraqui, SH; Keehn, PM. *J. Am. Chem. Soc.* 1982,

104, 4461-4465. The synthesis of substituted 5-aminomethylthiazoles (XCI) was achieved from 5-hydroxymethylthiazole (XC) by the procedure described in: Alterman et al. *J. Med. Chem.* 1998, 41, 3782-3792. All other thiazole analogs were transformed to the hydroxymethyl derivative using CHART W, and
5 converted to the aminomethyl derivative by the Alterman procedure without notable changes.

CHART X discloses general methods for preparing isoxazolyl containing C-terminal amines as represented by the preparation of C-terminal amines (XCII). The synthesis of isoxazole derivatives was modified from the procedure in: Felman, SW
10 et al. *J. Med. Chem.* 1992, 35, 1183-1190 and is readily understood by those skilled in the art making non-notable changes to achieve the title compounds. The substituted hydroxylamine precursors were synthesized using the procedure taught by Bousquet, EW. *Org. Synth. Coll. Vol II*, 313-315. Commercially available propargylamine may be protected using any number of methods known in the art
15 (see: Greene, TW; Wuts, PGM. *Protective Groups in Organic Synthesis*, 3rd Ed. New York: John Wiley, 1999. Chapter 7.), preferred is a BOC protecting group. Substituted propargyl amines may be obtained by a number of methods commonly known in the art.

CHART Y discloses a general route to prepare hydroxyethylamines where
20 one carbon atom of the peptide backbone, along with R₂ and R₃ form a ring. It is understood that the present invention also allows for a heteroatom to be incorporated into the ring. In summary, the synthesis of compounds where R₂ and R₃ may form a ring proceeds from a suitably protected amino acid aldehyde and cycloalkyllithium species, both of which are commercially available or where known procedures for
25 making such compounds are known in the art. The general procedure involved is also precedent in the literature, for example, see Klumpp, et al., *J. Am. Chem. Soc.*, 1979, 101, 7065, and it is intended that making non-critical variations, one may obtain the title compounds provided for by CHART Y. Treatment of a suitably protected amino acid aldehyde and cycloalkyllithium species affords alcohol
30 (XCIII). These reactions are carried out in an inert solvent such as, for example, tetrahydrofuran or diethyl ether. Optimally the reactions are conducted at low temperatures, for example below 0 degrees C. Carbonylation via the Klumpp procedure yields the acid (XCIV) which when exposed to Curtius, or related

procedures well known to those skilled in the art, generates the primary amine (XCV). The primary amines (XCV) may be capped C-terminally via the conditions set forth in CHART C & D followed by nitrogen deprotection and capping N-terminally via the conditions set forth in CHART A.

5 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. Furthermore, the invention includes pure enantiomers and diastereomers as well as mixtures thereof, including racemic mixtures. The individual geometric isomers, enantiomers, or diastereomers may be prepared or isolated by methods known in the art.

 Compounds of the invention with the stereochemistry designated in formula X may be included in mixtures, including racemic mixtures, with other enantiomers, diastereomers, geometric isomers or tautomers. Compounds of the invention with the stereochemistry designated in formula X are typically present in these mixtures in excess of 50 percent. Preferably, compounds of the invention with the stereochemistry designated in formula X are present in these mixtures in excess of 80 percent. Most preferably, compounds of the invention with the stereochemistry designated in formula X are present in these mixtures in excess of 90 percent.

20 The (S,R)-substituted amines (X) and the substituted amine with R_N cyclized (X') are amines and as such form salts when reacted with acids. Pharmaceutically acceptable salts are preferred over the corresponding (S,R)-substituted amines (X) and the substituted amines with R_N cyclized (X') 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, camsyllic, carbonic, chlorobenzoic, citric, edetic, edisylic, estolic, esyl, esylic, formic, fumaric, gluceptic, gluconic, glutamic, glycolylarsanilic, hexamic, hexylresorcinic, 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 present 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 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 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 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 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 present invention are useful when administered to a patient who has not been diagnosed as possibly
5 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
10 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
15 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
20 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
25 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
30 prevent or delay the outset of the disease.

Dosage forms and amounts

The compounds of the invention can be administered orally, parenterally, (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
5 suitable pharmaceutical preparations such as tablets, capsules, or elixirs for oral administration or in sterile solutions or suspensions for parenteral 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
10 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
15 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 form" 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
20 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
25 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
30 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 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 parenteral 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
5 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
10 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
15 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
20 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
25 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.

30 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
5 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
10 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 parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent
15 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
20 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. Parenteral 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
25 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
30 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.

5 Methods for preparation of such formulations are known to those skilled in the art.

The compounds of the invention can be administered orally, parenterally (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.

10 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
15 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
20 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
25 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
30 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
5 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
10 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
15 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
20 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 parenteral 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.

25 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,
30 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
5 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
10 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 preventing or delaying the onset of
15 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 preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of
20 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
25 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
30 inhibitors; anti-oxidants such as Vitamin E and ginkgolides; 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, fluorimetric 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

5 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
10 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
15 (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.

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

APP substrate

Assays that demonstrate inhibition of beta-secretase-mediated cleavage of
25 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,
30 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
5 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

10 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
15 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
20 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

25 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

30 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 beta-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.

5 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
10 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.

15

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
20 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
25 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.

30 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

20

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

I. CONVENTIONS FOR FORMULAS AND DEFINITIONS OF VARIABLES

25

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, "Z₁" 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 Z₁ would represent a bivalent variable if attached to the formula CH₃-C(=Z₁)H. Groups R_i and R_j would represent monovalent variable substituents if attached to the formula CH₃-CH₂-C(R_i)(R_j)H₂. 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 parentheses. 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 "R₆" 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., $HC\equiv C-CH(R_i)-CH_2-CH_3$. Carbonyl groups are represented in either one of two ways: -CO- or -C(=O)-, with the former being preferred for simplicity.

Chemical formulas of cyclic (ring) compounds or molecular fragments can be represented in a linear fashion. Thus, the compound 4-chloro-2-methylpyridine can be represented in linear fashion by $N^*=C(CH_3)-CH=CCl-CH=C^*H$ with the convention that the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring. Likewise, the cyclic molecular fragment, 4-(ethyl)-1-piperazinyl can be represented by $-N^*-(CH_2)_2-N(C_2H_5)-CH_2-C^*H_2$.

A rigid cyclic (ring) structure for any compounds herein defines an orientation with respect to the plane of the ring for substituents attached to each carbon atom of the rigid cyclic compound. For saturated compounds which have two substituents attached to a carbon atom which is part of a cyclic system, -C(X₁)(X₂)- the two substituents may be in either an axial or equatorial position relative to the ring and may change between axial/equatorial. However, the position of the two substituents relative to the ring and each other remains fixed. While

either substituent at times may lie in the plane of the ring (equatorial) rather than above or below the plane (axial), one substituent is always above the other. In chemical structural formulas depicting such compounds, a substituent (X_1) which is "below" another substituent (X_2) will be identified as being in the alpha configuration and is identified by a broken, dashed or dotted line attachment to the carbon atom, i.e., by the symbol "- - -" or "...". The corresponding substituent attached "above" (X_2) the other (X_1) is identified as being in the beta configuration and is indicated by an unbroken line attachment to the carbon atom.

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 $\beta-R_{i-k}$. When a bivalent variable, R_i , is defined to consist of two monovalent variable substituents, the convention used to define the bivalent variable is of the form " $\alpha-R_{i-j}:\beta-R_{i-k}$ " or some variant thereof. In such a case both $\alpha-R_{i-j}$ and $\beta-R_{i-k}$ are attached to the carbon atom to give $-C(\alpha-R_{i-j})(\beta-R_{i-k})-$. For example, when the bivalent variable R_6 , $-C(=R_6)-$ is defined to consist of two monovalent variable substituents, the two monovalent variable substituents are $\alpha-R_{6-1}:\beta-R_{6-2}$, ..., $\alpha-R_{6-9}:\beta-R_{6-10}$, etc, giving $-C(\alpha-R_{6-1})(\beta-R_{6-2})-$, ..., $-C(\alpha-R_{6-9})(\beta-R_{6-10})-$, etc. Likewise, for the bivalent variable R_{11} , $-C(=R_{11})-$, two monovalent variable substituents are $\alpha-R_{11-1}:\beta-R_{11-2}$. For a ring substituent for which separate alpha and beta orientations do not exist (e.g. due to the presence of a carbon carbon double bond in the ring), and for a substituent bonded to a carbon atom which is not part of a ring the above convention is still used, but the alpha and beta designations are omitted.

Just as a bivalent variable may be defined as two separate monovalent variable substituents, two separate monovalent variable substituents may be defined to be taken together to form a bivalent variable. For example, in the formula $-C_1(R_i)H-C_2(R_j)H-$ (C_1 and C_2 define arbitrarily a first and second carbon atom, respectively) R_i and R_j may be defined to be taken together to form (1) a second bond between C_1 and C_2 or (2) a bivalent group such as oxa $(-O-)$ and the formula thereby describes an epoxide. When R_i and R_j are taken together to form a more complex entity, such as the group $-X-Y-$, then the orientation of the entity is such

that C_1 in the above formula is bonded to X and C_2 is bonded to Y. Thus, by convention the designation "... R_i and R_j are taken together to form $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CO}-$..." means a lactone in which the carbonyl is bonded to C_2 . However, when designated "... R_j and R_i are taken together to form $-\text{CO}-\text{O}-\text{CH}_2-\text{CH}_2-$ the convention means a lactone in which the carbonyl is bonded to C_1 .

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 alkoxy carbonyl describes a group $\text{CH}_3-(\text{CH}_2)_n-\text{O}-\text{CO}-$ where n is zero, one or two. 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) alkoxy carbonyl has the same meaning as C_2-C_4 alkoxy carbonyl because the " C_1-C_3 " refers only to the carbon atom content of the alkoxy group. Similarly while both C_2-C_6 alkoxy alkyl and (C_1-C_3) alkoxy (C_1-C_3) alkyl define alkoxy alkyl 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.

II. DEFINITIONS

All temperatures are in degrees Celsius.

TLC refers to thin-layer chromatography.

psi refers to pounds/in².

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-
5 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.

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

CBZ refers to benzyloxycarbonyl, -CO-O-CH₂-phenyl.

Fmoc refers to 9-fluorenylmethyl carbonate.

TFA refers to trifluoroacetic acid, CF₃-COOH.

15 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
20 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 (δ) downfield from TMS.

25 IR refers to infrared spectroscopy.

-phenyl refers to phenyl (C₆H₅).

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
30 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
5 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).

10 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.

15 The following terms are used (in EXAMPLEs 321 and above) for the amide forming agent (IX):

"PHTH" refers to $(\text{CH}_3\text{-CH}_2\text{-CH}_2)_2\text{N-CO-phenyl-CO-OH}$ where the attachment to the - phenyl- ring is 1,3-;

20 "5-Me-PHTH" refers to $(\text{CH}_3\text{-CH}_2\text{-CH}_2)_2\text{N-CO-(CH}_3\text{-) phenyl -CO-OH}$ where the attachment to the - phenyl - ring is 1,3- for the carbonyl groups and 5- for the methyl group;

"3,5-pyridinyl" refers to $(\text{CH}_3\text{-CH}_2\text{-CH}_2)_2\text{N-CO-(pyridinyl)-CO-OH}$ where the attachment to the -pyridinyl- ring is 3,5- for the carbonyl groups;

25 "-SO₂-" refers to $(\text{CH}_3\text{-CH}_2\text{-CH}_2)_2\text{CH-SO}_2\text{- phenyl -CO-OH}$ where the attachment to the - phenyl - ring is 1,3-;

"5-OMe-PHTH" refers to $(\text{CH}_3\text{-CH}_2\text{-CH}_2)_2\text{N-CO-(CH}_3\text{-O-) phenyl -CO-OH}$ where the attachment to the - phenyl - ring is 1,3- for the carbonyl groups and 5- for the methoxy group;

30 "5-Cl-PHTH" refers to $(\text{CH}_3\text{-CH}_2\text{-CH}_2)_2\text{N-CO-(Cl-)phenyl-CO-OH}$ where the attachment to the -phenyl- ring is 1,3- for the carbonyl groups and 5- for the chlorine atom;

"5-F-PHTH" refers to $(\text{CH}_3\text{-CH}_2\text{-CH}_2)_2\text{N-CO-(F-)phenyl-CO-OH}$ where the attachment to the -phenyl- ring is 1,3- for the carbonyl groups and 5- for the fluorine atom;

“thienyl” refers to $(\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-})_2\text{N-CO-thienyl-CO-OH}$ where the attachment to the thiophene ring is -2,5;

“2,4-pyridinyl” refers to $(\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-})_2\text{N-CO-(pyridinyl)-CO-OH}$ where the attachment to the -pyridinyl- ring is 2,4- for the carbonyl groups;

5 “4,6-pyrimidinyl” refers to $(\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-})_2\text{N-CO-(pyrimidinyl-phenyl)-CO-OH}$ where the attachment to the -pyrimidinyl ring is 4,6- for the carbonyl groups;

“morpholinyl” refers to morpholinyl-CO-phenyl-CO-OH where the attachment to the -phenyl- ring is 1,3 for the carbonyl groups.

10 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
15 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.

20 “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.

25 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.

The present invention provides compounds, compositions, and methods for inhibiting beta-secretase enzyme activity and A beta peptide production. Inhibition
30 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.

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent.

- 5 The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and
- 10 techniques.

PREPARATION 1 3-Amino-5-(methoxycarbonyl)benzoic acid (XVII)

- A suspension of *mono*-methyl 5-nitro-isophthalate (22.5 g, 100 mmol) and palladium on carbon (5%, 2.00 g) in methanol (100 mL) is shaken in a
- 15 hydrogenation apparatus under hydrogen (50 psi) for 3 hours. The mixture is then filtered through diatomaceous earth and concentrated to give the title compound, NMR (300 MHz, CDCl₃) δ 7.67, 7.41, 7.40 and 3.83; MS (ESI-) for C₉H₉NO₄ m/z (M-H)⁻ = 194.

20 PREPARATION 2 3-Bromo-5-(methoxycarbonyl)benzoic acid (XIX)

- A mixture of copper (II) bromide (1.85 g, 8.30 mmol), *n*-butyl nitrite (1.07 g, 10.4 mmol), and acetonitrile (30 mL) is stirred in a round bottomed flask in a water bath to which a few chunks of ice has been added. 3-Amino-5-
- (methoxycarbonyl)benzoic acid (XVII, PREPARATION 1, 1.35 g, 6.92 mmol) is
- 25 added as a slurry in warm acetonitrile (70 mL) over 15 min and the mixture is stirred at 20-25 degrees C for an additional 2 hour, at which time the mixture is partitioned between dichloromethane and hydrochloric acid (3N). The organic phase is separated and dried over sodium sulfate and concentrated to dryness.
- Chromatography (silica gel, 125 mL; methanol/dichloromethane, 15/85) and
- 30 concentration of the appropriate fractions gives a solid which is crystallized from methanol to give the title compound in two crops, NMR (DMSO-*d*₆) δ 3.90, 8.26 and 8.65.

PREPARATION 3 Methyl 3-bromo-5-[(dipropylamino)carbonyl]benzoate (XXI)

Carbonyl diimidazole (3.0 g, 18 mmol) is added to a solution of 3-bromo-5-(methoxycarbonyl)benzoic acid (XIX, PREPARATION 2, 3.9 g, 15 mmol) in THF (30 mL). The mixture is stirred for 0.5 hours. Dipropylamine (AMINE, 4.2 mL, 30 mmol) is added to the mixture, which is then stirred for 24 hours. The solvent is then removed under reduced pressure and the mixture is partitioned between ethyl acetate and water. The organic phase is then washed with saline, dried over anhydrous magnesium sulfate, filtered, and concentrated. Column chromatography (silica gel; ethyl acetate/hexanes, 15/85) gives the title compound, IR (diffuse reflectance) 2968, 2958, 1714, 1637, 1479, 1440, 1422, 1321, 1310, 1288, 1273, 1252, 889, 772 and 718 cm^{-1} ; NMR (300 MHz, CDCl_3) δ 8.21, 7.96, 7.70, 3.95, 3.46, 3.15, 1.69, 1.57, 1.00 and 0.78; MS (ESI+) for $\text{C}_{15}\text{H}_{20}\text{BrNO}_3$ m/z (M+H)⁺ = 344.1.

PREPARATION 4 3-Bromo-5-[(dipropylamino)carbonyl]benzoic acid

To a solution of methyl 3-bromo-5-[(dipropylamino)carbonyl]benzoate (XXI, PREPARATION 3, 1.4 g, 4.1 mmol) in THF/water/methanol (4/2/2, 8 mL) is added to lithium hydroxide monohydrate (0.17 g, 4.05 mmol). The mixture is stirred at 20 degrees -25 degrees C for 1 hour and then solvent is removed under reduced pressure. The residue is dissolved in water (50 mL) and hydrochloric acid (1 N) is added to adjust the pH to about 3. The aqueous mixture is extracted with ethyl acetate and the organic phase is separated and dried over magnesium sulfate to give the title compound. Analytical calculated for $\text{C}_{14}\text{H}_{18}\text{BrNO}_3$: C, 51.23; H, 5.53; N, 4.27; Br, 24.35. Found: C, 51.37; H, 5.56; N, 4.28.

PREPARATION 5 Methyl 3-(aminocarbonyl)-5-[(dipropylamino)carbonyl]benzoate (XXII)

To a mixture of methyl 3-bromo-5-[(dipropylamino)carbonyl]benzoate (XXI, PREPARATION 3, 0.5 g, 1.47 mmol) in dry N-methyl pyrrolidinone under a carbon monoxide atmosphere is added palladium (II) acetate (0.017 g, 0.074 mmol), 1,3-bis(diphenylphosphino)propane (0.045 g, 0.11 mmol), hexamethyldisilazane (1.0 mL, 4.7 mmol), and diisopropylethylamine (0.38 g, 2.94 mmol). The mixture is heated at 100 degrees C for 24 hours. The mixture is cooled to 20-25 degrees C and partitioned between water and ethyl acetate. The layers are separated and the

aqueous phase is back-washed with ethyl acetate. The organic phases are combined and washed three times with saline, dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography (silica gel, 75 mL; methanol/methylene chloride, 2.5/97.5) gives the title compound, NMR (CDCl₃)
5 delta 0.77, 1.02, 1.57, 1.71, 3.17, 3.49, 3.98, 5.78, 6.34, 8.07, 8.20 and 8.48.

