(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 March 2006 (30.03.2006)

PCT

(10) International Publication Number
WO 2006/032999 A1

(51) International Patent Classification:
C07C 233/37 (2006.01) *C07C 233/73* (2006.01)
C07C 233/39 (2006.01) *A61K 31/165* (2006.01)
C07C 233/40 (2006.01) *A61K 31/166* (2006.01)

(21) International Application Number:
PCT/IB2005/002877

(22) International Filing Date:
9 September 2005 (09.09.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/611,777 21 September 2004 (21.09.2004) US

(71) Applicant *(for all designated States except US)*: **PFIZER PRODUCTS INC.** [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **KLEINMAN, Edward, Fox** [US/US]; Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06340 (US). **MURRAY, John, Charles** [US/US]; Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06340 (US).

(74) Agents: **FULLER, Grover, F., Jr.** et al.; Pfizer Inc., 201 Tabor Road, Morris Plains, NJ 07950 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/032999 A1

(54) Title: N-METHYL HYDROXYETHYLAMINE USEFUL IN TREATING CNS CONDITIONS

(57) Abstract: An N-methyl hydroxyethyleneamine useful in treating CNS conditions, including neurodegenerative ones such as Alzheimer's Disease, is disclosed.

N-METHYL HYDROXYETHYLAMINE USEFUL IN TREATING CNS CONDITIONS

The invention pertains to an N-methyl hydroxyethylamine compound useful e.g. in treating conditions of the Central Nervous System (CNS); a pharmaceutical composition comprising same; and a method of treating such conditions and those in which inhibition of beta-secretase is indicated.

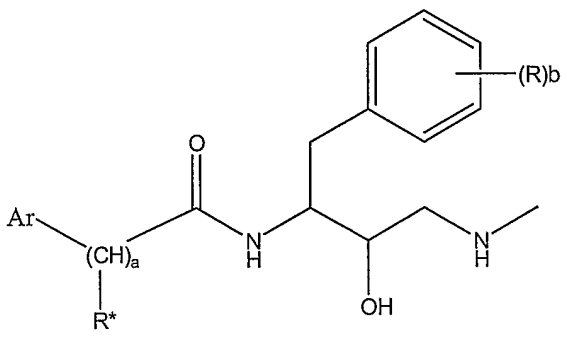
Background of the Invention

Conditions affecting the Central Nervous System include neurodegenerative conditions such as Alzheimer's Disease. Various of these conditions are typified by physical changes in the brain. For example, certain pathologies are evidenced by the presence of neurofibrillary tangles and/or plaque deposits which, as they progress, cause cognitive, motor, sensory and other impairments on multiple fronts. Commonly, said plaques are comprised principally of beta-amyloid --a highly aggregative protein that tends to accumulate, forming insoluble deposits that ultimately can cause cellular injury and death. Beta-amyloid (Aβ) derives from an amyloid precursor protein (APP), which is a transmembrane protein existing in several isoforms, the more salient of which contain 695, 714, 751 or 771 amino acids (denominated APP_{695}, APP_{714}, APP_{751}, APP_{771}). The formation of beta-amyloid is due to the sequential cleavage of APP by various proteases: beta-secretease cleaves APP at an N-terminus while gamma-secreatase cleaves APP at a C-terminus. The resulting fragment is a protein of 38, 40, 42 or 43 amino acids (denominated $A\beta_{1-38}$, $A\beta_{1-40}$, $A\beta_{1-42}$, $A\beta_{1-43}$). This fragment is released into the extracellular space where it accumulates with other such insoluble fragments to form the proteinacious deposits aforesaid that are neuronally toxic.

Among the treatment strategies under investigation for such conditions are the development of compounds that will effectively inhibit beta-secretase and/or its processing of APP to reduce the formation of beta-amyloid and ameliorate plaque deposition and related pathogenesis.

Summary of the Invention

The present invention is directed to an N-methyl hydroxyethylamine compound of Formula (I) having beta-secretase inhibitory characteristics:



(I)

Detailed Description of the invention

The compound of the invention as represented by the above formula includes all stereoisomeric forms including without limitation the (R) or (S) enantiomer thereof, diastereomers, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or of any of the foregoing. Pharmaceutically acceptable salts include acid addition salts, base addition salts and the like as understood by and as fabricated according to methods known in the art. The present compound may also have optical centers and thus occur in different enantiomeric configurations, all of which are contemplated herein. The compound of the invention further includes radiolabelled forms wherein e.g. one or more H, C, F atoms and the like are replaced with radioactive species of the same.

As appreciated by the artisan, the use of Formula I is a convenience and the invention is understood to envision and embrace each and every species thereunder as though individually identified and set forth herein. Thus the present invention severally contemplates each species separately and any and all combinations and permutations of species falling within Formula I.

Turning to Formula (I): in one embodiment a = 0, 1, 2, or 3; b = 0, 1, 2, or 3; each R is independently halogen, OH, CN, SH, NH_2, C_{1-6}alkyl, C_{1-6}alkoxy, $S(C_{1-6}alkyl)$, $NH(C_{1-6}alkyl)$, $N(C_{1-6}alkyl)(C_{1-6}alkyl)$, $NHC(=O)O(C_{1-6}alkyl)$, $NHSO_2(C_{1-6}alkyl)$, $C(=O)NH(C_{1-6}alkyl)$, $C(=O)N(C_{1-6}alkyl)(C_{1-6}alkyl)$, C_{6-10}aryl, (5 to 12 member)heteroaryl, wherein each alkyl group aforesaid may be independently optionally substituted with up to three F, OH or C_{1-3}alkoxy groups. As noted, each R may independently be chosen from the foregoing, i.e. each and every R can be the same or different irrespective of the value of b; R* is H, C_{1-6}alkyl, $-(CH_2)_{0-5}(C_6-C_{10}aryl)$, $-(CH_2)_{0-5}$(5 to 12 member)heteroaryl; and Ar is selected from (A), (B), (C), (D), (E) or (F):

(A) C_{6-10}aryl, (5 to 12 member)heteroaryl, $(C_{6-10}aryl)$-W-$(C_{6-10}aryl)$, $(C_{6-10}aryl)$-W-(5 to 12 member)heteroaryl, $(C_{6-10}aryl)$-W-(5 to 7 member)heterocycloalkyl, (5 to 12 member)heteroaryl-W-$(C_{6-10}aryl)$, (5 to 12 member)heteroaryl-W-(5 to 12 member)heteroaryl, (5 to 12 member)heteroaryl-W-(5 to 7 member)heterocycloalkyl, (5 to 7 member)heterocycloalkyl-W-$(C_{6-10}aryl)$, (5 to 7 member)heterocycloalkyl-W-(5 to 12 member)heteroaryl, (5 to 7 member)heterocycloalkyl-W-(5 to 7 member)heterocycloalkyl, wherein W is selected from $-(CH_2)_{0-4}$-, -O-, -C(=O)-, $-S(=O)_{0-2}$-, $-N(R_{N-5})$- where R_{N-5} is as defined herein;

(B) $-C(=O)(C_{1-10}alkyl)$ where alkyl is optionally independently substituted with up to three substitutents (denominated herein as "SB") selected from: OH; C_{1-6}alkoxy; C_{1-6}thioalkoxy; $C(=O)OR_{N-8}$; $-C(=O)NR_{N-2}R_{N-3}$; $-C(=O)R_{N-4}$; $-SO_2(C_{1-8}alkyl)$; $-SO_2NR_{N-2}R_{N-3}$; $-NHC(=O)(C_{1-6}alkyl)$; $-NHC(=O)OR_{N-8}$; $-NR_{N-2}R_{N-3}$; $-R_{N-4}$; $-OC(=O)(C_{1-6}alkyl)$; -O-

$C(=O)NR_{N-8}R_{N-8}$ where each R_{N-8} is the same or different; $-O(C_{1-6}alkyl)C(=O)OH$; $-O-(C_{1-6}alkyl$ optionally substituted with up to three halogens); $-NHSO_2(C_{1-6}$ alkyl); F; Cl;