PREPARATION 6 3-(Aminocarbonyl)-5-[(dipropylamino)carbonyl]benzoic acid
(XXIII)

To a mixture of methyl 3-(aminocarbonyl)-5-[(dipropylamino)carbonyl]benzoate
10 (XXII, PREPARATION 5, 0.197 g, 0.64 mmol) in methanol (5.0 mL) is added sodium hydroxide (1N, 3.0 mL). The mixture is stirred at 20-25 degrees C for 24 hours. The mixture is acidified to about pH 5 with hydrochloric acid (10%). Water (50 mL) is added and the mixture is washed twice with ethyl acetate (2 x 50 mL). The organic extracts are combined and dried over anhydrous magnesium sulfate and
15 concentrated to give the title compound, NMR (DMSO-*d*₆) delta 0.66, 0.930, 1.48, 1.62, 3.12, 3.35, 7.54, 7.98, 8.22 and 8.51.

PREPARATION 7 3-Cyano-5-[(dipropylamino)carbonyl]benzoic acid
(IX/XXXII)

20 A mixture of 3-bromo-5-[(dipropylamino)carbonyl]benzoic acid (PREPARATION 4, 0.596 g, 1.82 mmol) and copper nitrile (0.325 g, 3.63 mmol) in N-methylpyrrolidinone (1.5 mL) is stirred at 175 degrees C for 2.5 hour, at which time the mixture is cooled and partitioned between ethyl acetate and hydrochloric acid (3N). The organic layer is washed twice more with hydrochloric acid (3N) and
25 then twice more with saline which had been acidified with a small amount of hydrochloric acid (3N). The organic layer is dried over magnesium sulfate and concentrated under high vacuum to give the title compound, NMR (CDCl₃) delta 0.80, 1.02, 1.60, 1.73, 3.17, 3.51, 7.90, 8.31 and 8.41; an aliquot is crystallized from ethyl ether/dichloromethane/hexane - IR (diffuse reflectance) 3017, 2970, 2937,
30 2898, 2877, 2473, 2432, 2350, 2318, 2236, 1721, 1608, 1588, 1206 and 1196 cm⁻¹.

PREPARATION 8 3-(Aminocarbonyl)-5-[(dipropylamino)carbonyl]benzoic acid
(XXXIII)

A mixture of 3-cyano-5-[(dipropylamino)carbonyl]benzoic acid (IX/XXXII, PREPARATION 7, 0.602 g, 2.19 mmol), potassium carbonate (0.212 g, 1.53 mmol), and acetone (2.5 mL) is stirred at 20-25 degrees C. Water (2.5 mL) and urea-hydrogen peroxide adduct (0.825 g, 8.78 mmol) are added and the mixture is stirred
5 for 15 hours at 20-25 degrees C, at which time additional urea-hydrogen peroxide adduct (0.204 g) is added; after stirring for another 3 hours, an additional 0.205 g of urea-hydrogen peroxide is added. After a total of 39 hours has elapsed, the acetone is removed under reduced pressure and the residue is acidified with hydrochloric acid (3N) to pH = 2-4. The mixture is extracted with dichloromethane, the organic
10 layer is separated and washed with hydrochloric acid (0.5 N), and the organic phase is dried with anhydrous magnesium sulfate to a solid. The solid is crystallized from dichloromethane/hexane/methanol to give the title compound, MS (ESI+) for $C_{15}H_{20}N_2O_4$ m/z (M+H)⁺ = 293.2.

15 PREPARATION 9 Methyl 3-[(dipropylamino)carbonyl]-5-nitrobenzoate (XXX)

Carbonyl diimidazole (3.90 g, 24.0 mmol) is added to a mixture of *mono*-methyl 5-nitro-isophthalate (XXVIII, 4.50 g, 20.0 mmol) in dry THF (50 mL). The mixture is stirred for 0.5 hours. Dipropylamine (3.28 mL, 24.0 mmol) is added slowly to the mixture. The reaction mixture is then stirred for 4 hours. The solvent
20 is removed under reduced pressure and the mixture is partitioned between ethyl acetate and water. The organic phase is separated and washed with saline, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (silica gel; ethyl acetate/hexanes, 15/85) gives the title compound, NMR (300 MHz, CDCl₃) delta 8.88, 8.41, 8.35, 4.00, 3.48, 3.15, 1.72, 1.57, 1.00 and 0.77; MS (ESI+) for $C_{15}H_{20}N_2O_5$ m/z (M+H)⁺ = 309.2.
25

PREPARATION 10 Methyl 3-amino-5-[(dipropylamino)carbonyl]benzoate (XXXI)

A suspension of methyl 3-[(dipropylamino)carbonyl]-5-nitrobenzoate (XXX, PREPARATION 9, 6.00g, 20.0 mmol) and palladium on carbon (5%, 0.600 g) in methanol (40 mL) is shaken in a hydrogenation apparatus under hydrogen (45 psi) for 3 hours. The mixture is then filtered through diatomaceous earth and concentrated to give the title compound, NMR (300 MHz, CDCl₃) delta 7.27, 6.77, 4.10, 3.82, 3.38, 3.10, 1.62, 1.46, 0.91 and 0.68.
30

PREPARATION 11 Methyl 3-(chlorosulfonyl)-5-[(dipropylamino)carbonyl]-benzoate (XXXVII)

Methyl 3-amino-5-[(dipropylamino)carbonyl]benzoate (XXXI,

- 5 PREPARATION 10, 1.11 g, 4 mmol) is added to a mixture of water (5 mL) and concentrated hydrochloric acid (1 mL). Sodium nitrite (0.276 g, 4 mmol) is added to the mixture slowly at 0 degrees C. The mixture is then added to an acetic acid solution (5 mL) of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ saturated with sulfur dioxide. The mixture is stirred for 0.5 hours and poured into ice water. The mixture is extracted with ethyl acetate.
- 10 The organic phase is separated and washed with saturated sodium bicarbonate, water, and saline and dried over anhydrous sodium sulfate, filtered, and concentrated to give the title compound, NMR (300 MHz, CDCl_3) delta 8.69, 8.38, 8.20, 4.01, 3.49, 3.14, 1.72, 1.59, 1.01 and 0.79; MS (ESI+) for $\text{C}_{15}\text{H}_{20}\text{ClNO}_5\text{S}$ m/z (M+H)⁺ = 362.2

15

PREPARATION 12 Methyl 3-(aminosulfonyl)-5-[(dipropylamino)carbonyl]-benzoate (XXXVIII)

To a solution of methyl 3-(chlorosulfonyl)-5-

- 20 [(dipropylamino)carbonyl]benzoate (XXXVII, PREPARATION 11, 0.100 g, 0.300 mmol) in dry THF (3 mL) is added ammonia (7 N solution in methanol, 0.214 mL, 1.50 mmol). The mixture is stirred for 18 hours and solvent is then removed. The residue is partitioned between ethyl acetate and water. The organic phase is separate and washed with saline, dried over anhydrous sodium sulfate, filtered, and
- 25 concentrated to give the title compound, NMR (300 MHz, CDCl_3) delta 8.45, 8.07, 8.01, 6.05, 3.93, 3.44, 3.09, 1.67, 1.52, 0.96 and 0.73; MS (ESI+) for $\text{C}_{12}\text{H}_{22}\text{N}_2\text{O}_5\text{S}$ m/z (M+H)⁺ = 343.3.

PREPARATION 13 3-(Aminosulfonyl)-5-[(dipropylamino)carbonyl]benzoic acid (XXXVIII)

30

Lithium hydroxide monohydrate (0.011 g, 0.263 mmol) is added to a solution of methyl 3-(aminosulfonyl)-5-[(dipropylamino)carbonyl]benzoate (XXXVIII, PREPARATION 12, 0.090 g, 0.263 mmol) in a mixture of THF/methanol/water (2/1/1, 2 mL). The mixture is stirred at 20-25 degrees C for 3

hours. The mixture is then diluted with water and hydrochloric acid (1 N) is added to bring the pH to less than 3. The aqueous solution is extracted with ethyl acetate. The organic phase is separated and washed with saline, dried over anhydrous sodium sulfate, filtered and concentrated to give the title compound. ¹H NMR (300 MHz, CDCl₃) delta 10.36 (s, 1 H), 8.39 (s, 1 H), 8.09 (s, 2 H), 6.06 (s, 2 H), 3.48 (t, *J* = 7 Hz, 2 H), 3.15 (t, *J* = 7 Hz, 2 H), 1.71 (m, 2 H), 1.55 (m, 2 H), 0.97 (t, *J* = 7 Hz, 3 H), 0.74 (t, *J* = 7 Hz, 3 H). MS (ESI+) for C₁₁H₂₀N₂O₅S *m/z* 329.2 (M+H)⁺.

10 PREPARATION 14 Methyl 3-[(dipropylamino)carbonyl]-5-(1-pyrrolidinylsulfonyl)- benzoate (XXXVIII)

Following the general procedure of PREPARATION 12 and making non-critical variations but using pyrrolidine (0.347 mL, 4.16 mmol), the title compound is obtained, MS (ESI+) for C₁₉H₂₈N₂O₅S *m/z* (M+H)⁺ = 397.1.

15 PREPARATION 15 3-[(Dipropylamino)carbonyl]-5-(1-pyrrolidinylsulfonyl)benzoic acid (XXXIX)

Following the general procedure of PREPARATION 13 and making non-critical variations, the title compound is obtained, MS (ESI+) for C₁₈H₂₆N₂O₅S *m/z* (M+H)⁺ = 383.3.

20

PREPARATION 16 Methyl 3-[(dipropylamino)carbonyl]-5-[(methylamino)-sulfonyl]benzoate (XXXVIII)

Following the general procedure of PREPARATION 12 and making non-critical variations but using methyl amine (2 N solution in THF, 0.692 mL, 1.38 mmol), the title compound is obtained, MS (ESI+) for C₁₆H₂₄N₂O₅S *m/z* (M+H)⁺ = 357.1.

25

PREPARATION 17 3-[(Dipropylamino)carbonyl]-5-[(methylamino)-sulfonyl]benzoic acid (XXXIX)

30 Following the general procedure of PREPARATION 13 and making non-critical variations, the title compound is obtained, MS (ESI+) for C₁₅H₂₂N₂O₅S *m/z* (M+H)⁺ = 343.1.

PREPARATION 18 Methyl 3-[(dimethylamino)sulfonyl]-5-[(dipropylamino)-
carbonyl]benzoate (XXXVIII)

Following the general procedure of PREPARATION 12 and making non-critical variations but using dimethylamine (2 N solution in THF, 0.692 mL, 1.38 mmol), the title compound is obtained, MS (ESI+) for $C_{17}H_{26}N_2O_5S$ m/z $(M+H)^+ = 371.1$.

PREPARATION 19 3-[(Dimethylamino)sulfonyl]-5-[(dipropylamino)carbonyl]-
benzoic acid (XXXIX)

Following the general procedure of PREPARATION 13 and making non-critical variations, the title compound is obtained, MS (ESI+) for $C_{16}H_{24}N_2O_5S$ m/z $(M+H)^+ = 357.1$.

PREPARATION 20 Methyl 3-[(dipropylamino)carbonyl]-5-ethylbenzoate (IX)

Ethylboronic acid (0.800 g, 10.8 mmol), dichlorobis(triphenylphosphine)-palladium(II) (0.252 g, 0.360 mmol), potassium carbonate (2.50 g, 18.0 mmol) and lithium chloride (0.151 g, 3.60 mmol) are added to a mixture of methyl 3-bromo-5-[(dipropylamino)carbonyl]benzoate (1.23 g, 3.60 mmol) in dry DMF (20 mL). The mixture is heated at 100 degrees C for 18 hours. The mixture is then partitioned between ethyl acetate and water. The phases are separated and the ethyl acetate phase is washed with saline, dried over sodium sulfate and concentrated. The concentrate is column chromatographed (silica gel; ethyl acetate/hexanes, 15/85) to give the title compound, MS (ESI+) for $C_{17}H_{25}NO_3$ m/z $(M+H)^+ = 292.2$.

PREPARATION 21 3-[(Dipropylamino)carbonyl]-5-ethylbenzoic acid (IX)

Lithium hydroxide monohydrate (0.0680 g, 1.6 mmol) is added to a mixture of methyl 3-[(dipropylamino)carbonyl]-5-ethylbenzoate (PREPARATION 20, 0.450 g, 1.6 mmol) in a mixture of THF/methanol/water (2/1/1, 8 mL). The mixture is stirred at 20-25 degrees C for 3 hours. The mixture is then diluted with water (20 mL) and hydrochloric acid (1 N) is added to bring the pH to less than 3. The aqueous mixture is extracted with ethyl acetate. The organic phase is separated and washed with saline, dried over anhydrous magnesium sulfate, filtered and concentrated to give the title compound, MS (ESI+) for $C_{16}H_{23}NO_3$ m/z $(M+H)^+ = 278.2$.

EXAMPLE 1 tert-Butyl (1S)-3-bromo-1-(3,5-difluorobenzyl)-2-oxopropylcarbamate (III)

N-methyl-morpholine (5.83 Ml, 53 mmole, 1.05 eq.) is added to (2S)-2-
5 [(tert-butoxycarbonyl)amino]-3-(3,5-difluorophenyl)propanoic acid (II, 15 g, 50 mmole) in THF (100 mL) and the reaction is cooled to -78 degrees C. Isobutyl chloroformate (6.87 mL, 53 mmole, 1.05 eq.) is added rapidly. The cold bath is then removed and the mixture stirred for 1 hour. The reaction is monitored by TLC to insure completion of the reaction and the mixture is then filtered and washed with
10 dry THF (50 ml) and kept cold in the filtered flask at -20 degrees C.

In an ice-salt bath is placed a 500 ml graduate cylinder containing ether (200 mL) and aqueous potassium hydroxide (40%, 60 ml). 1-Methyl-3-nitro-1-nitrosoguanidine (5.6 g, 106 mmole, 2.1 eq.) is added slowly with stirring and temperature kept below 0 degrees C. The mixture turned yellow and the bubbling
15 lasted for 10 minutes. The stirring is stopped and without mixing the layers, the top diazomethane ethereal layer is transferred with non-ground tip pipette into the stirred mixed anhydride mixture at -20 degrees C. The reaction is monitored by TLC (ethyl acetate/hexane, 50/50; $R_f = 0.69$). After 1 hour nitrogen is then bubbled into the mixture. The solvent is removed under reduced pressure (with heat) and the
20 mixture is partitioned between ether and water. The phases are separated, the organic phase is washed with bicarbonate, saline, dried over anhydrous sodium sulfate and solvent removed under reduced pressure (with heat). The residue is dissolved in ether (100 mL) and hydrobromic acid (48%, 15 mL, 135 mmole, 2.7 eq.) is added at -20 degrees C, the cold bath is removed and the mixture is stirred for
25 another 0.5 hours. The reaction is monitored by TLC (ethyl acetate/hexane, 50/50; $R_f = 0.88$). The mixture is partitioned between ether and water, washed with bicarbonate, saline, dried over anhydrous sodium sulfate and the solvent removed. The residue is recrystallized from ethanol to give the title compound, TLC (ethyl acetate/hexane, 50/50) $R_f = 0.88$; MS (MH^+) = 379.3.

30

EXAMPLE 2 tert-Butyl (1S, 2S)-3-bromo-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (IV)

Sodium borohydride (1.32 g, 34.9 mmole, 1.1 eq.) is added to tert-Butyl (1S)-3-bromo-1-(3,5-difluorobenzyl)-2-oxopropylcarbamate (III, EXAMPLE 1, 12

g, 31.75 mmole) dissolved in absolute alcohol (500 mL) at -78 degrees C. The reaction mixture is stirred for 0.5 hour and monitored by TLC (ethyl acetate/hexane, 20/80; $R_f = 0.2$). The mixture is quenched with water (10 mL) and the solvent removed under reduced pressure with heat (not exceeding 30 degrees C) to dryness.

- 5 The solid is partitioned between dichloromethane and water, washed with saline, dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure to give the title compound, TLC (ethyl acetate/hexane, 20/80) $R_f = 0.2$; MS (MH^+) = 381.2.

10 EXAMPLE 3 *tert*-Butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V)

- tert-Butyl (1S, 2S)-3-bromo-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (IV, EXAMPLE 2) is dissolved in absolute alcohol (150 mL) and ethyl acetate (100 mL) and potassium hydroxide (2.3 g, 34.9 mmole, 15 1.1eq.) in ethyl alcohol (85%, 5mL) is added at -20 degrees C. The cold bath is then removed and the mixture stirred for 0.5 hour. The reaction is monitored by TLC (ethyl acetate/hexane, 20/80). When the reaction is complete, it is diluted with dichloromethane and extracted, washed with water, saline, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The crude material 20 is purified by flash chromatography on silica gel to give the title compound, TLC (ethyl acetate/hexane, 20/80) $R_f = 0.3$; MS (MH^+) = 300.4.

EXAMPLE 4 *tert*-Butyl (1S, 2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (VII)

- 25 *tert*-Butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, EXAMPLE 3, 245 mg, 0.82 mmol) is suspended in isopropyl alcohol (6 mL) and 3-methoxybenzylamine (160 microL, 1.22 mmol) is added with stirring at 20-25 degrees C. This mixture is heated to gentle reflux (bath temp 85 degrees C) under nitrogen for 2 hours, whereupon the resulting mixture is concentrated under reduced 30 pressure to give the title compound. The title compound is purified by flash chromatography (2-5% methanol/methylene chloride; gradient elution) to give purified title compound.

EXAMPLE 5 (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methoxybenzyl)amino]-2-butanol trifluoroacetate (VIII)

tert-Butyl (1S, 2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (VII, EXAMPLE 4, 258 mg, 0.59 mmol) is dissolved in methylene chloride (1 mL) at 20-25 degrees C, and trifluoroacetic acid (1 mL) is added with stirring under nitrogen. The reaction mixture is stirred at 20-25 degrees C for 1 hour, whereupon the reaction mixture is concentrated under reduced pressure to give the title compound. The title compound is used in the next reaction without further purification.

EXAMPLE 6 N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-methyl- N^3,N^3 -dipropylisophthalamide (X)

(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methoxybenzyl)amino]-2-butanol trifluoroacetate salt (VIII, EXAMPLE 5) is dissolved in anhydrous DMF (3 mL) and cooled to 0 degrees C. Triethylamine (500 microliter, 3.6 mmol) and 5-methyl-*N,N*-dipropylisophthamic acid (156 mg, 0.59 mmol) are added with stirring. The mixture is warmed to 20-25 degrees C briefly to allow for complete dissolution of the carboxylic acid, before recooling to 0 degrees C. 1-

Hydroxybenzotriazole (157 mg, 1.2 mmol) is added with stirring, followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (229 mg, 1.2 mmol). The resulting mixture is stirred at 0 degrees C for 5 minutes, then warmed to 20-25 degrees C for 15 hours. The reaction mixture is then quenched with aqueous citric acid (10%), and the mixture extracted three times with ethyl acetate. The combined organic extracts are washed with saturated sodium bicarbonate, saline, dried over sodium sulfate, filtered and concentrated under reduced pressure to give the title compound in crude form. This material is purified by flash chromatography (2-10% methanol/methylene chloride gradient elution) to give purified title compound, MS (ES) $MH^+ = 582.3$.

EXAMPLES 7-9

Following the general procedure of EXAMPLE 1 and making non critical variations but starting with the protecting group of Column A and using the acid of Column B, the protected compound (III) of Column C is obtained:

EXAMPLE	Column A	Column B	Column C
7	BOC	Hydrochloric	tert-butyl (1S)-3-chloro-1-(3,5-difluorobenzyl)-2-oxopropylcarbamate
8	CBZ	Hydrobromic	benzyl (1S)-3-bromo-1-(3,5-difluorobenzyl)-2-oxopropylcarbamate
9	CBZ	Hydrochloric	benzyl (1S)-3-chloro-1-(3,5-difluorobenzyl)-2-oxopropylcarbamate

5 EXAMPLES 10-12

Following the general procedure of EXAMPLE 2 and making non critical variations but starting with the protected compound (III) of Column A, the alcohol (IV) of Column B is obtained:

EXAMPLE	Column A	Column B
10	7	Tert-butyl (1S, 2S)-3-chloro-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate
11	8	Benzyl (1S, 2S)-3-bromo-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate
12	9	Benzyl (1S, 2S)-3-chloro-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate

10 EXAMPLE 13 Benzyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V)

Following the general procedure of EXAMPLE 3 and making non critical variations but starting with the alcohol (IV) of EXAMPLE 12, the title compound is obtained.

15

EXAMPLES 14-107

Following the general procedure of EXAMPLE 4 and making non-critical variations but reacting tert-butyl (1S,2S)-1-(2-oxiranyl)-2-phenylethylcarbamate (V, commercially available) with the C-terminal amine (VI) of Column A, the protected

20 alcohol (VII) of Column B is obtained.

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
14	H ₂ N-CH ₂ CH ₃	tert-butyl (1S,2R)-1-benzyl-3-(ethylamino)-2-hydroxypropylcarbamate
15	H ₂ N-CH ₂ -phenyl	tert-butyl (1S,2R)-1-benzyl-3-(benzylamino)-2-hydroxypropylcarbamate
16	H ₂ N-CH(CH ₃) ₂	tert-butyl (1S,2R)-1-benzyl-3-(isopropylamino)-2-hydroxypropylcarbamate
17	H ₂ N-CH ₂ -phenyl-4-CH ₃	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(4-methylbenzyl)amino]propylcarbamate
18	H ₂ N-(CH ₂) ₂ -phenyl-4-OCH ₃	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[2-(4-methoxyphenyl)ethyl]amino}propylcarbamate
19	H ₂ N-CH ₂ -phenyl-3-OCH ₃	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate
20	H ₂ N-CH(-phenyl)-CO-OC ₂ H ₅	ethyl ({(2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-4-phenylbutyl}amino)(phenyl)acetate
21	H ₂ N-(CH ₂) ₂ -phenyl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(2-phenylethyl)amino]propylcarbamate
22	H ₂ N-CH(-CH ₂ OH)-	tert-butyl (1S,2R)-1-benzyl-2-

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
	CH(OH)-phenyl-4-NO ₂	hydroxy-3-{[(1S)-2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl]amino}propylcarbamate
23	H ₂ N-CH ₂ -phenyl-2-Cl	tert-butyl (1S,2R)-1-benzyl-3-[(2-chlorobenzyl)amino]-2-hydroxypropylcarbamate
24	H ₂ N-CH ₂ -phenyl-4-Cl	tert-butyl (1S,2R)-1-benzyl-3-[(4-chlorobenzyl)amino]-2-hydroxypropylcarbamate
25	H ₂ N-(CH ₂) ₂ -O-(CH ₂) ₂ -OH	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[2-(2-hydroxyethoxy)ethyl]amino}propylcarbamate
26	H ₂ N-1-indanyl	tert-butyl (1S,2R)-1-benzyl-3-(2,3-dihydro-1H-inden-1-ylamino)-2-hydroxypropylcarbamate
27	H ₂ N-CH ₂ -CH(OH)-CH ₃	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(2-hydroxypropyl)amino]propylcarbamate
28	H ₂ N-CH ₂ -tetrahydrofuranyl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(tetrahydro-2-furanylmethyl)amino]propylcarbamate
29	H ₂ N-CH ₂ -CH(-OCH ₂ CH ₃)	tert-butyl (1S,2R)-1-benzyl-3-[(2,2-diethoxyethyl)amino]-2-hydroxypropylcarbamate
30	H ₂ N-(CH ₂) ₄ -CH ₃	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-(pentylamino)

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
		propylcarbamate
31	H ₂ N-cyclohexyl	tert-butyl (1S,2R)-1-benzyl-3-(cyclohexylamino)-2-hydroxypropylcarbamate
32	H ₂ N-CH ₂ -pyridin-2-yl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(2-pyridinylmethyl)amino]propylcarbamate
33	H ₂ N-CH ₂ -phenyl-2-NH ₂	tert-butyl (1S,2R)-3-[(2-aminobenzyl)amino]-1-benzyl-2-hydroxypropylcarbamate
34	H ₂ N-CH ₂ -pyridin-3-yl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-pyridinylmethyl)amino]propylcarbamate
35	H ₂ N-(CH ₂) ₂ -pyrrolidin-1-yl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[2-(1-pyrrolidinyl)ethyl]amino}propylcarbamate
36	H ₂ N-CH ₂ -CH(OH)-phenyl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(2-hydroxy-2-phenylethyl)amino]propylcarbamate
37	H ₂ N-(CH ₂) ₃ -O-(CH ₂) ₃ -CH ₃	tert-butyl (1S,2R)-1-benzyl-3-[(3-butoxypropyl)amino]-2-hydroxypropylcarbamate
38	H ₂ N-(CH ₂) ₃ -O-CH(CH ₃) ₂	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-isopropoxypropyl)amino]propylcarbamate

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
39	$\text{H}_2\text{N}-(\text{CH}_2)_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-(isopentylamino) propylcarbamate
40	$\text{H}_2\text{N}-(\text{CH}_2)_3\text{-phenyl}$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-phenylpropyl)amino]propylcarbamate
41	$\text{H}_2\text{N}-(\text{CH}_2)_2-\text{OCH}_3$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(2-methoxyethyl)amino]propylcarbamate
42	$\text{H}_2\text{N}-(\text{CH}_2)_2-\text{O-phenyl}$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(2-phenoxyethyl)amino]propylcarbamate
43	$\text{H}_2\text{N}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{CH}_3$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(2-propoxyethyl)amino]propylcarbamate
44	$\text{H}_2\text{N}-(\text{CH}_2)_2-\text{C}(\text{CH}_3)_3$	tert-butyl (1S,2R)-1-benzyl-3-[(3,3-dimethylbutyl)amino]-2-hydroxypropylcarbamate
45	$\text{H}_2\text{N}-(\text{CH}_2)_4\text{-phenyl}$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(4-phenylbutyl)amino]propylcarbamate
46	$\text{H}_2\text{N}-\text{CH}_2\text{-phenyl-3-I}$	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-iodobenzyl)amino]propylcarbamate
47	$\text{H}_2\text{N}-\text{CH}_2\text{-phenyl-4-NO}_2$	tert-butyl (1S,2R)-1-benzyl-2-

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
		hydroxy-3-[(4-nitrobenzyl)amino]propylcarbamate
48	H ₂ N-CH ₂ -phenyl-3-Cl	tert-butyl (1S,2R)-1-benzyl-3-[(3-chlorobenzyl)amino]-2-hydroxypropylcarbamate
49	H ₂ N-(CH ₂) ₂ -phenyl-4-Cl	tert-butyl (1S,2R)-1-benzyl-3-{[2-(4-chlorophenyl)ethyl]amino}-2-hydroxypropylcarbamate
50	H ₂ N-(CH ₂) ₂ -pyridin-2-yl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[2-(2-pyridinyl)ethyl]amino}propylcarbamate
51	H ₂ N-CH ₂ -pyridin-4-yl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(4-pyridinylmethyl)amino]propylcarbamate
52	H ₂ N-(CH ₂) ₂ -(N-methylpyrrolidin-2-yl)	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[2-(1-methyl-2-pyrrolidinyl)ethyl]amino}propylcarbamate
53	H ₂ N-CH ₂ -phenyl-2,3-dimethyl	tert-butyl (1S,2R)-1-benzyl-3-[(2,3-dimethylbenzyl)amino]-2-hydroxypropylcarbamate
54	H ₂ N-CH ₂ -phenyl-2-OCF ₃	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[2-(trifluoromethoxy)benzyl]amino}propylcarbamate
55	H ₂ N-CH ₂ -phenyl-2-Cl-6-O-phenyl	tert-butyl (1S,2R)-1-benzyl-3-[(2-chloro-6-

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
		phenoxybenzyl)amino]-2-hydroxypropylcarbamate
56	H ₂ N-CH ₂ -phenyl-4-CF ₃	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3- {[4-(trifluoromethyl)benzyl]amino} propylcarbamate
57	H ₂ N-CH ₂ -phenyl-2,3-dichloro	tert-butyl (1S,2R)-1-benzyl-3- [(2,3-dichlorobenzyl)amino]-2-hydroxypropylcarbamate
58	H ₂ N-CH ₂ -phenyl-3,5-dichloro	tert-butyl (1S,2R)-1-benzyl-3- [(3,5-dichlorobenzyl)amino]-2-hydroxypropylcarbamate
59	H ₂ N-CH ₂ -phenyl-3,5-difluoro	tert-butyl (1S,2R)-1-benzyl-3- [(3,5-difluorobenzyl)amino]-2-hydroxypropylcarbamate
60	H ₂ N-CH ₂ -phenyl-4-OCF ₃	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3- {[4-(trifluoromethoxy)benzyl]amino} propylcarbamate
61	H ₂ N-(CH ₂) ₂ -phenyl-4-SO ₂ -NH ₂	tert-butyl (1S,2R)-3- {[4-(aminosulfonyl)benzyl]amino}-1-benzyl-2-hydroxypropylcarbamate
62	H ₂ N-CH ₂ -phenyl-4-OCH ₃	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3- [(4-methoxybenzyl)amino] propylcarbamate
63	H ₂ N-CH ₂ -phenyl-4-CH ₃	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3- [(4-methylbenzyl)amino] propylcarbamate

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
64	H ₂ N-CH ₂ -Ph-(3,4,5-trimethoxy)	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3,4,5-trimethoxybenzyl)amino]propylcarbamate
65	H ₂ N-CH ₂ -phenyl-3-OCF ₃	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[3-(trifluoromethoxy)benzyl]amino]propylcarbamate
66	H ₂ N-CH ₂ -phenyl-3,5-dimethoxy	tert-butyl (1S,2R)-1-benzyl-3-[(3,5-dimethoxybenzyl)amino]-2-hydroxypropylcarbamate
67	H ₂ N-CH ₂ -phenyl-2,4-dimethoxy	tert-butyl (1S,2R)-1-benzyl-3-[(2,4-dimethoxybenzyl)amino]-2-hydroxypropylcarbamate
68	H ₂ N-CH ₂ -phenyl-phenyl	tert-butyl (1S,2R)-1-benzyl-3-[[[1,1'-biphenyl]-3-ylmethyl]amino]-2-hydroxypropylcarbamate
69	H ₂ N-CH ₂ -phenyl-3,4-dichloro	tert-butyl (1S,2R)-1-benzyl-3-[(3,4-dichlorobenzyl)amino]-2-hydroxypropylcarbamate
70	H ₂ N-CH ₂ -phenyl-4-F	tert-butyl (1S,2R)-1-benzyl-3-[(4-fluorobenzyl)amino]-2-hydroxypropylcarbamate
71	H ₂ N-CH ₂ -phenyl-3-CF ₃	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propylcarbamate
72	H ₂ N-CH ₂ -phenyl-2-CH ₃	tert-butyl (1S,2R)-1-benzyl-2-

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
		hydroxy-3-[(2-methylbenzyl)amino]propylcarbamate
73	H ₂ N-CH((R)-CH ₃)-phenyl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[(1R)-1-phenylethyl]amino}propylcarbamate
74	H ₂ N-CH((S)-CH ₃)-phenyl	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[(1S)-1-phenylethyl]amino}propylcarbamate
75	H ₂ N-CH ₂ -phenyl-3,5-(bis)trifluoromethyl	tert-butyl (1S,2R)-1-benzyl-3-{{3,5-bis(trifluoromethyl)benzyl]amino}-2-hydroxypropylcarbamate
76	H ₂ N-CH ₂ -phenyl-2-CF ₃	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{{2-(trifluoromethyl)benzyl]amino}propylcarbamate
77	H ₂ N-CH((S)-CH ₃)-(naphth-1-yl)	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[(1S)-1-(1-naphthyl)ethyl]amino}propylcarbamate
78	-NH ₂ -CH((R)-CH ₃)-(naphth-1-yl)	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[(1R)-1-(1-naphthyl)ethyl]amino}propylcarbamate
79	H ₂ N-CH ₂ -phenyl-3-OCH ₃ -4-OH	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(4-hydroxy-3-methoxybenzyl)amino]propylcarbamate

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
80	H ₂ N-CH ₂ -phenyl-3,4-dihydroxy	tert-butyl (1S,2R)-1-benzyl-3-[(3,4-dihydroxybenzyl)amino]-2-hydroxypropylcarbamate
81	H ₂ N-(CH ₂) ₃ -OCH ₃	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxypropyl)amino]propyl carbamate
82	H ₂ N-CH((S)-CH ₃)-CH ₂ -OH	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[(1S)-2-hydroxy-1-methylethyl]amino}propyl carbamate
83	H ₂ N-CH((R)-CH ₃)-CH ₂ -OH	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-{[(1R)-2-hydroxy-1-methylethyl]amino}propyl carbamate
84	H ₂ N-CH ₂ -C≡CH	tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-(2-propynylamino)propylcarbamate
85	H ₂ N-(CH ₂) ₂ -phenyl-2-F	tert-butyl (1S,2R)-1-benzyl-3-{{2-(2-fluorophenyl)ethyl]amino}-2-hydroxypropylcarbamate
86	H ₂ N-(CH ₂) ₂ -phenyl-3-F	tert-butyl (1S,2R)-1-benzyl-3-{{2-(3-fluorophenyl)ethyl]amino}-2-hydroxypropyl carbamate
87	H ₂ N-(CH ₂) ₂ -phenyl-4-F	tert-butyl (1S,2R)-1-benzyl-3-{{2-(4-fluorophenyl)ethyl]amino}-2-hydroxypropyl carbamate

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
88	H ₂ N-(CH ₂) ₂ -phenyl-4-Br	tert-butyl (1S,2R)-1-benzyl-3- {[2-(4-bromophenyl)ethyl] amino}-2-hydroxypropyl carbamate
89	H ₂ N-(CH ₂) ₂ -phenyl-3-OCH ₃	tert-butyl (1S,2R)-1-benzyl-2- hydroxy-3-{[2-(3- methoxyphenyl)ethyl]amino} propylcarbamate
90	H ₂ N-(CH ₂) ₂ -phenyl-2,4- dichloro	tert-butyl (1S,2R)-1-benzyl-3- {[2-(2,4- dichlorophenyl)ethyl]amino}- 2-hydroxypropylcarbamate
91	H ₂ N-(CH ₂) ₂ -phenyl-3-Cl	tert-butyl (1S,2R)-1-benzyl-3- {[2-(3- chlorophenyl)ethyl]amino}-2- hydroxypropylcarbamate
92	H ₂ N-(CH ₂) ₂ -phenyl-2,5- dimethoxy	tert-butyl (1S,2R)-1-benzyl-3- {[2-(2,5-dimethoxyphenyl) ethyl]amino}-2- hydroxypropylcarbamate
93	H ₂ N-(CH ₂) ₂ -phenyl-4-CH ₃	tert-butyl (1S,2R)-1-benzyl-2- hydroxy-3-{[2-(4- methylphenyl)ethyl]amino}pr opylcarbamate
94	H ₂ N-CH(-(R)CH ₂ -OH)-CH ₂ - phenyl	tert-butyl (1S,2R)-1-benzyl-3- {[(1R)-1-benzyl-2- hydroxyethyl]amino}-2- hydroxypropylcarbamate
95	H ₂ N-(CH ₂) ₃ -(1-morpholinyl)	tert-butyl (1S,2R)-1-benzyl-2- hydroxy-3-{[3-(4- morpholinyl)propyl]amino}pr