(C) $-C(=O)(C_{1-6}alkyl)O(C_{1-6}alkyl)$ where each alkyl is optionally independently substituted with up to three substituents SB as defined above in (A);

(D) $-C(=O)(C_{1-6}alkyl)S(C_{1-6}alkyl)$ where each alkyl is optionally independently substituted with up to three of substituents SB as defined above in (A);

(E) $-C(=O)CH(-(CH_2)_{0-2}-O-R_{N-10})-(CH_2)_{0-2}-C_{6-10}aryl$, or $-C(=O)CH(-(CH_2)_{0-2}-O-R_{N-10})-(CH_2)_{0-2}-$(5 to 12 member)heteroaryl; or

(F) $-C(=O)(C_{3-8}cycloalkyl)$ where said cycloalkyl is optionally independently substituted with up to two substituents selected from: $-(CH_2)_{0-4}OH$; $-(CH_2)_{0-4}C_{1-6}alkoxy$; $-(CH_2)_{0-4}C_{1-6}thioalkoxy$; $-(CH_2)_{0-4}C(=O)-O-R_{N-8}$; $-(CH_2)_{0-4}C(=O)-NR_{N-2}R_{N-3}$; $-(CH_2)_{0-4}C(=O)-R_{N-4}$; $-(CH_2)_{0-4}SO_2-(C_{1-6}alkyl)$; $-(CH_2)_{0-4}SO_2-NR_{N-2}R_{N-3}$; $-(CH_2)_{0-4}NH-C(=O)-(C_{1-6}alkyl)$; $-NH-C(=O)-O-R_{N-8}$; $-(CH_2)_{0-4}NR_{N-2}R_{N-3}$; $-(CH_2)_{0-4}R_{N-4}$; $-O-C(=O)-(C_{1-6}alkyl)$; $-O-C(=O)-NR_{N-8}R_{N-8}$ where each R_{N-8} is the same or different; $-O-(C_{1-6}alkyl)-C(=O)OH$; $-O-(C_{1-6}alkyl$, wherein said alkyl is optionally substituted with up to three halogens); $-NHSO_2(C_{1-6}alkyl)$; F; Cl.

Unless otherwise indicated, the following representative definitions of terms and substituents and related variations of same obtain:

"Halogen" and "halo" and the like independently includes fluoro (F), chloro (Cl), bromo (Br) and iodo (I).

"Alkyl" including as may appear in the terms "alkoxy," "thioalkoxy" and "alkyoxy" and the like includes saturated monovalent hydrocarbon radicals having straight or branched moieties. Examples of alkyl groups include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, and and *t*-butyl.

"Alkenyl" and "Alkynyl" include alkyl moieties having at least one carbon-carbon double or triple bond, respectively.

"Cycloalkyl" includes non-aromatic saturated cyclic alkyl moieties wherein alkyl is defined as above. Examples included without limitation: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl; and bicycloalkyl and tricycloalkyl groups that are non-aromatic saturated carbocyclic groups consisting of two or three rings respectively wherein said rings share at least one carbon atom. Unless otherwise indicated herein bicycloalkyl groups include spiro groups and fused ring groups, e.g. bicycle-[3.1.0]-hexyl, bicycle-[2.2.1]-hept-1-yl, norbornyl, spiro[4.5]decyl, spiro[4.4]nonyl, spiro[4.3]octyl and spiro[4.2]heptyl. An example of a tricycloalkyl group is adamantanyl. Cycloalkyl groups also include groups substituted with one or more oxo moieties, e.g. oxocyclopentyl and oxocyclobutyl.

As appreciated, the term $(CH_2)_{0-5}$ and the like denotes the optional presence of a methylene linkage up to the carbon number indicated (here, 5), the connecting substituent to which may be in the normal or branched configuration, e.g. in $(CH_2)_{0-5}(C_{6-10}aryl)$ the aryl may be in the branched or normal position in the methylene chain.

The term "alkyl", "alkoxy", "thioalkoxy", "alkyoxy", "alkenyl", "alkynyl", "cycloalkyl" as defined and used herein are further intended to include moieties of same that may each be optionally substituted with up to 3 fluoros (F) irrespective of whether such substitutions are specifically mentioned as optional or otherwise.

"Treatment" and "treating" refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such condition or disorder. As used herein, the term also encompasses, depending on the condition of the patient, preventing the disorder, including preventing onset and/or recurrence of any symptoms associated therewith, as well as reducing the severity of the disorder or any of its symptoms prior to onset.

"Mammal" refers to any member of the class "Mammalia", including, but not limited to, humans, dogs, and cats.

"Condition" refers to a disease or disorder.

"Aryl" refers to an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen; and fused ring groups wherein at least one ring is aromatic. Examples without limitation include: phenyl, 1-naphthyl, 2-naphthyl, tetralinyl, indanyl, dihydronaphthyl, indenyl, fluorenyl and 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl. Aryl groups contemplated herein may further be optionally independently substituted with up to three of any of the following substituents (1)-(39): (1) $-C_{1-6}$alkyl, optionally substituted with up to three substituents selected from C_{1-3}alkyl, halogen, OH, SH, CN, CF_3, C_{1-3}alkoxy, $NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b}; such C_{1-6} alkyl-substituted aryl groups include, e.g. benzyl; (2) OH; (3) NO_2; (4) halogen, with F being preferred (5) -C(=O)OH; (6) -CN; (7) $-(CH_2)_{0-4}C(=O)NR_{N-2}R_{N-3}$; (8) $-(CH_2)_{0-4}C(=O)(C_{1-12}alkyl)$; (9) $-(CH_2)_{0-4}C(=O)(C_{2-12}$alkenyl with one, two or three double bonds); (10) $-(CH_2)_{0-4}C(=O)(C_{2-12}$alkynyl with one, two or three triple bonds); (11) $-(CH_2)_{0-4}C(=O)(C_{3-7}cycloalkyl)$; (12) $-(CH_2)_{0-4}C(=O)(C_{6-10}aryl)$; (13) $-(CH_2)_{0-4}C(=O)$(5 to 12 member)heteroaryl; (14) $-(CH_2)_{0-4}C(=O)$(5 to 7 member)heterocycloalkyl; (15) $-(CH_2)_{0-4}C(=O)R_{N-4}$; (16) $-(CH_2)_{0-4}C(=O)OR_{N-5}$; (17) $-(CH_2)_{0-4}SO_2-NR_{N-2}R_{N-3}$; (18) $-(CH_2)_{0-4}S(=O)(C_{1-6}alkyl)$; (19) $-(CH_2)_{0-4}SO_2-(C_{1-12}alkyl)$; (20) $-(CH_2)_{0-4}SO_2(C_{3-7}cycloalkyl)$; (21) $-(CH_2)_{0-4}N(H$ or $R_{N-5})C(=O)OR_{N-5}$ where each R_{N-5} can be the same or different; (22) $-(CH_2)_{0-4}N(H$ or $R_{N-5})-C(=O)N(R_{N-5})_2$, where each R_{N-5} can be the same or different; (23) $-(CH_2)_{0-4}N-C(=S)N(R_{N-5})_2$, where each R_{N-5} can be the same or different; (24) $-(CH_2)_{0-4}N(H$ or $R_{N-5})-C(=O)R_{N-2}$; (25) $-(CH_2)_{0-4}NR_{N-2}R_{N-3}$; (26) $-(CH_2)_{0-4}R_{N-4}$; (27) $-(CH_2)_{0-4}OC(=O)(C_{1-6}alkyl)$; (28) $-(CH_2)_{0-4}OP(=O)-(O-C_{6-10}aryl)_2$; (29) $-(CH_2)_{0-4}OC(=O)N(R_{N-5})_2$ where each R_{N-5} can be the same or different;

(30) $-(CH_2)_{0-4}OC(=S)N(R_{N-5})_2$ where each R_{N-5} can be the same or different; (31) $-(CH_2)_{0-4}O(R_{N-5})_2$ where each R_{N-5} can be the same or different; (32) $-(CH_2)_{0-4}O(R_{N-5})_2-C(=O)OH$ where each R_{N-5} can be the same or different; (33) $-(CH_2)_{0-4}S(R_{N-5})_2$ where each R_{N-5} can be the same or different; (34) $-(CH_2)_{0-4}O(C_{1-6}$alkyl optionally substituted with up to five F as obtains); (35) C_{3-7}cycloalkyl; (36) C_{2-6}alkenyl with one or two double bonds, said alkenyl optionally substituted with C_{1-3}alkyl, halogen, OH, SH, CN, CF_3, C_{1-3}alkoxy, $NR_{1-a}R_{1-b}$; (37) -C_{2-6}alkynyl with one or two triple bonds, said alkynyl optionally substituted with C_{1-3}alkyl, halogen, OH, SH, CN, CF_3, C_{1-3}alkoxy, $NR_{1-a}R_{1-b}$; (38) $-(CH_2)_{0-4}N(H$ or $R_{N-5})SO_2R_{N-2}$; or (39) -$(CH_2)_{0-4}C_{3-7}$cycloalkyl.

"Heteroaryl" refers to a heteroaryl group constituted of one or more aromatic groups containing one or more heteroatoms (O, S, or N), preferably from one to four heteroatoms. As used herein, a multicyclic group containing one or more heteroatoms wherein at least one ring of the group is aromatic is also a "heteroaryl" group. The heteroaryl groups of this invention can also include ring systems which exist in one or more tautomeric forms (e.g. keto, enol, and like forms), and/or substituted with one or more oxo moieties. Examples of heteroaryl groups are, without limitation: quinolyl, isoquinolyl, 1,2,3,4-tetrahydroguinolyl, 1,2,4-trizainyl, 1,3,5-triazinyl, 1-oxoisoindolyl, furazanyl, benzofurazanyl, benzothiophenyl, dihydroquinolyl, dihydroisoquinolyl, benzofuryl, furopyridinyl, pyrolopyrimidinyl, and azaindolyl, pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pryidazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, coumarinyl, isocoumarinyl, chromonyl, chromanonyl, pyridinyl-N-oxide, tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyrrolyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide, thiazolyl N-oxide, indolizinyl N-oxide, indazolyl N-oxide, benzothiazolyl N-oxide, benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide, benzothiopyranyl

S-oxide, benzothiopyranyl S,S-dioxide. Each heteroaryl may also be optionally independently substituted with up to four of any of the following substituents (1)-(13): (1) C_{1-6}alkyl, said alkyl optionally substituted with up to three substituents selected from C_{1-3}alkyl, halogen, OH, SH, $NR_{1-a}R_{1-b}$, CN, CF_3, C_{1-3}alkoxy; (2) C_{2-6}alkenyl with one or two double bonds, said alkenyl optionally substituted with up to three substituents selected from F, Cl, OH, SH, CN, CF_3, C_{1-3}akoxy, $NR_{1-a}R_{1-b}$; (3) C_{2-6}alkynyl with one or two triple bonds, said alkynyl optionally substituted with up to three substituents selected from F, Cl, OH, SH, CN, CF_3, C_{1-3}alkoxy, $NR_{1-a}R_{1-b}$; (4) halogen; (5) C_{1-6}alkoxy, said alkoxy optionally substituted with up to F; (6) $NR_{N-2}R_{N-3}$; (7) OH; (8) CN; (9) C_{3-7}cycloalkyl, said cycloalkyl optionally substituted with up to three substituents selected from F, Cl, OH, SH, CN, CF_3, C_{1-3}alkoxy, $NR_{1-a}R_{1-b}$; (10) C(=(O)(C_{1-4}alkyl); (11) $SO_2NR_{1-a}R_{1-b}$; (12) $C(=O)NR_{1-a}R_{1-b}$; (13) $SO_2(C_{1-4}$alkyl).

"Heterocycloalkyl" and "Heterocyclic" refer to a heterocycloalkyl group of one or more non-aromatic cyclic groups containing one or more heteroatoms, preferably from one to four heteroatoms, each selected from O, S and N. Heterocyclic groups also include ring systems substituted with one or more oxo moieties. Without limitation, examples of heterocyclic groups include: aziridinyl, azetidinyl, azepinyl, 1,2,3,6-tetrahydropyridinyl, oxiranyl, oxetanyl, tetrahydrothiopyranyl, morpholino, thiomorpholino, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, quinolizinyl, quinuclidinyl, 1,4-dioxaspiro[4.5]decyl, 1,4-dioxaspiro[4.4]nonyl, 1,4-dioxaspiro[4.3]octyl, and 1,4-dioxaspiro[4.2]heptyl, morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide, homothiomorpholinyl S-oxide. Each heterocycloalkyl may also be optionally independently substituted with up to four of any of the following substituents (1)-(14): (1) C_{1-6}alkyl, said alkyl optionally substituted with up to three substituents selected from C_{1-3}alkyl, halogen, OH, SH, $NR_{1-a}R_{1-b}$, CN, CF_3, C_{1-3}alkoxy; (2) C_{2-6}alkenyl with one or two double bonds, said alkenyl optionally substituted with up to three substituents selected from F, Cl, OH, SH, CN, CF_3, C_{1-3}alkoxy, $NR_{1-a}R_{1-b}$; (3) C_{2-6}alkynyl with one or two triple bonds, said alkynyl optionally substituted with up to three substituents selected from F, Cl, OH, SH, CN, CF_3, C_{1-3}alkoxy, $NR_{1-a}R_{1-b}$; (4) halogen; (5) C_{1-6}alkoxy, said alkoxy optionally substituted with up to three F; (6) $NR_{N-2}R_{N-3}$; (7) OH; (8) CN; (9) C_{3-7}cycloalkyl, said cycloalkyl optionally substituted with up to three substituents selected from F, Cl, OH, SH, CN, CF_3, C_{1-3}alkoxy, $NR_{1-a}R_{1-b}$; (10) C(=O)(C_{1-4}alkyl); (11) $SO_2NR_{1-a}R_{1-b}$; (12) $C(=O)NR_{1-a}R_{1-b}$; (13) -$SO_2(C_{1-4}$alkyl); (14) =O.

The foregoing groups, as derived from the compounds listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). The terms referring to the groups also encompass all possible tautomers.

"R_{1-a}" and "R_{1-b}" are each independently H, C_{1-6} alkyl.

"R_{N-2}" and "R_{N-3}" are each independently selected from the group (a) H; (b) C_{1-6}alkyl optionally substituted with one substituent selected from: OH or NH_2; (c) C_{1-6}alkyl optionally substituted with up to three halogen; (d) C_{3-7}cycloalkyl; (e) -(C_{1-2}alkyl)(C_{3-7}cycloalkyl); (f) -(C_{1-6}alkyl)O(C_{1-3}alkyl); (g) C_{2-6}alkenyl with one or two double bonds; (h) C_{2-6}alkynyl with one or two triple bonds; (i) C_{1-6}alkyl chain with one double bond and one triple bond; (j) C_{6-10}aryl; or (k) (5 to 12 member)heteroaryl.

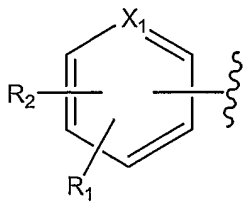
"R_{N-4}" is selected from the group: morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl where each group is optionally substituted with one, two, three, or four of C_{1-6}alkyl.

"R_{N-5}" is selected from the group: (a) C_{1-6}alkyl, (b) -$(CH_2)_{0-2}$(C_{6-10}aryl), (c) C_{2-6}alkenyl containing one or two double bonds, (d) C_{2-6}alkynyl containing one or two triple bonds, (e) C_{3-7}cycloalkyl, (f) -$(CH_2)_{0-2}$(5 to 12 member)heteroaryl.

"R_{N-8}" is H, C_{1-6}alkyl, or phenyl.

"R_{N-10}" is H, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl with one double bond, or C_{2-6} alkynyl with one triple bond.