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
		opylcarbamate
96	$\text{H}_2\text{N}-\text{CH}_2-\text{C}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-benzyl-3- [(3,3-dimethylbutyl)amino]-2- hydroxypropylcarbamate
97	$\text{H}_2\text{N}-(\text{CH}_2)_2-(1\text{-morpholinyl})$	tert-butyl (1S,2R)-1-benzyl-2- hydroxy-3-{[2-(4- morpholinyl)ethyl]amino}pro pylcarbamate
98	$\text{H}_2\text{N}-\text{CH}(\text{OH})-\text{CH}_2-\text{CH}_3$	tert-butyl (1S,2R)-1-benzyl-2- hydroxy-3-[(1- hydroxypropyl)amino]propylc arbamate
99	$\text{H}_2\text{N}-(\text{CH}_2)_2-(\text{thien-2-yl})$	tert-butyl (1S,2R)-1-benzyl-2- hydroxy-3-[(2- thienylmethyl)amino]propylca rbamate
100	$\text{H}_2\text{N}-(\text{CH}_2)_4-\text{OH}$	tert-butyl (1S,2R)-1-benzyl-2- hydroxy-3-[(4- hydroxybutyl)amino]propylca rbamate
101	$\text{H}_2\text{N}-\text{CH}(-(\text{S})\text{CH}_2-\text{OH})\text{-phenyl}$	tert-butyl (1S,2R)-1-benzyl-2- hydroxy-3-{[(1S)-2-hydroxy- 1-phenylethyl]amino} propylcarbamate
102	$\text{H}_2\text{N}-\text{CH}_2\text{-phenyl-2,4-dichloro}$	tert-butyl (1S,2R)-1-benzyl-3- [(2,4-dichlorobenzyl)amino]- 2-hydroxypropylcarbamate
103	$\text{H}_2\text{N}-\text{CH}(-(\text{R})\text{CH}_2-\text{OH})\text{-phenyl}$	tert-butyl (1S,2R)-1-benzyl-2- hydroxy-3-{[(1R)-2-hydroxy- 1-phenylethyl]amino} propylcarbamate

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
104	H ₂ N-CH ₂ -phenyl-4-C(CH ₃) ₃	tert-butyl (1S,2R)-1-benzyl-3- [(4-tert-butylbenzyl)amino]-2- hydroxypropylcarbamate
105	H ₂ N-CH(CH ₃)-phenyl	tert-butyl (1S,2R)-1-benzyl-2- hydroxy-3-[(1- phenylethyl)amino]propylcarb amate
106	H ₂ N-(1R,2S)-2- hydroxyinden-1-yl	tert-butyl (1S,2R)-1-benzyl-2- hydroxy-3-{[(1R,2S)-2- hydroxy-2,3-dihydro-1H- inden-1- yl]amino}propylcarbamate
107	H ₂ N-CH ₂ -phenyl-3,4- dimethyl	tert-butyl (1S,2R)-1-benzyl-3- [(3,4-dimethylbenzyl)amino]- 2-hydroxypropylcarbamate

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- Following the general procedure of EXAMPLE 4 and making non-critical variations but reacting tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-
- 5 oxiranyl]ethylcarbamate (V, EXAMPLE 3) with the C-terminal amine (VI) of Column A, the protected alcohol (VII) of Column B is obtained.

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
108	H ₂ N-(CH ₂) ₆ -CO-O-CH ₃	methyl 7-{[(2R,3S)-3-[(tert- butoxycarbonyl)amino]-4- (3,5-difluorophenyl)-2- hydroxybutyl]amino}heptano ate
109	H ₂ N-CH(-CH ₃)-CO-NH- CH ₂ -CH(CH ₃) ₂ r/s	tert-butyl (1S,2R)-1-(3,5- difluorobenzyl)-2-hydroxy-3-

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
		{[2-(isobutylamino)-1-methyl-2-oxoethyl]amino}propylcarbamate
110	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{CH}_3)-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{{(1S)-2-(isobutylamino)-1-methyl-2-oxoethyl]amino}propylcarbamate
111	$\text{H}_2\text{N}-\text{C}(-\text{CH}_3)_2-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{{[2-(isobutylamino)-1,1-dimethyl-2-oxoethyl]amino}propylcarbamate
112	$\text{H}_2\text{N}-\text{CH}_2-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{{[2-(isobutylamino)-2-oxoethyl]amino}propylcarbamate
113	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{CH}_2\text{CH}_3)-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({(1S)-1-[(isobutylamino)carbonyl]propyl}amino)propylcarbamate
114	$\text{H}_2\text{N}-\text{CH}((\text{R})-\text{CH}_2\text{CH}_3)-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({(1R)-1-[(isobutylamino)carbonyl]propyl}amino)propylcarbamate

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
115	H ₂ N-CH ₂ -phenyl	tert-butyl (1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate
116	H ₂ N-CH ₂ -CH ₃	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-(ethylamino)-2-hydroxypropylcarbamate
117	H ₂ N-CH ₂ -CH(CH ₃) ₂	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(isobutylamino)propylcarbamate
118	H ₂ N-CH ₂ -CH(CH ₃)-CONH-CH ₂ -CH(CH ₃) ₂	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(isobutylamino)-2-methyl-3-oxopropyl]amino}propylcarbamate
119	H ₂ N-CH ₂ -phenyl-4-N(CH ₃) ₂	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-{[4-(dimethylamino)benzyl]amino}-2-hydroxypropylcarbamate
120	H ₂ N-CH((S)-CH ₂ -phenyl)-CO-NH-CH ₂ -CH(CH ₃) ₂	tert-butyl (1S,2R)-3-{[(1S)-1-(3,5-difluorobenzyl)-2-(isobutylamino)-2-oxoethyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate
121	H ₂ N-CH((S)-CH(CH ₃) ₂)-CO-NH-CH ₂ -CH(CH ₃) ₂	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((1S)-1-

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
		[(isobutylamino)carbonyl]-3-methylbutyl} amino)propylcarbamate
122	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-{[2-(dimethylamino)ethyl]amino}-2-hydroxypropylcarbamate
123	$\text{H}_2\text{N}-\text{CH}_2-(\text{pyridin-3-yl})$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-pyridinylmethyl)amino]propylcarbamate
124	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{CH}_2-\text{O}-\text{CH}_2-\text{phenyl})-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-3-{[(1S)-1-[(benzyloxy)methyl]-2-(isobutylamino)-2-oxoethyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate
125	$\text{H}_2\text{N}-\text{C}(-\text{CH}_3)_2-\text{phenyl}$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1-methyl-1-phenylethyl)amino]propylcarbamate
126	$\text{H}_2\text{N}-\text{CH}((\text{R})-\text{CH}(\text{CH}_3)_2)-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({(1R)-1-[(isobutylamino)carbonyl]-3-methylbutyl} amino)propylcarbamate
127	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{CH}_2-\text{CH}_2-\text{CH}_3)-\text{CO}-\text{NH}-\text{CH}_2-$	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
	$\text{CH}(\text{CH}_3)_2$	((1S)-1- [(isobutylamino)carbonyl]but yl} amino)propylcarbamate
128	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{CH}_2-\text{OH})-\text{CO}-$ $\text{NH}-\text{CH}_2-\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5- difluorobenzyl)-2-hydroxy-3- {[(1S)-1-(hydroxymethyl)-2- (isobutylamino)-2- oxoethyl]amino}propylcarba mate
129	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2$ -phenyl	tert-butyl (1S,2R)-1-(3,5- difluorobenzyl)-2-hydroxy-3- [(2- phenylethyl)amino]propylcarb amate
130	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{CH}_3)-\text{CO}-\text{NH}-$ CH_2 -phenyl	tert-butyl (1S,2R)-3-{[2- (benzylamino)-1-methyl-2- oxoethyl]amino}-1-(3,5- difluorobenzyl)-2- hydroxypropylcarbamate
131	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{CH}_2-\text{CH}_3)-$ phenyl	tert-butyl (1S,2R)-1-(3,5- difluorobenzyl)-3-{[(1S)-2- (benzylamino)-1-methyl-2- oxoethyl]amino}-2- hydroxypropylcarbamate
132	$\text{H}_2\text{N}-\text{CH}_2$ -phenyl-3-OCH ₃	tert-butyl (1S,2R)-1-(3,5- difluorobenzyl)-2-hydroxy-3- [(3- methoxybenzyl)amino]propyl carbamate
133	$\text{H}_2\text{N}-\text{CH}((\text{S})-\text{phenyl})\text{CO}-$ $\text{NHCH}_2\text{CH}(\text{CH}_3)_2$	tert-butyl (1S,2R)-1-(3,5- difluorobenzyl)-2-hydroxy-3-

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
		{[(1S)-2-(isobutylamino)-2-oxo-1-phenylethyl]amino}propylcarbamate
134	H ₂ N-CH ₂ -CH ₂ -CH(CH ₃) ₂	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(isopentylamino)propylcarbamate
135	H ₂ N-cyclohexyl	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclohexylamino)-2-hydroxypropylcarbamate
136	H ₂ N-(CH ₂) ₃ -CH ₃	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-(butylamino)-2-hydroxypropylcarbamate
137	H ₂ N-(CH ₂) ₃ -O-CH ₃	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxypropyl)amino]propylcarbamate
138	H ₂ N-CH ₂ -CH(OH)-phenyl	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-hydroxy-2-phenylethyl)amino]propylcarbamate
139	H ₂ N-cyclohexyl-3,5-dimethoxy	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-{[(3R,5S)-3,5-dimethoxycyclohexyl]amino}-2-hydroxypropylcarbamate

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
140	H ₂ N-cyclohexyl-3,5-di-(-CO-OCH ₃)	dimethyl (1R,3S)-5-((2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-4-phenylbutyl)amino)-1,3-cyclohexanedicarboxylate
141	H ₂ N-cyclohexyl-3,5-di-(-COOH)	(1R,3S)-5-((2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-4-phenylbutyl)amino)-1,3-cyclohexanedicarboxylic acid
142	H ₂ N-CH((R)-CH ₂ -CH ₃)-phenyl	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([(1R)-1-phenylpropyl]amino)propyl carbamate
143	H ₂ N-CH ₂ -phenyl-3-Cl	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-chlorobenzyl)amino]-2-hydroxypropyl carbamate
144	H ₂ N-CH ₂ -phenyl-3-OCH ₃	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl carbamate
145	H ₂ N-CH ₂ -phenyl-phenyl	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-([(1,1'-biphenyl]-3-ylmethyl)amino]-2-hydroxypropyl carbamate
146	H ₂ N-CH ₂ -phenyl-3-I	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
		[(3-iodobenzyl)amino]propylcarbamate
147	H ₂ N-CH ₂ -phenyl-3-CH ₃	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methylbenzyl)amino]propylcarbamate
148	H ₂ N-CH ₂ -CH(-CH ₃)-phenyl	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-phenylpropyl)amino]propylcarbamate
149	H ₂ N-CH ₂ -(thiazol-5-yl)	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1,3-thiazol-5-ylmethyl)amino]propylcarbamate
150	H ₂ N-CH ₂ -(thien-2-yl)	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-thienylmethyl)amino]propylcarbamate
151	H ₂ N-4-methoxytetralin-1-yl	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(5-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)amino]propylcarbamate
152	H ₂ N-CH ₂ -pyrazin-2-yl	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
		[(2-pyrazinylmethyl)amino]propylcarbamate
153	H ₂ N-CH ₂ -phenyl-3,5-difluoro	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3,5-difluorobenzyl)amino]-2-hydroxypropylcarbamate
154	H ₂ N-CH ₂ -phenyl-3,4-methylenedioxy	tert-butyl (1S,2R)-3-[(1,3-benzodioxol-5-ylmethyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate
155	H ₂ N-CH ₂ -phenyl-3,5-dimethoxy	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3,5-dimethoxybenzyl)amino]-2-hydroxypropylcarbamate
156	H ₂ N-CH ₂ -phenyl-3-CF ₃	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propylcarbamate
157	H ₂ N-CH ₂ -(furan-2-yl)	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-furylmethyl)amino]-2-hydroxypropylcarbamate
158	H ₂ N-(7-methoxytetralin-1-yl)	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(7-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)amino]propylcarbamate

EXA	Column A C-terminal amine (VI)	Column B Protected alcohol (VII)
159	H ₂ N-CH ₂ -phenyl-3-O-CF ₃	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3- {[3-(trifluoromethoxy)benzyl]amino}propylcarbamate
160	H ₂ N-CH ₂ -phenyl-3-F	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-fluorobenzyl)amino]-2-hydroxypropylcarbamate
161	H ₂ N-CH ₂ -phenyl-3-O-CH(CH ₃) ₂	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3- [(3-isopropoxybenzyl)amino]propylcarbamate
162	H ₂ N-CH ₂ -phenyl-3-Br	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-bromobenzyl)amino]-2-hydroxypropylcarbamate
163	H ₂ N-CH ₂ -(5-methylfuran-2-yl)	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3- {[(5-methyl-2-furyl)methyl]amino}propylcarbamate
164	H ₂ N-(5-methoxytetralin-1-yl)	tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3- [(5-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)amino]propylcarbamate

EXAMPLE 165 tert-Butyl-(1S, 2R)-3-azido-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (XII)

Sodium azide (0.22 g, 4 mmole) and ammonium chloride (2 eq) are added to tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, 5 EXAMPLE 3, 0.6 g, 2 mmole). The reaction is heated to 75-80 degrees C and stirred for 16 hours. The reaction is monitored by TLC to insure completion. The solvent is removed under reduced pressure. The concentrate is partitioned between ethyl acetate and water, the phases are separated and the organic phase is washed with bicarbonate and saline, dried over anhydrous sodium sulfate and concentrated 10 to give the title compound, TLC (ethyl acetate/hexane) $R_f = 0.45$; MS (MH^+) = 343.

EXAMPLE 166 (2R, 3S)-3-amino-1-azido-4-(3,5-difluorophenyl)-2-butanol (XIV)

tert-Butyl-(1S, 2R)-3-azido-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (XII, EXAMPLE 165, 0.48 g, 1.41 mmole) is dissolved in 15 dichloromethane (20 ml) to which trifluoroacetic acid (5 ml) is added. The reaction is stirred at 20-25 degrees C for 16 hours and the solvent is removed under reduced pressure with heat. Ethyl acetate is added twice and evaporated twice to give the title compound as the trifluoroacetic acid salt which is used in the next reaction 20 without further purification; MS (MH^+) = 242.

EXAMPLE 167 N^1 -[(1S,2R)-3-azido-1-(3,5-difluorobenzyl)-2-hydroxypropyl]5-methyl- N^3,N^3 -dipropylisophthalamide (XV)

To (2R, 3S)-3-amino-1-azido-4-(3,5-difluorophenyl)-2-butanol (XIV, 25 EXAMPLE 166, 0.34 g, 1.4 mmole) in dichloromethane (20 ml) is added N,N-dipropylamidophthalic acid (IX, 0.53 g, 2 mmole), *t*-butyl alcohol (0.27 g, 2 mmole) and triethylamine (0.84 ml, 6 mmole) and ethyl-1-(3-dimethylaminopropyl)carbodiimide (0.58 g, 3 mmole). The mixture is stirred at 20-25 degrees C for 16 hours. The reaction is monitored by TLC (methanol/dichloromethane, 20/80 + ethyl acetate/hexane, 50/50; $R_f = 0.76$). When 30 the reaction is complete as measured by TLC, the reaction mixture is partitioned between dichloromethane and water, washed with hydrochloric acid (0.5 N), bicarbonate, saline, dried over anhydrous sodium sulfate and the solvent is removed under reduced pressure with heat to produce a concentrate. The concentrate is

column chromatographed on silica gel to give the title compound; MS (MH^+) = 488.

5 EXAMPLE 168 N¹-[(1S,2R)-3-amino-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N³,N³-dipropylisophthalamide acetic acid salt (XVI)

N¹-[(1S,2R)-3-azido-1-(3,5-difluorobenzyl)-2-hydroxypropyl]5-methyl-N³,N³-dipropylisophthalamide (XV, EXAMPLE 167, 0.3 g, 0.62 mmole) in ethyl acetate (20 ml) and acetic acid (5ml) is placed in a Parr pressure bottle. Palladium on carbon (10%, 5 g) is added and the mixture shaken under hydrogen at 50 psi for 2 hours. The mixture is filtered through a diatomaceous earth and the filtrate is concentrated to give the title compound; MS (MH⁺) = 462.

EXAMPLE 169 N¹-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(2-
15 furylmethyl)amino]-2-hydroxypropyl}-5-methyl-N³,N³-dipropylisophthalamide (X)

N¹-[(1S,2R)-3-amino-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N³,N³-dipropylisophthalamide acetic acid salt (XVI, EXAMPLE 168, 76 mg, 0.146 mmol) is dissolved in absolute ethanol (2 mL). 3-Furaldehyde (20 microL, 0.231 mmol) and triethylamine (30 microL, 0.215 mmol) are added via syringe, with stirring at 20-25 degrees C. After 10 minutes, palladium on carbon 122 mg, 5 weight %) is added and the mixture placed under a hydrogen atmosphere (50 psi) and shaken for 20 minutes. The resulting mixture is then filtered through diatomaceous earth, with ethanol washings. The filtrate is purified by flash chromatography (2-10% methanol/methylene chloride) to give purified title compound, MS (MH⁺) = 542.2.

EXAMPLE 169a tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-3-{{[(1S)-2-(ethylamino)-1-methyl-2-oxoethyl]amino}-2-hydroxypropylcarbamate (VII) -

30 Following the general procedure of EXAMPLEs 4 and 14-164 and making non-critical variations and reacting tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, EXAMPLE 3) with (2S)-2-amino-N-ethylpropanamide (VI), the title compound is obtained.

EXAMPLES 170-320

Following the general procedure of EXAMPLE 5 and making non-critical variations but starting with the protected alcohol (VII) of Column A, the amine (VIII) of Column B is obtained.