In a preferred embodiment of Formula (I): a = 0, 1, 2, or 3 (a = 0 or 1 being more preferred); b = 0, 1, 2, or 3 (b = 2 being more preferred); each R is independently halogen, OH, C_{1-6}alkyl, CN, C_{1-6}alkoxy, C_{6-10}aryl, (5 to 12 member)heteroaryl, wherein said alkyl and alkoxy may each optionally independently be substituted with up to three halogen (F preferred) or OH groups; (i.e. each and every R can be the same or different irrespective of the value of b). R* is H, C_{1-6}alkyl, -$(CH_2)_{0-5}$(C_{6-10}aryl), -$(CH_2)_{0-5}$(5 to 12 member)heteroaryl, wherein said alkyl, aryl, or heteroaryl may each optionally independently be substituted with up to three halogen (F preferred), C_{1-6}alkoxy or OH groups; and Ar is selected from (i), (ii), (iii), or (iv) any of which Ar may be optionally substituted with a fluoro (F) at a ring carbon atom (preferably when Ar is (i)):



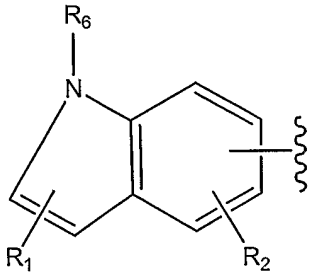
(i)

wherein:

X_1 is CH or N; R_1 is H, halogen (Br preferred), C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, (5 to 12 member)heteroaryl, OH, CN, SH, C_{1-6}alkoxy, $S(C_{1-6})$alkyl, $-NR_3(C=O)_cR_4$, $-NR_3SO_2R_4$, $-(CH_2)_c(C=O)R_5$, $-(CH_2)_c(C=O)OR_5$, $-(S=O)R_5$, $-S(=O)_2R_5$ wherein c = 0 or 1, R_3, R_4 and R_5 are each independently H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl, $(CH_2)_{0-5}(C_{6-10}$aryl), $(CH_2)_{0-5}$(5 to 12 member)heteroaryl or $NR_3(Y)R_4$ wherein Y is CO or SO_2, and R_3 and R_4 together with the N and the C or S atoms of Y to which they are attached form a (5 to 7 member)heterocycloalkyl, and wherein any of said alkyl, cycloalkyl, or heterocycloalkyl may be each be optionally independently substituted with up to three halogen (F preferred), OH, C_{1-6}alkyl, C_{1-6}alkoxy, or CN groups;

R_2 is independently $-C(=O)R_3$, $-(C=O)_cNR_3R_4$, $-NR_3SO_2R_4$ or $-OR_5$ wherein c = 0 or 1, and R_3, R_4, and R_5 are as defined above, or R_2 is $-NR_3SO_2R_4$ wherein R_3 and R_4 together with the N and S atoms to which they are attached form a (5 to 7 member)heterocycloalkyl and wherein any of said alkyl, cycloalkyl or heterocycloalkyl moieties of R_2 may each be optionally independently substituted with up to three halogen (F preferred), OH, C_{1-6}alkyl, C_{1-6} alkoxy or CN groups;

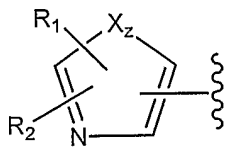
or R_1 and R_2 together with the C atoms to which they are attached form a fused C_{5-10} cycloalkyl, C_{5-10} aryl or (5 to 10 member)heteroaryl group wherein said fused cycloalkyl, aryl or heteroaryl group is optionally independently substituted with up to three groups selected from R_7 and R_8 wherein R_7 is C_{1-6} alkyl said alkyl optionally substituted with up to three F, OH, C_{1-3}alkoxy groups; and R_8 is $-(C=O)_dR_5$ wherein d = 0 or 1, and R_5 is as defined above;



(ii)

wherein:

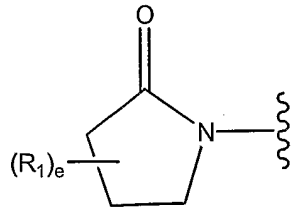
R_1 and R_2 are as defined above in (i); and R_6 is H, C_{1-6} alkyl, $-(CH_2)_{0-5}(C_{6-10}$aryl), $-(CH_2)_{0-5}$(5 to 12 member) heteraryl, wherein said alkyl maybe optionally independently substituted with up to three halogen, C_{1-6}alkoxy or OH groups;



(iii)

wherein:

X_2 is NH, N(C_{1-6}alkyl), O or S; and R_1 and R_2 are as defined above; or



(iv)

wherein:

e = 1 or 2; and each R_1 is independently as defined above irrespective of the value of e (wherein when e = 2, each R_1 is preferably –NH(C=O)$_c$(C_{1-6}alkyl) and C_{1-6}alkyl); preferably, when Ar is (iv), a is not zero; more preferably, when Ar is (iv), a = 1.

In one preferred practice: Ar = (i); independently each R is halogen; a = 0; b = 2; and R_2 is -C(=O)$_c$NR_3R_4. More preferably, c = 1; R_3 and R_4 are each C_3alkyl; R = F; and R_1 is C_{1-6}alkyl, halogen, a (5 to 12 member)heteroaryl or C_{2-12}alkynyl. Still more preferably, R_1 is methyl, bromine, oxazolyl or ethynyl. Representative compounds in this regard include:

(1S, 2R) N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-5-methyl-N',N'-dipropyl-isophthalamide;

(1S, 2R) 5-Bromo-N-[1-(3,5-difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-N',N'-dipropyl-isophthalamide;

(1S, 2R) N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-5-oxazol-2-yl-N',N'-dipropyl-isophthalamide;

(1S, 2R) 6-Methyl-pyridine-2,4-dicarboxylic acid 4-{[1-(3,5-difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-amide} 2-dipropylamide; and

(1S, 2R) N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-5-ethynyl-N',N'-dipropyl-isophthalamide.

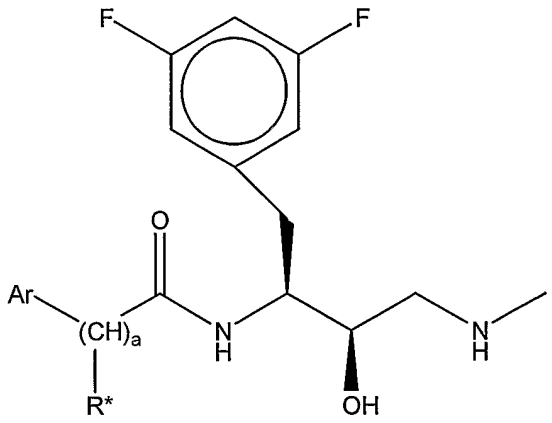
In a second preferred practice: Ar = (ii); R_2 = -C(=O)$_c$$R_3$; independently each R = halogen; a = 0; and b = 2. More preferably, c = 1; R_3 and R_4 are each C_3alkyl; R = F; R_1 = H; and R_6 = C_{1-6}alkyl. Still more preferably, R_6 = C_2-C_6alkyl. Representative compounds in this regard include:

(1S, 2R) 3-Acetyl-1-butyl-1H-indole-6-carboxylic acid [1-(3,5-difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-amide;

(1S, 2R) 3-Acetyl-1-hexyl-1H-indole-6-carboxylic acid [1-(3,5-difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-amide; and

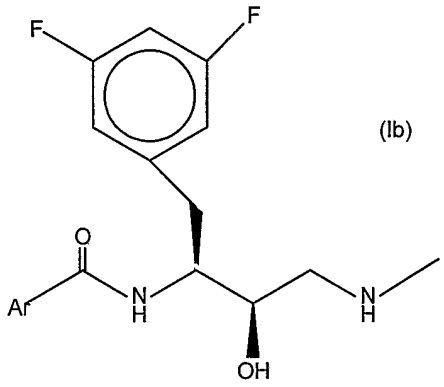
(1S, 2R) 1-Butyl-3-propionyl-1H-indole-6-carboxylic acid [1-(3,5-difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-amide.

In a particular practice the compound of the invention has Formula (Ia), whose constituents are as defined herein



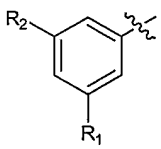
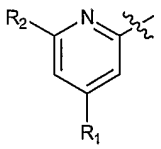
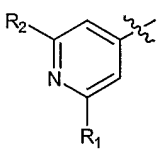
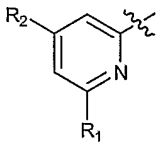
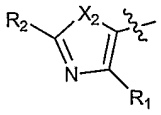
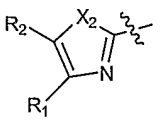
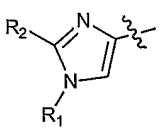
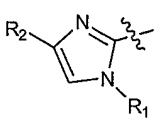
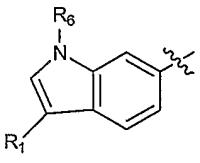
(Ia)

In a particularly preferred practice, the invention is of formula (Ib):

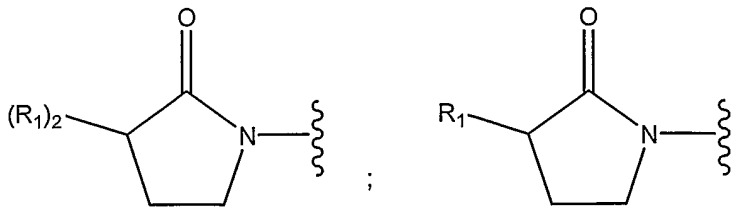


(Ib)

In particularly preferred practices, Ar is

In more particularly preferred practices Ar is:



In another embodiment, the invention is to a pharmaceutical composition comprising the compound of Formula (I) and a pharmaceutically acceptable carrier, such carriers as known in the art.

In another embodiment, the invention is to a method of treating a CNS condition comprising administering to a patient in need of such treatment a therapeutically effective amount of the compound of Formula (I). Preferably, said CNS condition is a neurodegenerative condition, such as Alzheimer's Disease.

In another embodiment, the invention is to a method of treating a condition in which inhibition of beta-secretase is indicated comprising administering to a patient in need of such treatment a beta-secretase inhibiting amount of the compound of Formula (I).

CNS conditions subject of the invention are those known in the art; and include without limitation:

Head trauma, spinal cord injury, inflammatory diseases of the central nervous system, neurodegenerative disorders (acute and chronic), Alzheimer's Disease, demyelinating diseases of the nervous system, Huntington's disease, Parkinson's Disease, peripheral neuropathy, pin, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, migraine, depression anorexia, Restless Leg Syndrome, dyskinesia associated with dopamine agonist therapy.

Anxiety or psychotic disorders such as: schizophrenia, for example of the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizophreniform disorder; schizoaffective disorder, for example of the delusional type or the depressive type; delusional disorder; substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type. Examples of anxiety disorders include, but are not limited to, panic disorder; agoraphobia; a specific phobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; acute stress disorder; and generalized anxiety disorder.

Movement disorders involving: Huntington's disease and dyskinesia associated with dopamine agonist therapy; Parkinson's disease and restless leg syndrome.

Chemical dependencies: for example alcohol, amphetamine, cocaine, opiate, nicotine addiction.

Disorders comprising, as a symptom thereof, a deficiency in cognition: for example, a subnormal functioning in one or more cognitive aspects such as memory, intellect, or learning and logic ability, in a particular individual relative to other individuals within the same general age population. Also, any reduction in any particular individual's functioning in one or more cognitive aspects, for example as occurs in age-related cognitive decline. Examples of disorders that comprise as a symptom a deficiency in cognition that can be treated according to the present invention are dementia, for example Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; and age-related cognitive decline.

Mood disorders or mood episodes such as: major depressive episode of the mild, moderate or severe type, a manic or mixed mood episode, a hypomanic mood episode; a depressive episode with atypical features; a depressive episode with melancholic features; a depressive episode with catatonic features; a mood episode with postpartum onset; post-stroke depression; major depressive disorder; dysthymic disorder; minor depressive disorder; premenstrual dysphoric disorder; post-psychotic depressive disorder of schizophrenia; a major depressive disorder superimposed on a psychotic disorder such as delusional disorder or schizophrenia; a bipolar disorder, for example bipolar I disorder, bipolar II disorder, and cyclothymic disorder.

In one embodiment, disorders subject to treatment by the invention include those selected from: hypertension, depression (e.g. depression in cancer patients, depression in Parkinson's patients, postmyocardial infarction depression, subsyndromal symptomatic depression, depression in infertile women, pediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, and post partum depression), generalized anxiety disorder, phobias (e.g. agoraphobia, social phobia and simple phobias), posttraumatic stress syndrome, avoidant personality disorder, premature ejaculation, eating disorders (e.g. anorexia nervosa and bulimia nervosa), obesity, chemical dependencies (e.g. addictions to alcohol, cocaine, heroin, phenobarbital, nicotine and benzodiazepines), cluster headache, migraine, pain, Alzheimer's disease, obsessive-compulsive disorder, panic disorder, memory disorders (e.g. dementia, amnestic disorders, and age-related cognitive decline (ARCD), Parkinson's diseases (e.g. dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias), endocrine disorders (e.g. hyperprolactinaemia), vasospasm (particularly in the cerebral vasculature), cerebellar ataxia, gastrointestinal tract disorders (involving changes in motility and secretion), negative

symptoms of schizophrenia, schizoaffective disorder, obsessive compulsive disorder, mania, premenstrual syndrome, fibromyalgia syndrome, stress incontinence, Tourette's syndrome, trichotillomania, kleptomania, male impotence, cancer (e.g. small cell lung carcinoma), chronic paroxysmal hemicrania and headache (associated with vascular disorders).

Preferably, the CNS condition is a neurodegenerative condition. Representative neurodegenerative conditions preferably include without limitation those in which plaques comprised of beta-amyloid in whole or in part are associated, and/or in which the inhibition of beta-secretase is indicated. By way of example only, such conditions include Alzheimer's disease, Parkinson's Disease, Multiple Sclerosis, inclusion body myositis. In other embodiments, the invention pertains to treating a neurodegenerative condition comprising administering to a patient in need of such treatment a therapeutically effective amount of the instant compound; and to treating a condition in which the inhibition of beta-secretase is indicated by administering an inhibitory effective amount of said compound.

The compound of the invention can also be used in combination with other drugs, e.g. those conventionally used to treat any of the CNS conditions herein described. For example, the compound of the invention can be used in combination with any or all of the following to treat CNS conditions: neurodegenerative diseases such as Alzheimer's Disease: acetylcholinesterase inhibitors, such as donepezil, memantine, ACAT inhibitors, COX_2 inhibitors, propentofyline, metryfonate, Vitamin E, Folic acid etc.; Parkinson's Disease: deprenyl, cabergoline, samanirole, L-dopa, mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, nicotime agonists, dopamine agonists and inhibitors of nitric oxide synthase (NOS), antidepressants such as selective serotonin reuptake inhibitors (SSRIs, sertraline), .

Administration is by means known in the art. The compound can thus be administered alone or in combination with pharmaceutically acceptable carriers or other therapeutic agents, e.g. other neurodegenerative active agents, psychotropics etc. Dosage forms include without restriction: tablets, powders, liquid preparations, injectable solutions and the like.

The compound of the invention may be administered either alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. The pharmaceutical compositions formed thereby can then be readily administered in a variety of dosage forms such as tablets, powders, lozenges, liquid preparations, syrups, injectable solutions and the like. These pharmaceutical compositions can optionally contain additional ingredients such as flavorings, binders, excipients and the like. Thus, the compound of the invention may be formulated for oral, buccal, intranasal, parenteral

(e.g. intravenous, intramuscular or subcutaneous), transdermal (e.g. patch) or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycolate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

The compound of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g. in ampules or in multi-dose containers, with an added preservative. They may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compound of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the compound of the invention is conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges

(made e.g. from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the compound of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above is about 0.1 to about 200 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

Aerosol formulations for treatment of the conditions referred to above (e.g. migraine) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains about 20 mg to about 1000 mg of the compound of the invention. The overall daily dose with an aerosol will be within the range of about 100 mg to about 10 mg. Administration may be several times daily, e.g. 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

In connection with the use of the compound of the invention it is to be noted that it may be administered either alone or in combination with pharmaceutically acceptable carriers by either of the routes previously indicated, and that such administration can be carried out in both single and multiple dosages. More particularly, the compound alone or in combination combination can be administered in a wide variety of different dosage forms, i.e. they may be combined with various pharmaceutically-acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspension, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, such oral pharmaceutical formulations can be suitably sweetened and/or flavored by means of various agents of the type commonly employed for such purposes. In general, the compounds of formula I are present in such dosage forms at concentration levels ranging from about 0.5% to about 90% by weight of the total composition,

A proposed daily dose of the compound of the invention in the combination formulation (a formulation containing the compound of the invention and e.g. an acetlycholinase inhibitor) for oral, parenteral, rectal or buccal administration to the average adult human for the treatment of the conditions referred to above is from about 0.01 mg to about 2000 mg, preferably from about 0.1 mg to about 200 mg of the active ingredient of Formula I per unit dose which could be administered, for example, 1 to 4 times per day.