EXA	Column A Protected Alcohol (VII) Compound of EXAMPLE	Column B Amine (VIII)
170	14	(2R,3S)-3-amino-1-(ethylamino)-4-phenyl-2-butanol
171	15	(2R,3S)-3-amino-1-(benzylamino)-4-phenyl-2-butanol
172	16	(2R,3S)-3-amino-1-(isopropylamino)-4-phenyl-2-butanol
173	17	(2R,3S)-3-amino-1-[(4-methylbenzyl)amino]-4-phenyl-2-butanol
174	18	(2R,3S)-3-amino-1-{[2-(4-methoxyphenyl)ethyl]amino}-4-phenyl-2-butanol
175	19	(2R,3S)-3-amino-1-[(3-methoxybenzyl)amino]-4-phenyl-2-butanol
176	20	ethyl {[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]amino} (phenyl)acetate
177	21	(2R,3S)-3-amino-4-phenyl-1-[(2-phenylethyl)amino]-2-butanol
178	22	(2S)-2-{[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]amino}-1-(4-nitorphenyl)-1,3-propanediol
179	23	(2R,3S)-3-amino-1-[(2-chlorobenzyl)amino]-4-phenyl-2-butanol
180	24	(2R,3S)-3-amino-1-[(4-chlorobenzyl)amino]-4-phenyl-2-butanol

EXA	Column A Protected Alcohol (VII) Compound of EXAMPLE	Column B Amine (VIII)
181	25	(2R,3S)-3-amino-1-{{[2-(2-hydroxyethoxy)ethyl]amino}-4-phenyl-2-butanol
182	26	(2R,3S)-3-amino-1-(2,3-dihydro-1H-inden-1-ylamino)-4-phenyl-2-butanol
183	27	(2R,3S)-3-amino-1-[(2-hydroxypropyl)amino]-4-phenyl-2-butanol
184	28	(2R,3S)-3-amino-4-phenyl-1-[(tetrahydro-2-furanylmethyl)amino]-2-butanol
185	29	(2R,3S)-3-amino-1-[(2,2-diethoxyethyl)amino]-4-phenyl-2-butanol
186	30	(2R,3S)-3-amino-1-(butylamino)-4-phenyl-2-butanol
187	31	(2R,3S)-3-amino-1-(cyclohexylamino)-4-phenyl-2-butanol
188	32	(2R,3S)-3-amino-4-phenyl-1-[(2-pyridinylmethyl)amino]-2-butanol
189	33	(2R,3S)-3-amino-1-[(2-aminobenzyl)amino]-4-phenyl-2-butanol
190	34	(2R,3S)-3-amino-4-phenyl-1-[(3-pyridinylmethyl)amino]-2-butanol
191	35	(2R,3S)-3-amino-4-phenyl-1-{{[2-(1-pyrrolidinyl)ethyl]amino}-2-butanol
192	36	(2R,3S)-3-amino-1-[(2-hydroxy-2-phenylethyl)amino]-4-phenyl-2-butanol
193	37	(2R,3S)-3-amino-1-[(3-butoxypropyl)amino]-4-phenyl-2-butanol
194	38	(2R,3S)-3-amino-1-[(3-

EXA	Column A Protected Alcohol (VII) Compound of EXAMPLE	Column B Amine (VIII)
		isopropoxypropyl)amino]-4-phenyl-2-butanol
195	39	(2R,3S)-3-amino-1-(isopentylamino)-4-phenyl-2-butanol
196	40	(2R,3S)-3-amino-4-phenyl-1-[(3-phenylpropyl)amino]-2-butanol
197	41	(2R,3S)-3-amino-1-[(2-methoxyethyl)amino]-4-phenyl-2-butanol
198	42	(2R,3S)-3-amino-1-[(2-phenoxyethyl)amino]-4-phenyl-2-butanol
199	43	(2R,3S)-3-amino-4-phenyl-1-[(2-propoxyethyl)amino]-2-butanol
200	44	(2R,3S)-3-amino-1-[(3,3-dimethylbutyl)amino]-4-phenyl-2-butanol
201	45	(2R,3S)-3-amino-4-phenyl-1-[(4-phenylbutyl)amino]-2-butanol
202	46	(2R,3S)-3-amino-1-[(3-iodobenzyl)amino]-4-phenyl-2-butanol
203	47	(2R,3S)-3-amino-1-[(4-nitrobenzyl)amino]-4-phenyl-2-butanol
204	48	(2R,3S)-3-amino-1-[(3-chlorobenzyl)amino]-4-phenyl-2-butanol
205	49	(2R,3S)-3-amino-1-{[2-(4-chlorophenyl)ethyl]amino}-4-phenyl-2-butanol
206	50	(2R,3S)-3-amino-4-phenyl-1-{[2-(2-pyridinyl)ethyl]amino}-2-butanol
207	51	(2R,3S)-3-amino-4-phenyl-1-[(4-pyridinylmethyl)amino]-2-butanol
208	52	(2R,3S)-3-amino-1-{[2-(1-methyl-2-

EXA	Column A Protected Alcohol (VII) Compound of EXAMPLE	Column B Amine (VIII)
		pyrrolidinyl)ethyl]amino}-4-phenyl-2-butanol
209	53	(2R,3S)-3-amino-1-[(2,3-dimethylbenzyl)amino]-4-phenyl-2-butanol
210	54	(2R,3S)-3-amino-4-phenyl-1-{[2-(trifluoromethoxy)benzyl]amino}-2-butanol
211	55	(2R,3S)-3-amino-1-[(2-chloro-6-phenoxybenzyl)amino]-4-phenyl-2-butanol
212	56	(2R,3S)-3-amino-4-phenyl-1-{[4-(trifluoromethyl)benzyl]amino}-2-butanol
213	57	(2R,3S)-3-amino-1-[(2,3-dichlorobenzyl)amino]-4-phenyl-2-butanol
214	58	(2R,3S)-3-amino-1-[(3,5-dichlorobenzyl)amino]-4-phenyl-2-butanol
215	59	(2R,3S)-3-amino-1-[(3,5-difluorobenzyl)amino]-4-phenyl-2-butanol
216	60	(2R,3S)-3-amino-4-phenyl-1-{[4-(trifluoromethoxy)benzyl]amino}-2-butanol
217	61	4-({[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]amino}methyl)benzenesulfonamide
218	62	(2R,3S)-3-amino-1-[(4-methoxybenzyl)amino]-4-phenyl-2-butanol
219	63	(2R,3S)-3-amino-1-[(4-methylbenzyl)amino]-4-phenyl-2-butanol
220	64	(2R,3S)-3-amino-4-phenyl-1-[(3,4,5-trimethoxybenzyl)amino]-2-butanol
221	65	(2R,3S)-3-amino-4-phenyl-1-{[3-(trifluoromethoxy)benzyl]amino}-2-butanol
222	66	(2R,3S)-3-amino-1-[(3,5-

EXA	Column A Protected Alcohol (VII) Compound of EXAMPLE	Column B Amine (VIII)
		dimethoxybenzyl)amino]-4-phenyl-2-butanol
223	67	(2R,3S)-3-amino-1-[(2,4-dimethoxybenzyl)amino]-4-phenyl-2-butanol
224	68	(2R,3S)-3-amino-1-[[1,1'-biphenyl]-3-ylmethyl)amino]-4-phenyl-2-butanol
225	69	(2R,3S)-3-amino-1-[(3,4-dichlorobenzyl)amino]-4-phenyl-2-butanol
226	70	(2R,3S)-3-amino-1-[(2-fluorobenzyl)amino]-4-phenyl-2-butanol
227	71	(2R,3S)-3-amino-4-phenyl-1-{[3-(trifluoromethyl)benzyl]amino}-2-butanol
228	72	(2R,3S)-3-amino-1-[(2-methylbenzyl)amino]-4-phenyl-2-butanol
229	73	(2R,3S)-3-amino-4-phenyl-1-{[(1R)-1-phenylethyl]amino}-2-butanol
230	74	(2R,3S)-3-amino-4-phenyl-1-{[(1S)-1-phenylethyl]amino}-2-butanol
231	75	(2R,3S)-3-amino-1-{[3,5-bis(trifluoromethyl)benzyl]amino}-4-phenyl-2-butanol
232	76	(2R,3S)-3-amino-4-phenyl-1-{[2-(trifluoromethyl)benzyl]amino}-2-butanol
233	77	(2R,3S)-3-amino-1-{[(1S)-1-(1-naphthyl)ethyl]amino}-4-phenyl-2-butanol
234	78	(2R,3S)-3-amino-1-{[(1R)-1-(1-naphthyl)ethyl]amino}-4-phenyl-2-butanol
235	79	4-({[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]amino}methyl)-2-methoxyphenol

EXA	Column A Protected Alcohol (VII) Compound of EXAMPLE	Column B Amine (VIII)
236	80	4-({[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]amino}methyl)-1,2-benzenediol
237	81	(2R,3S)-3-amino-1-[(3-methoxypropyl)amino]-4-phenyl-2-butanol
238	82	(2R,3S)-3-amino-1-{{[(1S)-2-hydroxy-1-methylethyl]amino}-4-phenyl-2-butanol
239	83	(2R,3S)-3-amino-1-{{[(1R)-2-hydroxy-1-methylethyl]amino}-4-phenyl-2-butanol
240	84	(2R,3S)-3-amino-4-phenyl-1-(2-propynylamino)-2-butanol
241	85	(2R,3S)-3-amino-1-{{[2-(2-fluorophenyl)ethyl]amino}-4-phenyl-2-butanol
242	86	(2R,3S)-3-amino-1-{{[2-(3-fluorophenyl)ethyl]amino}-4-phenyl-2-butanol
243	87	(2R,3S)-3-amino-1-{{[2-(4-fluorophenyl)ethyl]amino}-4-phenyl-2-butanol
244	88	(2R,3S)-3-amino-1-{{[2-(4-bromophenyl)ethyl]amino}-4-phenyl-2-butanol
245	89	(2R,3S)-3-amino-1-{{[2-(3-methoxyphenyl)ethyl]amino}-4-phenyl-2-butanol
246	90	(2R,3S)-3-amino-1-{{[2-(2,4-dichlorophenyl)ethyl]amino}-4-phenyl-2-butanol
247	91	(2R,3S)-3-amino-1-{{[2-(3-chlorophenyl)ethyl]amino}-4-phenyl-2-butanol
248	92	(2R,3S)-3-amino-1-{{[2-(2,5-dimethoxyphenyl)ethyl]amino}-4-phenyl-2-

EXA	Column A Protected Alcohol (VII) Compound of EXAMPLE	Column B Amine (VIII)
		butanol
249	93	(2R,3S)-3-amino-1-{[2-(4-methylphenyl)ethyl]amino}-4-phenyl-2-butanol
250	94	(2R,3S)-3-amino-1-{[(1R)-1-benzyl-2-hydroxyethyl]amino}-4-phenyl-2-butanol
251	95	(2R,3S)-3-amino-1-{[3-(4-morpholinyl)propyl]amino}-4-phenyl-2-butanol
252	96	(2R,3S)-3-amino-1-(isobutylamino)-4-phenyl-2-butanol
253	97	(2R,3S)-3-amino-1-{[2-(4-morpholinyl)ethyl]amino}-4-phenyl-2-butanol
254	98	(2R,3S)-3-amino-4-phenyl-1-[(2-hydroxybutyl)amino]-2-butanol
255	99	(2R,3S)-3-amino-4-phenyl-1-{[2-(2-thienyl)ethyl]amino}-2-butanol
256	100	4-{[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]amino}-1-butanol
257	101	(2R,3S)-3-amino-1-{[(1S)-2-hydroxy-1-phenylethyl]amino}-4-phenyl-2-butanol
258	102	(2R,3S)-3-amino-1-[(2,4-dichlorobenzyl)amino]-4-phenyl-2-butanol
259	103	(2R,3S)-3-amino-1-{[(1R)-2-hydroxy-1-phenylethyl]amino}-4-phenyl-2-butanol
260	104	(2R,3S)-3-amino-1-[(4-tert-butylbenzyl)amino]-4-phenyl-2-butanol
261	105	(2R,3S)-3-amino-4-phenyl-1-[(1-phenylethyl)amino]-2-butanol
262	106	(1R,2S)-1-{[(2R,3S)-3-amino-2-hydroxy-4-

EXA	Column A Protected Alcohol (VII) Compound of EXAMPLE	Column B Amine (VIII)
		phenylbutyl]amino}-2,3-dihydro-1H-inden-2-ol
263	107	(2R,3S)-3-amino-1-[(3,4-dimethylbenzyl)amino]-4-phenyl-2-butanol
264	108	methyl 7-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}heptanoate
265	109	2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutylpropanamide
266	110	(2S)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutylpropanamide
267	111	2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutyl-2-methylpropanamide
268	112	2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutylacetamide
269	113	(2S)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutylbutanamide
270	114	(2R)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutylbutanamide
271	115	(2R,3S)-3-amino-1-(benzylamino)-4-(3,5-difluorophenyl)-2-butanol
272	116	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-(ethylamino)-2-butanol
273	117	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-(isobutylamino)-2-butanol

EXA	Column A Protected Alcohol (VII) Compound of EXAMPLE	Column B Amine (VIII)
274	118	3- {[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino }-N-isobutyl-2-methylpropanamide
275	119	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1- {[4-(dimethylamino)benzyl]amino }-2-butanol
276	120	(2S)-2- {[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino }-N-isobutyl-3-phenylpropanamide
277	121	(2S)-2- {[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino }-N-isobutyl-3-methylbutanamide
278	122	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1- {[2-(dimethylamino)ethyl]amino }-2-butanol
279	123	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1- [(3-pyridinylmethyl)amino]-2-butanol
280	124	(2S)-2- {[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino }-3-(benzyloxy)-N-isobutylpropanamide
281	125	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1- [(1-methyl-1-phenylethyl)amino]-2-butanol
282	126	(2R)-2- {[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino }-N-isobutyl-3-methylbutanamide
283	127	(2S)-2- {[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino }-N-isobutylpentanamide
284	128	(2S)-2- {[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino }-3-

EXA	Column A Protected Alcohol (VII) Compound of EXAMPLE	Column B Amine (VIII)
		hydroxy-N-isobutylpropanamide
285	129	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(2-phenylethyl)amino]-2-butanol
286	130	(2S)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-benzylpropanamide
287	131	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[[(1S)-1-phenylpropyl]amino]-2-butanol
287a	169a	(2S)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-ethylpropanamide
288	132	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methoxybenzyl)amino]-2-butanol
289	133	(2S)-2-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-N-isobutyl-2-phenylethanamide
290	134	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-(isopentylamino)-2-butanol
291	135	(2R,3S)-3-amino-1-(cyclohexylamino)-4-(3,5-difluorophenyl)-2-butanol
292	136	(2R,3S)-3-amino-1-(butylamino)-4-(3,5-difluorophenyl)-2-butanol
293	137	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methoxypropyl)amino]-2-butanol
294	138	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(2-hydroxy-2-phenylethyl)amino]-2-butanol
295	139	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[[(3R,5S)-3,5-dimethoxycyclohexyl]amino]-2-

EXA	Column A Protected Alcohol (VII) Compound of EXAMPLE	Column B Amine (VIII)
		butanol
296	140	dimethyl (1R,3S)-5-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-1,3-cyclohexanedicarboxylate
297	141	(1R,3S)-5-{[(2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl]amino}-1,3-cyclohexanedicarboxylic acid
298	142	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[[[(1R)-1-phenylpropyl]amino]-2-butanol
299	143	(2R,3S)-3-amino-1-[(3-chlorobenzyl)amino]-4-(3,5-difluorophenyl)-2-butanol
300	144	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methoxybenzyl)amino]-2-butanol
301	145	(2R,3S)-3-amino-1-[[[1,1'-biphenyl]-3-ylmethyl]amino]-4-(3,5-difluorophenyl)-2-butanol
302	146	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]-2-butanol
303	147	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methylbenzyl)amino]-2-butanol
304	148	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(2-phenylpropyl)amino]-2-butanol
305	149	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(1,3-thiazol-5-ylmethyl)amino]-2-butanol
306	150	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(2-thienylmethyl)amino]-2-butanol
307	151	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(5-methoxy-1,2,3,4-tetrahydro-1-

EXA	Column A Protected Alcohol (VII) Compound of EXAMPLE	Column B Amine (VIII)
		naphthalenyl)amino]-2-butanol
308	152	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(2-pyrazinylmethyl)amino]-2-butanol
309	153	(2R,3S)-3-amino-1-[(3,5-difluorobenzyl)amino]-4-(3,5-difluorophenyl)-2-butanol
310	154	(2R,3S)-3-amino-1-[(1,3-benzodioxol-5-ylmethyl)amino]-4-(3,5-difluorophenyl)-2-butanol
311	155	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3,5-dimethoxybenzyl)amino]-2-butanol
312	156	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[3-(trifluoromethyl)benzyl]amino}-2-butanol
313	157	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(2-furylmethyl)amino]-2-butanol
314	158	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(7-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)amino]-2-butanol
315	159	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[3-(trifluoromethoxy)benzyl]amino}-2-butanol
316	160	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-fluorobenzyl)amino]-2-butanol
317	161	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-isopropoxybenzyl)amino]-2-butanol
318	162	(2R,3S)-3-amino-1-[(3-bromobenzyl)amino]-4-(3,5-difluorophenyl)-2-butanol
319	163	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(5-methyl-2-furylmethyl)amino]-2-butanol

EXA	Column A Protected Alcohol (VII) Compound of EXAMPLE	Column B, Amine (VIII)
320	164	(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(5-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)amino]-2-butanol

EXAMPLES 321-473

Following the general procedure of EXAMPLE 6 and making non-critical variations but starting with the amine (VIII) of Column A and reacting it with the amide forming agent (IX) of Column B, the substituted amine (X) of Column C is obtained.