Aerosol combination formulations for treatment of the conditions referred to above in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains from about 0.01 mg to about 100 mg of the active compound of this invention, preferably from about 1 mg to about 10 mg of such compound. Administration may be several times daily, e.g. 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

In practice, the IC50 of the compound of the invention in a BACE assay as described herein is about 600 nanomolar or less; preferably about 200 nanomolar or less, more preferably about 50 nanomolar or less.

Cell Free BACE1 Inhibition Assay Utilizing a Synthetic APP Substrate

A synthetic APP substrate that can be cleaved by beta-secretase and having N-terminal biotin and made fluorescent by the covalent attachment of Oregon green at the Cys residue is used to assay beta-secretase activity in the presence or absence of the inhibitory compounds. The substrate is Biotin-GLTNIKTEEISEISY^EVEFR-C[oregon green]KK-OH. The enzyme (0.1 nanomolar) and test compounds (0.00002 - 200 micromolar) are incubated in pre-blocked, low affinity, black plates (384 well) at RT for 30 minutes. The reaction is initiated by addition of 150 millimolar substrate to a final volume of 30 microliter per well. The final assay conditions are: 0.00002 - 200 micromolar compound inhibitor; 0.1 molar sodium acetate (pH 4.5); 150 nanomolar substrate; 0.1 nanomolar soluble beta-secretase; 0.001% Tween 20, and 2% DMSO. The assay mixture is incubated for 3 hours at 37 degrees C, and the reaction is terminated by the addition of a saturating concentration of immunopure streptavidin (0.75 micromolar). After incubation with streptavidin at room temperature for 15 minutes, fluorescence polarization is measured, for example, using a PerkinElmer Envision (Ex485 nm/ Em530 nm). The activity of the beta-secretase enzyme is detected by changes in the fluorescence polarization that occur when the substrate is cleaved by the enzyme. Incubation in the presence of compound inhibitor demonstrates specific inhibition of beta-secretase enzymatic cleavage of its synthetic APP substrate.

In preferred practices, the N-methyl compound of the invention exhibits unexpectedly improved liver microsome stability.

The ensuing methods and examples illustrate, without limitation, representative ways to make the compound of the invention.

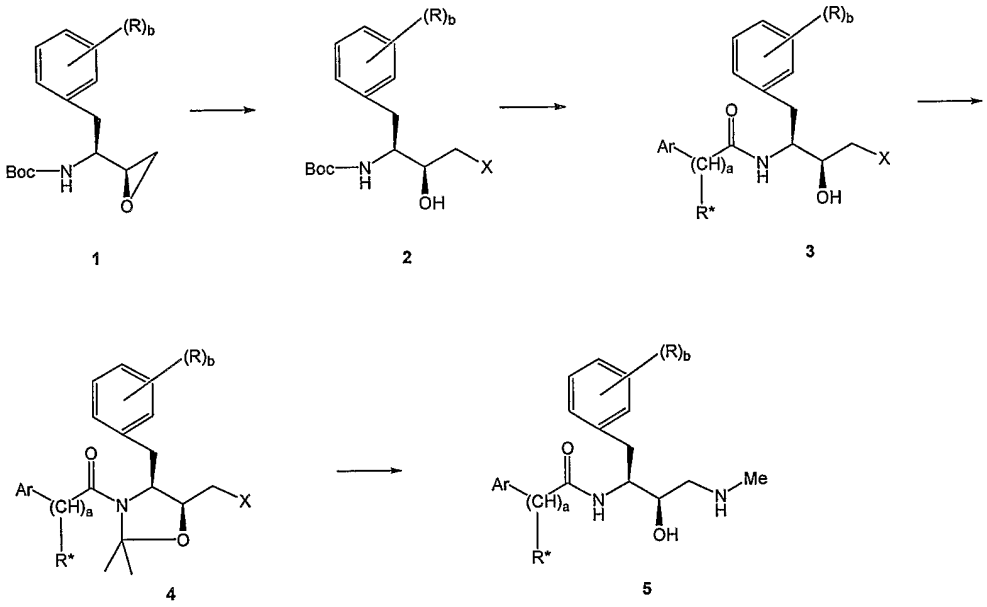
METHODS OF PREPARATION

As used herein: Ac = acetyl; Boc = t-butoxycarbonyl; EDCI = 1,(3, dimethylaminopropyl)-3-ethyl-carbiimide hydrochloride; CBZ = benzyloxycarbonyl; THF = tetrahydrofuran; DPPP = 1,3-bis(diphenylphosphanyl)propane; dba = dibenzylideneacetone; Et = ethyl; Me = methyl; n-Bu = n-butyl; n-Hex = n-hexyl.

The compounds of this invention, **5**, may be prepared by the sequence of reactions shown in Scheme 1. Epoxide **1** is reacted with an alkali metal-halide salt, preferably NaI, in the presence of a buffer, preferably HOAc/NaOAc, to give halohydrin **2**. The reaction is performed between a temperature range of 0°C to 60°C, preferably 25°C. The Boc-protecting group is removed by treatment with a strong acid, preferably aqueous HF, in a solvent such as acetonitrile, and the resulting amine salt is acylated with $Ar[CHR^{**}]_aCO_2H$ using a coupling reagent well-known to one skilled in the art, preferably EDCI, in the presence of base,

preferably a tertiary amine such as triethylamine, to give amide **3**. Alternatively, $Ar[CHR^{**}]_aCO_2H$ may be converted to the corresponding acid chloride using thionyl or oxalyl chloride and likewise reacted with the amine salt in the presence of a base. The reaction is performed between a temperature range of 0°C to 60°C, preferably 25°C. Hydroxy amide **3** is protected as the dimethyl acetonide derivative **4** using 2-methoxypropene in the presence of an acid such as a sulfonic acid, preferably p-toluenesulfonic acid. The reaction is performed between a temperature range of 0°C to 60°C, preferably 25°C. The halide group of **4** is displaced by methylamine by heating with an excess of the amine in an inert solvent, preferably THF. The reaction is performed between a temperature range of 25°C to 150°C, preferably 55°C when the halide is iodide. The product is subjected to hydrolysis by heating in a mixture of a strong aqueous acid, preferably HCl, and an alcoholic solvent, preferably methanol, between a temperature range of 35°C to 100°C, preferably 55°C, to give compounds **5**.