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substitued amine (X)	Column D Physical Data
321	170	"PHTH"	N ¹ -[(1S,2R)-1-benzyl-3-(ethylamino)-2-hydroxypropyl]-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 440.7
322	171	"PHTH"	N ¹ -[(1S,2R)-1-benzyl-3-(benzylamino)-2-hydroxypropyl]-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 502.7
323	172	"PHTH"	N ¹ -[(1S,2R)-1-benzyl-2-hydroxy-3-(isopropylamino)propyl]-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 454.6
324	173	"PHTH"	N ¹ -[(1S,2R)-1-benzyl-2-hydroxy-3-(4-toluidino)propyl]-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 502.2
325	174	"PHTH"	N ¹ -[(1S,2R)-1-benzyl-2-hydroxy-3-{[2-(4-methoxyphenyl)ethyl]amino}propyl]-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 546
326	175	"PHTH"	N ¹ -[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 532
327	176	"PHTH"	ethyl {[3S]-3-[(3-[(dipropylamino)	MH ⁺ =

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substitued amine (X)	Column D Physical Data
			carbonyl] benzoyl} amino)-2- hydroxy-4- phenylbutyl]amino}(phenyl)acetate	574
329	178	"PHTH"	N ¹ -((1S)-1-benzyl-2-hydroxy-3- {[(1S)-2-hydroxy-1- (hydroxymethyl)-2-(4- nitrophenyl)ethyl]amino}propyl) - N ³ ,N ³ -dipropylisophthalamide	MH+ = 607
330	179	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(2- chlorobenzyl)amino]-2- hydroxypropyl} -N ³ ,N ³ - dipropylisophthalamide	MH+ = 537
331	180	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(4- chlorobenzyl)amino]-2- hydroxypropyl} -N ³ ,N ³ - dipropylisophthalamide	MH+ = 537
332	181	"PHTH"	N ¹ -((1S,2R)-1-benzyl-2-hydroxy-3- {[2-(2-hydroxyethoxy) ethyl] amino}propyl)-N ³ ,N ³ - dipropylisophthalamide	MH+ = 500
333	182	"PHTH"	N ¹ -[(1S,2R)-1-benzyl-3-(2,3- dihydro-1H-inden-1-ylamino)-2- hydroxypropyl]-N ³ ,N ³ - dipropylisophthalamide	MH+ = 528
334	183	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- [(2-hydroxypropyl)amino]propyl}- N ³ ,N ³ -dipropylisophthalamide	MH+ = 470
335	184	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- [(tetrahydro-2- furanylmethyl)amino]propyl}-N ³ ,N ³ - dipropylisophthalamide	MH+ = 496
336	185	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(2,2- diethoxyethyl)amino]-2- hydroxypropyl} -N ³ ,N ³ - dipropylisophthalamide	MH+ = 528
337	186	"PHTH"	N ¹ -[(1S,2R)-1-benzyl-3-	MH+ =

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substitued amine (X)	Column D Physical Data
			(butylamino)-2-hydroxypropyl]- N ³ ,N ³ -dipropylisophthalamide	468
338	187	"PHTH"	N ¹ -[(1S,2R)-1-benzyl-3-((cyclohexylamino)-2- hydroxypropyl)-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 494
339	188	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- [(2-pyridinylmethyl)amino]propyl}- N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 507
340	189	"PHTH"	N ¹ -{(1S,2R)-3-[(2- aminobenzyl)amino]-1-benzyl-2- hydroxypropyl}-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 517
341	190	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- [(3-pyridinylmethyl)amino]propyl}- N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 503
342	191	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- {[2-(1-pyrrolidinyl)ethyl] amino} propyl}-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 509
343	192	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- [(2-hydroxy-2- phenylethyl)amino]propyl}-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 532
344	193	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(3- butoxypropyl)amino]-2- hydroxypropyl}-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 526
345	194	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- [(3- isopropoxypropyl)amino]propyl}- N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 512
346	195	"PHTH"	N ¹ -[(1S,2R)-1-benzyl-2-hydroxy-3- (isopentylamino)propyl]-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 482
347	196	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3-	MH ⁺ =

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substituted amine (X)	Column D Physical Data
			[(3-phenylpropyl)amino]propyl)- N ³ ,N ³ -dipropylisophthalamide	530
348	197	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- [(2-methoxyethyl)amino]propyl)- N ³ ,N ³ -dipropylisophthalamide	MH+ = 470
349	198	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- [(2-phenoxyethyl)amino]propyl)- N ³ ,N ³ -dipropylisophthalamide	MH+ = 532
350	199	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- [(2-propoxyethyl)amino]propyl)- N ³ ,N ³ -dipropylisophthalamide	MH+ = 498
351	200	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(3,3- dimethylbutyl)amino]-2- hydroxypropyl)-N ³ ,N ³ - dipropylisophthalamide	MH+ = 496
352	201	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- [(4-phenylbutyl)amino]propyl)- N ³ ,N ³ -dipropylisophthalamide	MH+ = 544
353	202	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- [(3-iodobenzyl)amino]propyl)- N ³ ,N ³ -dipropylisophthalamide	MH+ = 628
354	203	"PHTH"	N ¹ -{(1S)-1-benzyl-2-hydroxy-3-[(4- nitrobenzyl)amino]propyl)-N ³ ,N ³ - dipropylisophthalamide	MH+ = 547
355	204	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(3- chlorobenzyl)amino]-2- hydroxypropyl)-N ³ ,N ³ - dipropylisophthalamide	MH+ = 537
356	205	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-{[2-(4- chlorophenyl)ethyl]amino}-2- hydroxypropyl)-N ³ ,N ³ - dipropylisophthalamide	MH+ = 551
357	206	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- {[2-(2- pyridinyl)ethyl]amino}propyl)- N ³ ,N ³ -dipropylisophthalamide	MH+ = 517

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substitued amine (X)	Column D Physical Data
358	207	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- [(4-pyridinylmethyl)amino]propyl}- N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 503
359	208	"PHTH"	N ¹ -((1S,2R)-1-benzyl-2-hydroxy-3- {[2-(1-methyl-2- pyrrolidinyl)ethyl]amino}propyl)- N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 523
360	209	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(2,3- dimethylbenzyl)amino]-2- hydroxypropyl}-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 580
361	210	"PHTH"	N ¹ -((1S,2R)-1-benzyl-2-hydroxy-3- {[2-(trifluoromethoxy) benzyl] amino}propyl)-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 586
362	211	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(2-chloro- 6-phenoxybenzyl)amino]-2- hydroxypropyl}-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 629
363	212	"PHTH"	N ¹ -((1S,2R)-1-benzyl-2-hydroxy-3- {[4- (trifluoromethyl)benzyl]amino}propy l)-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 570
364	213	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(2,3- dichlorobenzyl)amino]-2- hydroxypropyl}-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 571
365	214	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(3,5- dichlorobenzyl)amino]-2- hydroxypropyl}-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 571
366	215	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(3,5- difluorobenzyl)amino]-2- hydroxypropyl}-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 538
367	216	"PHTH"	N ¹ -((1S,2R)-1-benzyl-2-hydroxy-3-	MH ⁺ =

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substituted amine (X)	Column D Physical Data
			{[4-(trifluoromethoxy)benzyl]amino}propyl)-N ³ ,N ³ -dipropylisophthalamide	586
368	217	"PHTH"	N ¹ -[(1S,2R)-3-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-1-benzyl-2-hydroxypropyl]-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 595
369	218	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3-[(4-methoxybenzyl)amino]propyl)-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 532
370	219	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3-[(4-methylbenzyl)amino]propyl)-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 516
371	220	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3-[(3,4,5-trimethoxybenzyl)amino]propyl)-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 592
372	221	"PHTH"	N ¹ -[(1S,2R)-1-benzyl-2-hydroxy-3-{[3-(trifluoromethoxy)benzyl]amino}propyl)-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 586
373	222	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(3,5-dimethoxybenzyl)amino]-2-hydroxypropyl)-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 562
374	223	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(2,4-dimethoxybenzyl)amino]-2-hydroxypropyl)-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 562
375	224	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(1,1'-biphenyl)-3-ylmethyl]amino]-2-hydroxypropyl)-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 578
376	225	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(3,4-dichlorobenzyl)amino]-2-	MH ⁺ = 571

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substitued amine (X)	Column D Physical Data
			hydroxypropyl}-N ³ ,N ³ - dipropylisophthalamide	
377	226	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(2- fluorobenzyl)amino]-2- hydroxypropyl}-N ³ ,N ³ - dipropylisophthalamide	MH+ = 520
378	227	"PHTH"	N ¹ -((1S,2R)-1-benzyl-2-hydroxy-3- {[3-(trifluoromethyl)benzyl]amino} propyl)-N ³ ,N ³ - dipropylisophthalamide	MH+ = 570
379	228	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- [(2-methylbenzyl)amino]propyl)- N ³ ,N ³ -dipropylisophthalamide	MH+ = 516
380	229	"PHTH"	N ¹ -((1S,2R)-1-benzyl-2-hydroxy-3- {[(1R)-1- phenylethyl]amino}propyl)-N ³ ,N ³ - dipropylisophthalamide	MH+ = 516
381	230	"PHTH"	N ¹ -((1S,2R)-1-benzyl-2-hydroxy-3- {[(1S)-1-phenylethyl]amino}propyl)- N ³ ,N ³ -dipropylisophthalamide	MH+ = 516
382	231	"PHTH"	N ¹ -((1S,2R)-1-benzyl-3-{[3,5- bis(trifluoromethyl)benzyl]amino}-2- hydroxypropyl)-N ³ ,N ³ - dipropylisophthalamide	MH+ = 638
383	232	"PHTH"	N ¹ -((1S,2R)-1-benzyl-2-hydroxy-3- {[2-(trifluoromethyl)benzyl]amino} propyl)-N ³ ,N ³ - dipropylisophthalamide	MH+ = 570
384	233	"PHTH"	N ¹ -((1S,2R)-1-benzyl-2-hydroxy-3- {[(1S)-1-(1- naphthyl)ethyl]amino}propyl)-N ³ ,N ³ - dipropylisophthalamide	MH+ = 566
385	234	"PHTH"	N ¹ -((1S,2R)-1-benzyl-2-hydroxy-3- {[(1R)-1-(1- naphthyl)ethyl]amino}propyl)-N ³ ,N ³ - dipropylisophthalamide	MH+ = 566

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substituted amine (X)	Column D Physical Data
386	235	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- [(4-hydroxy-3- methoxybenzyl)amino]propyl}- N ³ ,N ³ -dipropylisophthalamide	MH+ = 548
387	236	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[(3,4- dihydroxybenzyl)amino]-2- hydroxypropyl}-N ³ ,N ³ - dipropylisophthalamide	MH+ = 534
388	237	"PHTH"	N ¹ -{(1S)-1-benzyl-2-hydroxy-3-[(3- methoxypropyl)amino]propyl}- N ³ ,N ³ -dipropylisophthalamide	MH+ = 484
389	238	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- {[(1S)-2-hydroxy-1- methylethyl]amino}propyl)-N ³ ,N ³ - dipropylisophthalamide	MH+ = 470
390	239	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-2-hydroxy-3- {[(1R)-2-hydroxy-1- methylethyl]amino}propyl)-N ³ ,N ³ - dipropylisophthalamide	MH+ = 470
391	240	"PHTH"	N ¹ -[(1S,2R)-1-benzyl-2-hydroxy-3- (2-propynylamino)propyl]-N ³ ,N ³ - dipropylisophthalamide	MH+ = 450
392	241	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[[2-(2- fluorophenyl)ethyl]amino]-2- hydroxypropyl)-N ³ ,N ³ - dipropylisophthalamide	MH+ = 534
393	242	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[[2-(3- fluorophenyl)ethyl]amino]-2- hydroxypropyl)-N ³ ,N ³ - dipropylisophthalamide	MH+ = 534
394	243	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[[2-(4- fluorophenyl)ethyl]amino]-2- hydroxypropyl)-N ³ ,N ³ - dipropylisophthalamide	MH+ = 534
395	244	"PHTH"	N ¹ -{(1S,2R)-1-benzyl-3-[[2-(4- bromophenyl)ethyl]amino]-2-	MH+ = 595

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substituted amine (X)	Column D Physical Data
			hydroxypropyl)-N ³ ,N ³ - dipropylisophthalamide	
396	245	"PHTH"	N ¹ -((1S)-1-benzyl-2-hydroxy-3-{{2-(3-methoxyphenyl)ethyl}amino}propyl)-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 546
397	246	"PHTH"	N ¹ -((1S,2R)-1-benzyl-3-{{2-(2,4-dichlorophenyl)ethyl}amino}-2-hydroxypropyl)-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 585
398	247	"PHTH"	N ¹ -((1S,2R)-1-benzyl-3-{{2-(3-chlorophenyl)ethyl}amino}-2-hydroxypropyl)-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 551
399	248	"PHTH"	N ¹ -((1S)-1-benzyl-3-{{2-(2,5-dimethoxyphenyl)ethyl}amino}-2-hydroxypropyl)-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 576
400	249	"PHTH"	N ¹ -((1S,2R)-1-benzyl-2-hydroxy-3-{{2-(4-methylphenyl)ethyl}amino}propyl)-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 530
401	250	"PHTH"	N ¹ -((1S,2R)-1-benzyl-3-{{(1R)-1-benzyl-2-hydroxyethyl}amino}-2-hydroxypropyl)-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 546
402	251	"PHTH"	N ¹ -((1S,2R)-1-benzyl-2-hydroxy-3-{{3-(4-morpholinyl)propyl}amino}propyl)-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 539
403	252	"PHTH"	N ¹ -((1S,2R)-1-benzyl-2-hydroxy-3-(isobutylamino)propyl)-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 468
404	253	"PHTH"	N ¹ -((1S,2R)-1-benzyl-2-hydroxy-3-{{2-(4-morpholinyl)ethyl}amino}propyl)-	MH ⁺ = 525

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substituted amine (X)	Column D Physical Data
			N ³ ,N ³ -dipropylisophthalamide	
405	254	"PHTH"	N ¹ -{[(1S,2R)-1-benzyl-2-hydroxy-3- [(2-hydroxybutyl)amino]propyl]- N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 484
406	255	"PHTH"	N ¹ -{[(1S,2R)-1-benzyl-2-hydroxy-3- {[2-(2-thienyl)ethyl]amino}propyl]- N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 522
407	256	"PHTH"	N ¹ -{[(1S,2R)-1-benzyl-2-hydroxy-3- [(4-hydroxybutyl)amino]propyl]- N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 484
408	257	"PHTH"	N ¹ -{[(1S,2R)-1-benzyl-2-hydroxy-3- {[(1S)-2-hydroxy-1- phenylethyl]amino}propyl]-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 532
409	258	"PHTH"	N ¹ -{[(1S,2R)-1-benzyl-3-[(2,4- dichlorobenzyl)amino]-2- hydroxypropyl]-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 571
410	259	"PHTH"	N ¹ -{[(1S,2R)-1-benzyl-2-hydroxy-3- {[(1R)-2-hydroxy-1- phenylethyl]amino}propyl]-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 532
411	260	"PHTH"	N ¹ -{[(1S,2R)-1-benzyl-3-[(4-tert- butylbenzyl)amino]-2- hydroxypropyl]-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 558
412	261	"PHTH"	N ¹ -{[(1S,2R)-1-benzyl-2-hydroxy-3- [(1-phenylethyl)amino]propyl]- N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 516
413	262	"PHTH"	N ¹ -{[(1S,2R)-1-benzyl-2-hydroxy-3- {[(1R,2S)-2-hydroxy-2,3-dihydro- 1H-inden-1-yl]amino}propyl]-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 544
414	263	"PHTH"	N ¹ -{[(1S,2R)-1-benzyl-3-[(3,4- dimethylbenzyl)amino]-2- hydroxypropyl]-N ³ ,N ³ -	MH ⁺ = 530

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substitued amine (X)	Column D Physical Data
			dipropylisophthalamide	
416	265	"PHTH"	N ¹ -((1S,2R)-1-(3,5-difluorobenzyl)- 2-hydroxy-3-{{2-(isobutylamino)-1- methyl-2-oxoethyl}amino}propyl)- N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 575
417	266	"PHTH"	N ¹ -((1S,2R)-1-(3,5-difluorobenzyl)- 2-hydroxy-3-{{(1S)-2- (isobutylamino)-1-methyl-2- oxoethyl}amino}propyl)-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 575
418	266	"3,5-pyridinyl"	N ³ -((1S,2R)-1-(3,5-difluorobenzyl)- 2-hydroxy-3-{{(1S)-2- (isobutylamino)-1-methyl-2- oxoethyl}amino}propyl)-N ⁵ ,N ⁵ - dipropyl-3,5-pyridinedicarboxamide	MH ⁺ = 576
419	267	"5-Me-PHTH"	N ¹ -((1S,2R)-1-(3,5-difluorobenzyl)- 2-hydroxy-3-{{2-(isobutylamino)- 1,1-dimethyl-2- oxoethyl}amino}propyl)-5-methyl- N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 603
420	268	"5-Me-PH"	N ¹ -((1S,2R)-1-(3,5-difluorobenzyl)- 2-hydroxy-3-{{2-(isobutylamino)-2- oxoethyl}amino}propyl)-5-methyl- N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 575.3
421	269	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)- 2-hydroxy-3-((1S)-1- [(isobutylamino)carbonyl]propyl)am ino]propyl]-5-methyl-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 603.8
422	270	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)- 2-hydroxy-3-((1R)-1- [(isobutylamino)carbonyl]propyl)am ino]propyl]-5-methyl-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 603.8
423	271	"5-Me-PHTH"	N ¹ -[(1S,2R)-3-(benzylamino)-1-(3,5- difluorobenzyl)-2-hydroxypropyl]-5-	MH ⁺ = 552.3