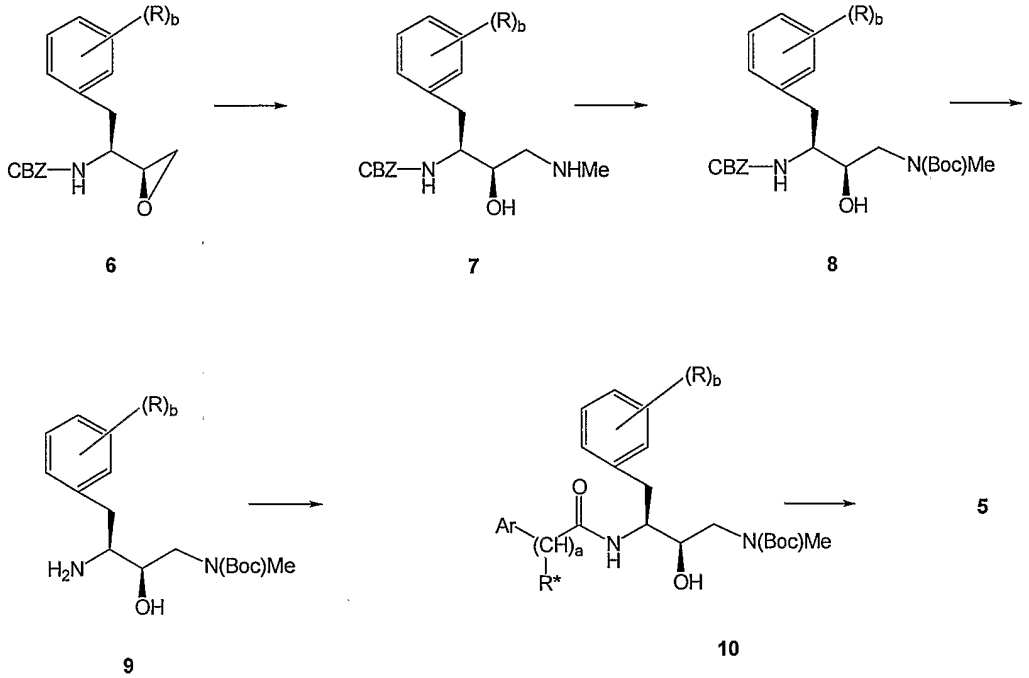
SCHEME 1



The compounds of this invention, **5**, may also be prepared by the sequence of reactions shown in Scheme 2. Epoxide **6** is reacted with methylamine in an alcoholic solvent, preferably isopropanol, between a temperature range of 0°C to 50°C, preferably 25°C, to give amino alcohol **7**. The NH group is protected as a t-butoxycarbonyl derivative by treatment with di-t-butyl-dicarbonate in the presence of a tertiary amine, preferably triethylaime, to give **8**. The reaction is performed between a temperature range of 0°C to 50°C, preferably 25°C. The CBZ group of **8** is removed to give amine **9** by catalytic hydrogenolysis in an inert solvent, preferably methanol, at a hydrogen pressure of 1 to 5 atmospheres and a temperature range of 0°C to 50°C, preferably 25°C. The preferred catalyst is palladium but others well-known to

one skilled in the art may be substituted. Amine **9** is acylated with $Ar[CHR^*]_aCO_2H$ using a coupling reagent well-known to one skilled in the art, preferably EDCI, in the presence of a base, preferably a tertiary amine such as triethylamine, to give amide **10**. Alternatively, $Ar[CHR^*]_aCO_2H$ may be converted to the corresponding acid chloride using thionyl or oxalyl chloride and likewise reacted with amine **9** in the presence of a base. The reaction is performed between a temperature range of 0°C to 60°C, preferably 25°C. The Boc-protecting group of **10** is removed by treatment with a strong acid, preferably aqueous HF or HCl, in solvents such as acetonitrile or dioxane, respectively, to give **5**.

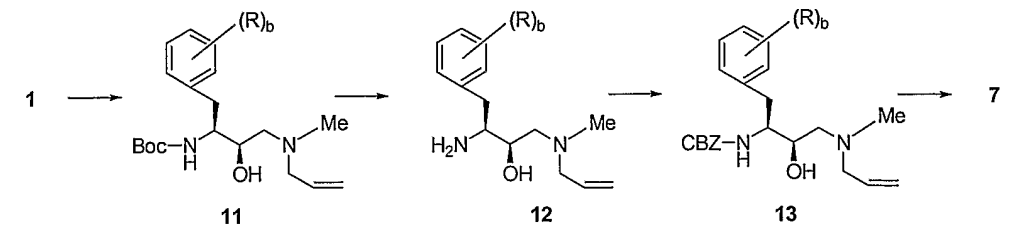
SCHEME 2



6 **7** **8** **9** **10** **5**

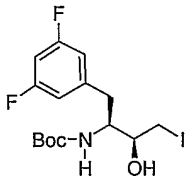
Intermediate **7** may also be prepared by the sequence of reactions shown in Scheme 3. Epoxide **1** is reacted with allylmethyl amine in an alcoholic solvent, preferably isopropanol, between a temperature range of 0°C to 50°C, preferably 25°C, to give amino alcohol **11**. The Boc-protecting group of **11** is removed by treatment with a strong acid, preferably aqueous HF or HCl, in solvents such as acetonitrile or dioxane, respectively, to give **12**. Protection of the NH_2 group of **12** is accomplished by treatment with benzyl chloroformate in the presence of a base, preferably pyridine or aqueous $NaHCO_3$ solution, and in an inert solvent, preferably CH_2Cl_2, THF or dioxane, between a temperature range of -15°C to 50°C, preferably 0°C, to give **13**. The allyl group of **13** is removed by treatment with N,N-dimethylbarbituric acid in the presence of a transition metal catalyst, preferably $Pd_2(dba)_3$/DPPP, in an inert solvent, preferably THF, between a temperature range of 25°C to 100°C, preferably 60°C to give **7**.

SCHEME 3



The following examples illustrate the preparation of specific compounds within the scope of the invention; these are representative only and are not to be construed as limiting the invention in any way.

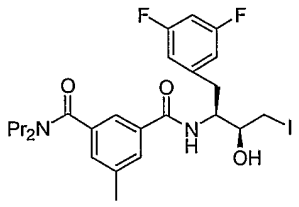
Preparation 1



(1S,2S) [1-(3,5-Difluoro-benzyl)-2-hydroxy-3-iodo-propyl]-carbamic acid tert-butyl ester

A mixture of (1R, 2S) [2-(3,5-difluoro-phenyl)-1-oxiranyl-ethyl]-carbamic acid tert-butyl ester (100 mg, 0.334 mmol), NaI (65 mg, 0.434 mmol), NaOAc (30.1 mg, 0.367 mmol), acetic acid (21 µL), and EtOAc (4 mL) was stirred overnight at room temperature. The mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated to give the title compound as a solid which was used directly in the next step without further purification; ESI LCMS: m/e 427.8 $[M+H]^+$.

Preparation 2



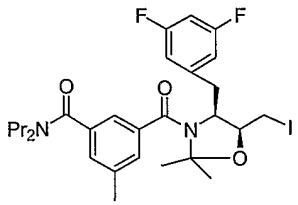
(1S, 2S) N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-iodo-propyl]-5-methyl-N',N'-dipropyl-isophthalamide

Step A: A mixture of the compound of Preparation 1 (96.9 mg, 0.227 mmol) and a solution of 1% aqueous (48%) HF in CH_3CN (5 mL) was stirred and heated to 40°C for 3 h. The mixture was evaporated using toluene as an azeotrope to remove excess water and dried under vacuum to give a solid.

Step B: To a solution of 3-[(propylamino)carbonyl]-5-methyl-benzoic acid (60 mg, 0.227 mmol) in CH_2Cl_2 (2 mL) was added $SOCl_2$ (2 mL) and the mixture was stirred for 3 h at room temperature. The mixture was evaporated, co-evaporated with toluene, and dried under vacuum to give an oil.

Step C: The products of Step A and Step B were combined, dissolved in CH_2Cl_2 (2 mL), and treated with triethylamine (0.095 mL, 0.681 mmol). After stirring overnight at room temperature, the mixture was diluted with water and extracted twice with EtOAc. The combined extracts were washed with sat'd. aqueous $NaHCO_3$ solution, brine, dried (Na_2SO_4), and evaporated to give 120 mg of a red oil. Purification by flash chromatography using 1:1 hexane:EtOAc as eluant afforded 48.9 mg of the title compound as a solid; ESI LCMS: 572.9 $[M+H]^+$.