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substitued amine (X)	Column D Physical Data
			methyl-N ³ ,N ³ - dipropylisophthalamide	
424	272	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)- 3-(ethylamino)-2-hydroxypropyl]-5- methyl-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 490.7
425	273	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)- 2-hydroxy-3-(isobutylamino)propyl]- 5-methyl-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 518.0
426	274	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)- 2-hydroxy-3-{[3-(isobutylamino)-2- methyl-3-oxopropyl]amino}propyl]- 5-methyl-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 603
427	275	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)- 3-{[4- (dimethylamino)benzyl]amino}-2- hydroxypropyl]-5-methyl-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 595.8
428	276	"5-Me-PHTH"	N ¹ -[(1S,2R)-3-{[(1S)-1-benzyl-2- (isobutylamino)-2-oxoethyl]amino}- 1-(3,5-difluorobenzyl)-2- hydroxypropyl]-5-methyl-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 665.9
429	277	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)- 2-hydroxy-3-({(1S)-1- [(isobutylamino)carbonyl]-2- methylpropyl}amino)propyl]-5- methyl-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 617.9
430	278	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)- 3-{[2-(dimethylamino)ethyl]amino}- 2-hydroxypropyl]-5-methyl-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 533.3
431	279	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)-	MH ⁺ = 553

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substituted amine (X)	Column D Physical Data
			2-hydroxy-3-[(3-pyridinylmethyl)amino]propyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	
432	280	"5-Me-PHTH"	N ¹ -[(1S,2R)-3-{[(1S)-1-[(benzyloxy)methyl]-2-(isobutylamino)-2-oxoethyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH+ = 695.9
433	281	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1-methyl-1-phenylethyl)amino]propyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH+ = 580.8
434	282	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({(1R)-1-[(isobutylamino)carbonyl]-2-methylpropyl} amino)propyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH+ = 617.9
435	283	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({(1S)-1-[(isobutylamino)carbonyl]butyl} amino)propyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH+ = 617.9
436	284	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(1S)-1-(hydroxymethyl)-2-(isobutylamino)-2-oxoethyl]amino}propyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH+ = 605.8
437	285	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-phenylethyl)amino]propyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH+ = 566.8

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substituted amine (X)	Column D Physical Data
438	286	"5-Me-PHTH"	N ¹ -[(1S,2R)-3-([(1S)-2-(benzylamino)-1-methyl-2-oxoethyl]amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 623.2
439	287	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([(1S)-1-phenylpropyl]amino)propyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 580.8
440	287a	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)-3-([(1S)-2-(ethylamino)-1-methyl-2-oxoethyl]amino)-2-hydroxypropyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 561.2
441	289	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([(1S)-2-(isobutylamino)-2-oxo-1-phenylethyl]amino)propyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 651.9
442	290	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 531.69
443	291	"5-Me-PHTH"	N ¹ -[(1S,2R)-3-(cyclohexylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 544.2
444	292	"5-Me-PHTH"	N ¹ -[(1S,2R)-3-(butylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 518.2
445	293	"5-Me-PHTH"	N ¹ -[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-	MH ⁺ = 534.2

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substitued amine (X)	Column D Physical Data
			methoxypropyl)amino]propyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	
446	294	"5-Me-PHTH"	N ¹ -{[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-hydroxy-2-phenylethyl)amino]propyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 582
447	295	"5-Me-PHTH"	N ¹ -{[(1S,2R)-1-(3,5-difluorobenzyl)-3-{[(3R,5S)-3,5-dimethoxycyclohexyl]amino}-2-hydroxypropyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 604.2
448	296	"5-Me-PHTH"	dimethyl (1R,3S)-5-{[(2R,3S)-4-(3,5-difluorophenyl)-3-(3-[(dipropylamino)carbonyl]-5-methylbenzoyl)amino)-2-hydroxybutyl]amino}-1,3-cyclohexanedicarboxylate	MH ⁺ = 660.2
449	297	"5-Me-PHTH"	(1R,3S)-5-{[(2R,3S)-4-(3,5-difluorophenyl)-3-(3-[(dipropylamino)carbonyl]-5-methylbenzoyl)amino)-2-hydroxybutyl]amino}-1,3-cyclohexanedicarboxylic acid	MH ⁺ = 632.2
450	298	"5-Me-PHTH"	N ¹ -{[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-1-phenylpropyl]amino]propyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 580.8
451	299	"5-Me-PHTH"	N ¹ -[(1S,2R)-3-[(3-chlorobenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 586.3
452	300	"-SO ₂ -"	N-[(1S,2R)-1-(3,5-difluorobenzyl)-	MH ⁺ =

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substitued amine (X)	Column D Physical Data
			2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(2-propylpentyl)sulfonyl]benzamide	603.2
453	301	"5-Me-PHTH"	N ¹ -[(1S,2R)-3-[[[1,1'-biphenyl]-3-ylmethyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 628.8
454	302	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 678
455	303	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methylbenzyl)amino]propyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 566.8
456	304	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-phenylpropyl)amino]propyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 694
457	305	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1,3-thiazol-5-ylmethyl)amino]propyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 559.5
458	306	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-thienylmethyl)amino]propyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 558.5
459	307	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(5-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)amino]propyl}-5-methyl-N ³ ,N ³ -	MH ⁺ = 814

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substituted amine (X)	Column D Physical Data
			dipropylisophthalamide	
460	308	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-pyrazinylmethyl)amino]propyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 554.3
461	309	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3,5-difluorobenzyl)amino]-2-hydroxypropyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 588.7
462	310	"PHTH"	N ¹ -{(1S,2R)-3-[(1,3-benzodioxol-5-ylmethyl)amino]-1-benzyl-2-hydroxypropyl}-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 546
463	311	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3,5-dimethoxybenzyl)amino]-2-hydroxypropyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 612.4
464	312	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 620.3
466	314	"5-Me-PHTH"	Racemic N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(7-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)amino]propyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 814
467	315	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(trifluoromethoxy)benzyl]amino]propyl}-5-methyl-N ³ ,N ³ -dipropylisophthalamide	MH ⁺ = 636.3
468	316	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-fluorobenzyl)amino]-2-	MH ⁺ = 570.3

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substituted amine (X)	Column D Physical Data
			hydroxypropyl}-5-methyl-N ³ ,N ³ - dipropylisophthalamide	
469	317	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)- 2-hydroxy-3-[(3- isopropoxybenzyl)amino]propyl}-5- methyl-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 610.4
470	318	"5-Me-PHTH"	N ¹ -[(1S,2R)-3-[(3- bromobenzyl)amino]-1-(3,5- difluorobenzyl)-2-hydroxypropyl]-5- methyl-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 631.6
471	319	"5-Me-PHTH"	N ¹ -((1S,2R)-1-(3,5-difluorobenzyl)- 2-hydroxy-3-[(5-methyl-2- furyl)methyl]amino}propyl)-5- methyl-N ³ ,N ³ - dipropylisophthalamide	MH ⁺ = 556
472	320	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)- 2-hydroxy-3-[(5-methoxy-1,2,3,4- tetrahydro-1- naphthalenyl)amino]propyl}-5- methyl-N ³ ,N ³ - dipropylisophthalamide "isomer A"	MH ⁺ = 622
473	320	"5-Me-PHTH"	N ¹ -{(1S,2R)-1-(3,5-difluorobenzyl)- 2-hydroxy-3-[(5-methoxy-1,2,3,4- tetrahydro-1- naphthalenyl)amino]propyl}-5- methyl-N ³ ,N ³ - dipropylisophthalamide "isomer B"	MH ⁺ = 622

EXAMPLE 474

N¹-[(1S,2R)-1-benzyl-2-hydroxy-3-(1,2,3,4-tetrahydro-1-naphthalenylamino)propyl]-N³,N³-dipropylisophthalamide
(X)

Following the general procedures of EXAMPLES 6 and 321-473 and making non-critical variations but starting with (2R,3S)-3-amino-4-phenyl-1-(1,2,3,4-tetrahydro-1-naphthalenylamino)-2-butanol (VIII) and using "PHTH", the title compound is obtained, $MH^+ = 542.3$.

5 EXAMPLES 475-483

Following the general procedure of EXAMPLE 6 and making non-critical variations but starting with the amine (VIII) of Column A and reacting it with the amide forming agent (IX) of Column B, the substituted amine (X) of Column C is obtained.

10

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substitued amine (X)	Column D Physical Data
475	271	"5-OMe-PHTH"	N^1 -[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methoxy- N^3,N^3 -dipropylisophthalamide	$MH^+ = 568.2$
476	271	"PHTH"	N^1 -[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]- N^3,N^3 -dipropylisophthalamide	$MH^+ = 538.2$
477	271	"5-Cl-PHTH"	N^1 -[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-chloro- N^3,N^3 -dipropylisophthalamide	$MH^+ = 572.1$
478	271	"3,5-pyridinyl"	N^3 -[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]- N^5,N^5 -dipropyl-3,5-pyridinedicarboxamide	$MH^+ = 539.5$
479	271	"5-F-PHTH"	N^1 -[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-fluoro- N^3,N^3 -dipropylisophthalamide	$MH^+ = 556.3$
480	271	"thienyl"	N^2 -[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]- N^5,N^5 -dipropyl-2,5-thiophenedicarboxamide	$MH^+ = 544.2$
481	271	"2,4-pyridinyl"	N^4 -[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]- N^2,N^2 -dipropyl-2,4-pyridinedicarboxamide	$MH^+ = 539.3$

EXA	Column A Amine (VIII) Compound of EXA	Column B Amide Forming Agent (IX)	Column C Substitued amine (X)	Column D Physical Data
482	271	"4,6- pyrimidinyl"	N ⁴ -[(1S,2R)-3-(benzylamino)-1-(3,5- difluorobenzyl)-2-hydroxypropyl]- N ⁶ ,N ⁶ dipropyl-4,6- pyrimidinedicarboxamide	MH ⁺ = 540
483	271	"morpholinyl"	N-[(1S,2R)-3-(benzylamino)-1-(3,5- difluorobenzyl)-2-hydroxypropyl]-3- (4-morpholinylcarbonyl)benzamide	MH ⁺ = 552

EXAMPLE 484 N¹-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methylbenzyl)amino]propyl}-N³,N³-dipropylisophthalamide (X)

- 5 Following the general procedures of EXAMPLEs 4 and 14-107 and making non-critical variations but starting with tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V, commercially available) and NH₂-CH₂-phenyl-(3-CH₃) (VI), the corresponding protected alcohol (VII) is obtained.

- 10 Following the general procedure of EXAMPLEs 5 and 170-320 and making non-critical variations, the corresponding amine (VIII) is obtained.

Following the general procedure of EXAMPLEs 6 and 321-483 and making non-critical variations but using "PHTH" (IX), the title compound is obtained, MH⁺ = 516.

- 15 EXAMPLE 485 N¹-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N⁵,N⁵-dipropylpentanediamide (X)

- 20 Following the general procedure of EXAMPLEs 6 and making non-critical variations and using (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methoxybenzyl)amino]-2-butanol (VIII, EXAMPLE 5) with 5-(dipropylamino)-5-oxopentanoic acid (IX), the title compound is obtained, MH⁺ = 534.2.

- 25 EXAMPLE 486 N¹-[(1S,2R)-3-{[(1R)-1-[(benzyloxy)methyl]-2-(isobutylamino)-2-oxoethyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N³,N³-dipropylisophthalamide (X)

Following the general procedures of EXAMPLEs 124, 280 and 432 and making non-critical variations but using the "R" C-terminal amine (VI), the title compound is obtained, $MH^+ = 695$.

5 EXAMPLE 487 $N^1-((1S,2R)-1-(3,5\text{-difluorobenzyl})-2\text{-hydroxy-3-}\{[(1R)-1\text{-}(\text{hydroxymethyl})-2\text{-(isobutylamino)-2-oxoethyl}]\text{amino}\}\text{propyl})-5\text{-methyl-}N^3,N^3\text{-dipropylisophthalamide (X)}$

Following the general procedures of EXAMPLEs 128, 284 and 436 and
10 making non-critical variations but using the "R" C-terminal amine (VI), the title compound is obtained, $MH^+ = 719$.

EXAMPLE 488 $N^1-[(1S,2R)-1\text{-benzyl-2-hydroxy-3-(pentylamino)propyl}]\text{-}N^3,N^3\text{-dipropylisophthalamide (X)}$

15 Following the general procedures of EXAMPLEs 96, 252 and 403 and making non-critical variations but using $NH_2-(CH_2)_4-CH_3$ as the C-terminal amine (VI), the title compound is obtained, $MH^+ = 481$.

EXAMPLE 489 $N^1-[(1S)-3-(\{2-[4\text{-(aminosulfonyl)phenyl}]\text{ethyl}\}\text{amino})-1\text{-benzyl-2-hydroxypropyl}]\text{-}N^3,N^3\text{-dipropylisophthalamide (X)}$
20

Following the general procedures of EXAMPLEs 61, 217 and 368 and making non-critical variations but using racemic C-terminal amine (VI), the title compound is obtained, $MH^+ = 595$.

25

EXAMPLE 491 $N^3-\{(1S,2R)-1-(3,5\text{-difluorobenzyl})-2\text{-hydroxy-3-}[(1,3\text{-thiazol-5-ylmethyl})\text{amino}]\text{propyl}\}\text{-}N^5,N^5\text{-dipropyl-3,5-pyridinedicarboxamide (X)}$

Following the general procedure of EXAMPLE 457 and making non-critical
30 variations and using (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(1,3-thiazol-5-ylmethyl)amino]-2-butanol (VIII, EXAMPLE 305) with "3,5-pyridinyl" as the amide forming agent (IX), the title compound is obtained.

EXAMPLE 492 3-Benzoyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-
[(3-methoxybenzyl)amino]propyl}benzamide (X)

Following the general procedure of EXAMPLE 452 and making non-critical variations and using (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-
5 methoxybenzyl)amino]-2-butanol trifluoroacetate (VIII, EXAMPLE 5) and reacting it with phenyl-CO-phenyl-CO-OH (IX) where the attachment to the -phenyl- ring is 1,3- for the carbonyl groups, the title compound is obtained, $MH^+ = 545.2$

EXAMPLE 493 N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-
10 methoxybenzyl)amino]propyl}[1,1'-biphenyl]-3-carboxamide
(X)

Following the general procedure of EXAMPLE 452 and making non-critical variations and using (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-
methoxybenzyl)amino]-2-butanol trifluoroacetate (VIII, EXAMPLE 5) and reacting
15 it with phenyl-phenyl-CO-OH (IX) where the attachment to the middle -phenyl- ring is 1,3- for the carbonyl group and other -phenyl , the title compound is obtained, $MH^+ = 517.2$.

EXAMPLE 494 N^1 -{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-
20 methylbenzyl)amino]propyl}- N^3, N^3 -dipropylisophthalamide
(X)

Following the general procedure of EXAMPLE 452 and making non-critical variations and using (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-
methoxybenzyl)amino]-2-butanol trifluoroacetate (VIII, EXAMPLE 5) and reacting
25 it with $(CH_3-O-CH_2-CH_2)_2N-CO-CO-OH$ (IX) where the attachment to the -phenyl - ring is 1,3- for the carbonyl groups, the title compound is obtained, $MH^+ = 570.3$.

EXAMPLE 495 N^1 -[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-
hydroxypropyl]- N^3 -(2-methoxyethyl)- N^3 -
30 propylisophthalamide (X)

Following the general procedure of EXAMPLE 452 and making non-critical variations and using (2R,3S)-3-amino-1-(benzylamino)-4-(3,5-difluorophenyl)-2-
butanol (VIII, EXAMPLE 271) and reacting it with $(CH_3-CH_2-CH_2)-(CH_3-O-CH_2-$

CH₂-)N-CO-phenyl-CO-OH (IX) where the attachment to the -phenyl- ring is 1,3- for the carbonyl groups, the title compound is obtained, MH⁺ = 554.5.

5 EXAMPLE 496 N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-ethoxybenzamide (X)

Following the general procedure of EXAMPLE 452 and making non-critical variations and using (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methoxybenzyl)amino]-2-butanol trifluoroacetate (VIII, EXAMPLE 5) and reacting it with CH₃-CH₂-O-phenyl-CO-OH (IX) where the attachment to the -phenyl- ring
10 is 1,3- for the carbonyl and ethoxy group, the title compound is obtained, MH⁺ = 485

EXAMPLE 497 N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-naphthamide (X)

Following the general procedure of EXAMPLE 452 and making non-critical
15 variations and using (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-methoxybenzyl)amino]-2-butanol trifluoroacetate (VIII, EXAMPLE 5) and reacting *ortho* position, the title compound is obtained, MH⁺ = 491.

20 EXAMPLE 498 N¹-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-1,2,3,4-tetrahydro-1-naphthalenylamino]propyl}-5-methyl-N³,N³-dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, EXAMPLE 3), 1,2,3,4-tetrahydro-1-naphthalenylamine
25 (VI) and "5-Me-PHTH" (IX), the title compound is obtained, MH⁺ = 588.

EXAMPLE 499 N¹-[(1R)-3-[[3,5-bis(trifluoromethyl)benzyl]amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N³,N³-dipropylisophthalamide (X)

30 Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-

oxiranyl]ethylcarbamate (V, EXAMPLE 3), $\text{H}_2\text{N-CH}_2\text{-phenyl-(3,5-ditrifluoromethyl)}$ (VI) and "5-Me-PHTH" (IX), the title compound is obtained, $\text{MH}^+ = 688$.

- 5 EXAMPLE 500 $\text{N}^1\text{}-((1\text{S},2\text{R})\text{-1-benzyl-3-}\{[2\text{-fluoro-5-(trifluoromethyl)benzyl]amino}\}\text{-2-hydroxypropyl})\text{-N}^3,\text{N}^3\text{-dipropylisophthalamide (X)}$

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V),
10 $\text{H}_2\text{N-CH}_2\text{-phenyl-(2-fluoro-5-trifluoromethyl)}$ (VI) and "PHTH" (IX), the title compound is obtained, $\text{MH}^+ = 588$.

- EXAMPLE 501 $\text{N}^1\text{}-\{(1\text{S},2\text{R})\text{-1-benzyl-3-}[(2,3\text{-difluorobenzyl})\text{amino}]\text{-2-hydroxypropyl}\}\text{-N}^3,\text{N}^3\text{-dipropylisophthalamide (X)}$

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V),
15 $\text{H}_2\text{N-CH}_2\text{-phenyl-(2,3-difluoro)}$ (VI) and "PHTH" (IX), the title compound is obtained, $\text{MH}^+ = 538$.

- EXAMPLE 502 $\text{N}^1\text{}-((1\text{S},2\text{R})\text{-1-benzyl-3-}\{[3\text{-fluoro-4-(trifluoromethyl)benzyl]amino}\}\text{-2-hydroxypropyl})\text{-N}^3,\text{N}^3\text{-dipropylisophthalamide (X)}$
20

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V),
 $\text{H}_2\text{N-CH}_2\text{-phenyl-(3-fluoro-4-trifluoromethyl)}$ (VI) and "PHTH" (IX), the title
25 compound is obtained, $\text{MH}^+ = 588$.

- EXAMPLE 503 $\text{N}^1\text{}-\{(1\text{S},2\text{R})\text{-1-benzyl-3-}[(2,5\text{-difluorobenzyl})\text{amino}]\text{-2-hydroxypropyl}\}\text{-N}^3,\text{N}^3\text{-dipropylisophthalamide (X)}$

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V),
30 $\text{H}_2\text{N-CH}_2\text{-phenyl-(2,5-difluoro)}$ (VI) and "PHTH" (IX), the title compound is obtained, $\text{MH}^+ = 538$.

EXAMPLE 504 N^1 -((1S,2R)-1-benzyl-3-{{3-fluoro-5-(trifluoromethyl)benzyl]amino}-2-hydroxypropyl)- N^3,N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V),
5 H_2N-CH_2 -phenyl-(3-fluoro-5-trifluoromethyl) (VI) and "PHTH" (IX), the title compound is obtained, $MH^+ = 588$.

EXAMPLE 505 N^1 -{{(1S,2R)-1-benzyl-3-[(3,4-difluorobenzyl)amino]-2-hydroxypropyl}- N^3,N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V),
10 H_2N-CH_2 -phenyl-(3,4-difluoro) (VI) and "PHTH" (IX), the title compound is obtained, $MH^+ = 538$.

EXAMPLE 506 N^1 -((1S,2R)-1-benzyl-3-{{4-fluoro-3-(trifluoromethyl)benzyl]amino}-2-hydroxypropyl)- N^3,N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V),
20 H_2N-CH_2 -phenyl-(3-trifluoromethyl-4-fluoro) (VI) and "PHTH" (IX), the title compound is obtained, $MH^+ = 588$.

EXAMPLE 507 N^1 -((1S,2R)-1-benzyl-3-{{2-chloro-5-(trifluoromethyl)benzyl]amino}-2-hydroxypropyl)- N^3,N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V),
25 H_2N-CH_2 -phenyl-(2-chloro-5-trifluoromethyl) (VI) and "PHTH" (IX), the title compound is obtained, $MH^+ = 605$.

EXAMPLE 508 N^1 -((1S,2R)-1-benzyl-3-{{4-chloro-3-(trifluoromethyl)benzyl]amino}-2-hydroxypropyl)- N^3,N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), $\text{H}_2\text{N}-\text{CH}_2$ -phenyl-(3-trifluoromethyl-4-chloro) (VI) and "PHTH" (IX), the title compound is obtained, $\text{MH}^+ = 605$.

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EXAMPLE 509 N^1 -[(1S,2R)-1-benzyl-3-(2,3-dihydro-1H-inden-2-ylamino)-2-hydroxypropyl]- N^3 , N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V),
10 H_2N -(2,3-dihydro-1H-inden-2-yl) and "PHTH" (IX), the title compound is obtained, $\text{MH}^+ = 528$.

EXAMPLE 510 N^1 -{(1S)-1-benzyl-2-hydroxy-3-[(3-nitrobenzyl)amino]propyl}- N^3 , N^3 -dipropylisophthalamide (X)

15 Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), $\text{H}_2\text{N}-\text{CH}_2$ -phenyl-3-nitro (VI) and "PHTH" (IX), the title compound is obtained, $\text{MH}^+ = 547$.

20 EXAMPLE 511 N^1 -((1S,2R)-1-benzyl-3-{[3-(difluoromethoxy)benzyl]amino}-2-hydroxypropyl)- N^3 , N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V),
25 $\text{H}_2\text{N}-\text{CH}_2$ -phenyl-3(-O- CHF_2) (VI) and "PHTH" (IX), the title compound is obtained, $\text{MH}^+ = 538$.

EXAMPLE 512 N^1 -{(1S,2R)-1-benzyl-3-[(3-ethoxybenzyl)amino]-2-hydroxypropyl}- N^3 , N^3 -dipropylisophthalamide (X)

30 Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), $\text{H}_2\text{N}-\text{CH}_2$ -phenyl-(3-O- $\text{CH}_2\text{-CH}_3$) (VI) and "PHTH" (IX), the title compound is obtained, $\text{MH}^+ = 546$.

EXAMPLE 513 N^1 -((1S,2R)-1-benzyl-2-hydroxy-3-[(5-methyl-2-pyrazinyl)methyl]amino}propyl)- N^3,N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 5-methyl-2-methylaminoprazine (VI) and "PHTH" (IX), the title compound is obtained, $MH^+ = 518$.

EXAMPLE 514 N^1 -{(1S,2R)-1-benzyl-3-[(3-bromo-4-fluorobenzyl)amino]-2-hydroxypropyl}- N^3,N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), H_2N-CH_2 -phenyl-(3-bromo-4-fluoro) (VI) and "PHTH" (IX), the title compound is obtained, $MH^+ = 599$.

EXAMPLE 515 N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3,5-dimethylbenzyl)amino]-2-hydroxypropyl}-5-methyl- N^3,N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V), H_2N-CH_2 -phenyl-(3,5-dimethyl) (VI) and "5-Me-PHTH" (IX), the title compound is obtained, $MH^+ = 580$.

EXAMPLE 516 N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethoxybenzyl)amino]-2-hydroxypropyl}-5-methyl- N^3,N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V), H_2N-CH_2 -phenyl-(3-ethoxy) (VI) and "5-Me-PHTH" (IX), the title compound is obtained, $MH^+ = 596$.

EXAMPLE 517 N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-phenoxyethyl)amino]propyl}-5-methyl- N^3,N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V), H₂N-CH₂-CH₂-O-phenyl (VI) and "5-Me-PHTH" (IX), the title compound is obtained, MH⁺ = 582.

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EXAMPLE 518 N¹-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isobutoxybenzyl)amino]propyl}-5-methyl-N³,N³-dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V), H₂N-CH₂-phenyl-O-*i*-butyl (VI) and "5-Me-PHTH" (IX), the title compound is obtained, MH⁺ = 624.

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EXAMPLE 519 N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(4-methyl-1,3-thiazol-2-yl)methyl]amino}propyl)-5-methyl-N³,N³-dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V), H₂N-CH₂-4-methyl-1,3-thiazol-2-yl (VI) and "5-Me-PHTH" (IX), the title compound is obtained, MH⁺ = 573.

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EXAMPLE 520 N¹-[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-N³-methyl-N³-propylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V), H₂N-CH₂-phenyl (VI) and (CH₃-CH₂-CH₂)-(CH₃-)N-CO-(CH₃-)phenyl-CO-OH (IX) where the attachment to the -phenyl- ring for the carbonyls is 1-,3- and 5- for the methyl group, the title compound is obtained, MH⁺ = 510.

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EXAMPLE 521 N²-[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-N⁵,N⁵-dipropyl-2,5-furandicarboxamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-

oxiranyl]ethylcarbamate (V), $\text{H}_2\text{N}-\text{CH}_2$ -phenyl (VI) and $(\text{CH}_3-\text{CH}_2-\text{CH}_2)_2\text{N}-\text{CO}-(2,5\text{-furanyl})-\text{CO}-$ (IX), the title compound is obtained, $\text{MH}^+ = 528$.

5 EXAMPLE 522 $\text{N}^3-((1\text{S},2\text{R})-1-(3,5\text{-difluorobenzyl})-2\text{-hydroxy-3-}\{[3\text{-}(\text{trifluoromethyl})\text{benzyl}]\text{amino}\}\text{propyl})-\text{N}^5,\text{N}^5\text{-dipropyl-3,5-pyridinedicarboxamide (X)}$

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V), $\text{H}_2\text{N}-\text{CH}_2$ -phenyl-3-trifluoromethyl (VI) and “3,5-pyridinyl” (IX), the title compound is obtained, $\text{MH}^+ = 607$.

EXAMPLE 523 $\text{N}^3-\{(1\text{S},2\text{R})-1-(3,5\text{-difluorobenzyl})-2\text{-hydroxy-3-}[(1\text{-methyl-1-phenylethyl})\text{amino}]\text{propyl}\}-\text{N}^5,\text{N}^5\text{-dipropyl-3,5-pyridinedicarboxamide (X)}$

15 Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V), $\text{H}_2\text{N}-\text{C}(-\text{CH}_3)_2$ -phenyl (VI) and “3,5-pyridinyl” (IX), the title compound is obtained, $\text{MH}^+ = 567$.

20 EXAMPLE 524 $\text{N}^1-[(1\text{S},2\text{R})-3\text{-amino-1-(3,5-difluorobenzyl)-2-hydroxypropyl}]-5\text{-methyl-}\text{N}^3,\text{N}^3\text{-dipropylisophthalamide (X)}$

Following the general procedure of CHARTS A, C and D and EXAMPLES 165-168 and making non-critical variations, but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V) and “5-Me-PHTH” (IX), the title compound is obtained, $\text{MH}^+ = 462$.

EXAMPLE 525 $\text{N}^1-\{(1\text{S},2\text{R})-1-(3,5\text{-difluorobenzyl})-3-[(1,2\text{-diphenylethyl})\text{amino}]-2\text{-hydroxypropyl}\}-5\text{-methyl-}\text{N}^3,\text{N}^3\text{-dipropylisophthalamide (X)}$

30 Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V), $\text{NH}_2-\text{CH}(\text{O})-\text{CH}_2$ -phenyl (VI) and “5-Me-PHTH” (IX), the title compound is obtained, $\text{MH}^+ = 642$.

EXAMPLE 526 N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(7-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)amino]propyl}-5-methyl- N^3,N^3 -dipropylisophthalamide, isomer A (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V), 7-methoxy-1,2,3,4-tetrahydro-1-naphthalenylamine (VI) and "5-Me-PHTH" (IX), the title compound is obtained, $MH^+ = 622$.

EXAMPLE 527 N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(7-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)amino]propyl}-5-methyl- N^3,N^3 -dipropylisophthalamide, isomer B (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V), 7-methoxy-1,2,3,4-tetrahydro-1-naphthalenylamine (VI) and "5-Me-PHTH" (IX), the title compound is obtained, $MH^+ = 622$.

EXAMPLE 528 Benzyl-(1S, 2R)-3-azido-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (XII)

Following the general procedure of EXAMPLE 165 and making non-critical variations but starting with benzyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, EXAMPLE 13), the title compound is obtained.

EXAMPLE 529 N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-(dimethylamino)benzamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 3-dimethylaminobenzoic acid (IX), the title compound is obtained, $MH^+ = 448$.

EXAMPLE 530 N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-2-methyl-1H-benzimidazole-5-carboxamide (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 2-methyl-1H-benzimidazole-5-carboxylic acid (IX), the title compound is obtained, $MH^+ = 459$.

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EXAMPLE 531 3-(aminosulfonyl)-N-{(1S)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-4-chlorobenzamide (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 3-(aminosulfonyl)-4-chlorobenzoic acid (IX), the title compound is obtained, $MH^+ = 519$.

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EXAMPLE 532 N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-cyanobenzamide (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 3-cyanobenzoic acid (IX), the title compound is obtained, $MH^+ = 430$.

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EXAMPLE 533 N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]-propyl}-4-chloro-3-nitrobenzamide (X)

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Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 4-chloro-3-nitrobenzoic acid (IX), the title compound is obtained, $MH^+ = 484$.

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EXAMPLE 534 Methyl 3-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]amino)carbonyl]-5-nitrobenzoate (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-

methoxybenzylamine (VI) and 3-nitro-5-(methyl-O-CO-)-phenyl-CO-OH (IX), the title compound is obtained, $MH^+ = 508$.

5 EXAMPLE 535 tert-butyl 3-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]amino)carbonyl]-phenylcarbamate (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 3-(*t*-butyl-O-CO-NH)-phenyl-CO-OH (IX),
10 the title compound is obtained, $MH^+ = 520$.

EXAMPLE 536 N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-9,10-dioxo-9,10-dihydro-2-anthourancenylcarboxamide (X)

15 Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 9,10-dioxo-9,10-dihydro-2-anthourancenylcarboxylic acid (IX), the title compound is obtained, $MH^+ = 535$.

20 EXAMPLE 537 N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-1H-1,2,3-benzotriazole-6-carboxamide (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 1H-1,2,3-benzotriazolyl-6-carboxylic acid (IX), the
25 title compound is obtained, $MH^+ = 446$.

EXAMPLE 538 N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-4-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide (X)

30 Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 4-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzoic acid (IX), the title compound is obtained, $MH^+ = 501$.

EXAMPLE 539 N- {(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]- propyl}-1H-indole-5-carboxamide (X)

5 Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and indole-5-carboxylic acid (IX), the title compound is obtained, $MH^+ = 444$.

10 EXAMPLE 540 N- {(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-fluoro-5-(trifluoromethyl)benzamide (X)

 Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 3-fluoro-5-(trifluoromethyl)benzoic acid (IX), the
15 title compound is obtained, $MH^+ = 491$.

EXAMPLE 541 N- {(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]- propyl}-3-(trifluoromethyl)benzamide (X)
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 Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 3-(trifluoromethyl)benzoic acid (IX), the title
25 compound is obtained, $MH^+ = 473$.

EXAMPLE 542 N- {(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]- propyl}-4-(butylamino)benzamide (X)
30

 Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 4-(butylamino)benzoic acid (IX), the title compound
35 is obtained, $MH^+ = 476$.

EXAMPLE 543 N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]-propyl}-3-(trifluoromethoxy)benzamide (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 3-(trifluoromethoxy)benzoic acid (IX), the title compound is obtained, $MH^+ = 489$.

EXAMPLE 544 N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]-propyl}-3,5-dimethoxybenzamide (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 3,5-dimethoxybenzoic acid (IX), the title compound is obtained, $MH^+ = 465$.

EXAMPLE 545 N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]-propyl}-3,5-dimethylbenzamide (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 3,5-dimethylbenzoic acid (IX), the title compound is obtained, $MH^+ = 433$.

EXAMPLE 546 N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]-propyl}-3,5-difluorobenzamide (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 3,5-difluorobenzoic acid (IX), the title compound is obtained, $MH^+ = 441$.

EXAMPLE 547 N-{{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]- propyl}-3,5-dichlorobenzamide (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 3,5-dichlorobenzoic acid (IX), the title compound is obtained, $MH^+ = 474$.

EXAMPLE 548 N-{{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]- propyl}-4-(benzyloxy)benzamide (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 4-(benzyloxy)benzoic acid (IX), the title compound is obtained, $MH^+ = 511$.

EXAMPLE 549 N-{{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]- propyl}-1,3-benzodioxole-5-carboxamide (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 1,3-benzodioxole-5-carboxylic acid (IX), the title compound is obtained, $MH^+ = 449$.

EXAMPLE 550 3-(acetylamino)-N-{{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}benzamide (X)

Following the general procedure of EXAMPLEs 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 3-(acetylamino)benzoic acid (IX), the title compound is obtained, $MH^+ = 462$.

EXAMPLE 551 4-(acetylamino)-N-{{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}benzamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V), 3-methoxybenzylamine (VI) and 4-(acetylamino)benzoic acid (IX), the title compound is obtained, $MH^+ = 462$.

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EXAMPLE 552 N^1 -((1S,2R)-1-(3,5-difluorobenzyl)-3-{[(3,5-dimethyl-4-isoxazolyl)methyl]amino}-2-hydroxypropyl)-5-methyl- N^3, N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, EXAMPLE 3), 3,5-dimethyl-4-isoxazolylmethylamine (VI) and "5-Me-PHTH" (IX), the title compound is obtained, $MH^+ = 571.3$.

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EXAMPLE 553 N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-phenylpropyl)amino]propyl}-5-methyl- N^3, N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, EXAMPLE 3), 3-phenylpropylamine (VI) and "5-Me-PHTH" (IX), the title compound is obtained, $MH^+ = 580$.

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EXAMPLE 554 N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-furylmethyl)amino]-2-hydroxypropyl}-5-methyl- N^3, N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, EXAMPLE 3), 3-furylmethylamine (VI) and "5-Me-PHTH" (IX), the title compound is obtained, $MH^+ = 542$.

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EXAMPLE 555 N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(tetrahydro-3-furanylmethyl)amino]propyl}-5-methyl- N^3, N^3 -dipropylisophthalamide (X)

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Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-

oxiranyl]ethylcarbamate (V, EXAMPLE 3), (tetrahydro-3-furanylmethyl)amine (VI) and "5-Me-PHTH" (IX), the title compound is obtained, $MH^+ = 546$.

5 EXAMPLE 556 N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-propoxybenzyl)amino]propyl}-5-methyl- N^3,N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, EXAMPLE 3), (3-propoxybenzyl)amine (VI) and "5-Me-PHTH" (IX), the title compound is obtained, $MH^+ = 610$.

15 EXAMPLE 557 N^1 -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-pyridinylmethyl)amino]propyl}-5-methyl- N^3,N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, EXAMPLE 3), (2-pyridinylmethyl)amine (VI) and "5-Me-PHTH" (IX), the title compound is obtained, $MH^+ = 553$.

20 EXAMPLE 558 N^1 -[(1S,2R)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-hydroxy- N^3,N^3 -dipropylisophthalamide (X)

Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, EXAMPLE 3), benzylamine (VI) and 5-hydroxy-N,N-dipropylisophthalic acid (IX), the title compound is obtained, $MH^+ = 554$.

25 EXAMPLE 559 N^1 -((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-methyl-1-(3-methylphenyl)ethyl]amino}propyl)-5-methyl- N^3,N^3 -dipropylisophthalamide (X)

30 Following the general procedure of EXAMPLES 4, 5 and 6 and making non-critical variations but using tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V, EXAMPLE 3), [1-methyl-1-(3-