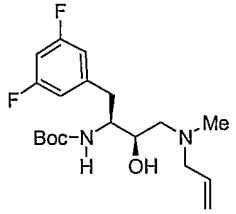
Preparation 3



(4S, 5S) 3-[4-(3,5-Difluoro-benzyl)-5-iodomethyl-2,2-dimethyl-oxazolidine-3-carbonyl]-5-methyl-N,N-dipropyl-benzamide

To a solution of the compound of Preparation 2 (45 mg, 0.079 mmol) in CH_2Cl_2 (3 mL) was added 2-methoxypropene (0.076 mL, 0.786 mmol) followed by anhydrous p-toluenesulphonic acid (5 mg). The mixture was stirred for 4 h at room temperature, treated with additional 2-methoxypropene (0.100 mL) and anhydrous p-toluenesulphonic acid (5 mg), stirred for an additional 3 h, and quenched by the addition of sat'd. aqueous $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined extracts were washed with brine (1 x 20 mL), dried (Na_2SO_4), and evaporated to give 258 mg of a brown oil. Purification by flash chromatography using 2:1 hexane:EtOAc as eluant afforded 38.6 mg of the title compound as a solid; ESI LCMS: 612.9 $[M+H]^+$.

Preparation 4

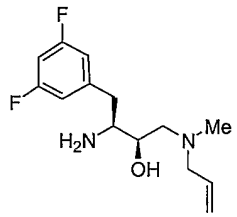


(1S, 2R) [3-(Allyl-methyl-amino)-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-carbamic acid tert-butyl ester

To a solution of a solution of (1R, 2S) [2-(3,5-difluoro-phenyl)-1-oxiranyl-ethyl]-carbamic acid tert-butyl ester (237 mg, 0.792 mmol) in 10 mL of isopropanol was added N,N-allylmethylamine (0.376 mL, 0.281 g, 3.94 mmol). The mixture was heated to 45°C for 16 h and then evaporated to afford 286 mg of the title compound as a solid; ESI LCMS: 371.0 $[M+H]^+$.

Preparation 5

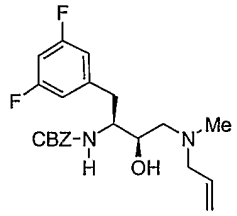
(1S, 2R) 1-(Allyl-methyl-amino)-3-amino-4-(3,5-difluoro-phenyl)-butan-2-ol



The compound of Preparation 4 (90 mg) was stirred in 2 mL of a 4 N solution of HCl in dioxane for 2 h at room temperature. The mixture was evaporated and partitioned between 15 mL of EtOAc and 15 mL of satd. $NaHCO_3$ solution. The EtOAc layer was separated, combined with a 15 mL backwash of the aqueous later, dried (Na_2SO_4), and evaporated to give the title compound (60 mg) as a yellow oil; ESI LCMS: 271.0 $[M+H]^+$.

Preparation 6

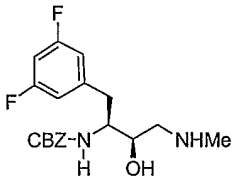
(1S, 2R) [3-(Allyl-methyl-amino)-1-(3,5-difluoro-benzyl)-2-hydroxy-propyl]-carbamic acid benzyl ester



To a solution of the compound of Preparation 5 (2.057 g, 7.61 mmol) in CH_2Cl_2 (40 mL) was added pyridine (1.85 mL, 1.81 g, 22.8 mmol). The mixture was chilled to 0°C, treated with benzyl chloroformate (2.17 mL, 2.59 mmol), and stirred for 2 hr at 0°C before being evaporated. The residue was stirred in a mixture of 1:1 1 N NaOH/MeOH for 30 min, diluted with water and extracted with EtOAc. The EtOAc extracts were washed successively with water and brine, dried (Na_2SO_4), and evaporated to give 3.35 g of the crude product. This material was purified by flash chromatography using 3% MeOH/$CHCl_3$ as eluant to give the title compound (1.69 g) as a solid; ; ESI LCMS: 405.0 $[M+H]^+$.

Preparation 7

(1S, 2R) [1-(3,5-Difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-carbamic acid benzyl ester



Method 1

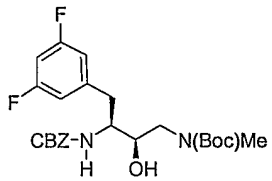
To a mixture of $Pd_2(dba)_3$ (56 mg, 0.061 mmol), DPPP (49.7 mg, 0.121 mmol), and THF (30 mL) was added the compound of Preparation 6 (650 mg 1.607 mmol) followed by N,N-dimethylbarbituric acid (1.239 g, 8. 035 mmol). The mixture was heated to 60°C for 4 h as a color change from greenish brown to brownish orange was observed. The mixture was evaporated and the residue was partitioned between 1 N HCl (40 mL) and ether (40 mL). The aqueous layer was separated and basified, and the precipitate was filtered and dried under high vaccum to give the title compound (418 mg) as a solid; ESI LCMS: 365.0 $[M+H]^+$.

An additional 82 mg of the title compound was obtained by extraction of the filtrate with EtOAc, drying (Na_2SO_4), and evaporation.

Method 2

To a solution of (1R, 2S) [2-(3,5-difluoro-phenyl)-1-oxiranyl-ethyl]-carbamic acid benzyl ester (150 mg, 0.450 mmol) of isopropanol (10 mL) was added a solution of 2 M methylamine in THF (4.5 mL, 9.0 mmol), and the mixture was stirred overnight at room temperature. The solvent was evaporated to give the title compound as a white solid which was used directly in the next step without further purification; ESI LCMS: 365.0 $[M+H]^+$.

Preparation 8

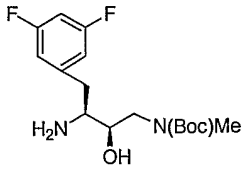


(2R, 3S) [3-Benzyloxycarbonylamino-4-(3,5-difluoro-phenyl)-2-hydroxy-butyl]-methyl-carbamic acid tert-butyl ester

A solution of the compound of Preparation 7 (0.45 mmol) in CH_2Cl_2 (5 mL) was treated with di-t-butyl-dicarbonate (196 mg, 0.900 mmol) followed by triethylamine (0.125 mL, 0.900 mmol). The mixture was stirred overnight at room temperature, evaporated, diluted with EtOAc (30 mL), and washed with saturated aqueous $NaHCO_3$ solution (25 mL). The aqueous layer was separated and extracted with EtOAc (25 ml), and the combined organic extracts were combined, dried (Na_2SO_4), and evaporated to give a yellow oil. Purification by

flash chromatography eluting with 2:1 hexane:EtOAc afforded the title compound (95 mg) as a solid; ESI LCMS: 464.9 $[M+H]^+$.

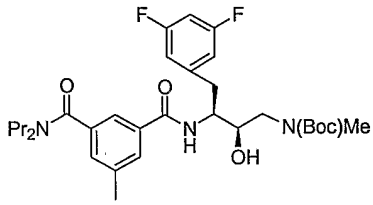
Preparation 9



(2R, 3S) [3-Amino-4-(3,5-difluoro-phenyl)-2-hydroxy-butyl]-methyl-carbamic acid tert-butyl ester

A mixture of the compound of Preparation 8 (90 mg, 0.194 mmol), 20% $Pd(OH)_2$ (75 mg) on carbon, and methanol (5 mL) was hydrogenated at 40 psi overnight. The mixture was filtered and evaporated to give the title compound (61.8 mg) as an oil; ESI LCMS: 331.0 $[M+H]^+$.

Preparation 10

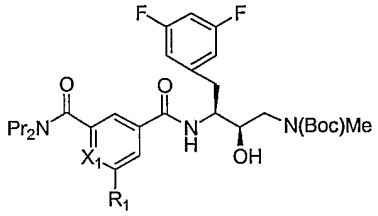


(2R, 3S) [4-(3,5-Difluoro-phenyl)-3-(3-dipropylcarbamoyl-5-methyl-benzoylamino)-2-hydroxy-butyl]-methyl-carbamic acid tert-butyl ester

To a solution of the compound of Preparation 9 (90.3 mg, 0.273 mmol) in CH_2Cl_2 (3 mL) was added 3-[(propylamino)carbonyl]-5-methyl-benzoic acid (108 mg, 0.410 mg) followed by EDCI (79 mg, 0.410 mmol). The mixture was stirred overnight at room temperature, diluted with 0.5 N HCl solution (20 mL), and extracted with EtOAc (1 x 25 ml). The EtOAc extract was washed with sat'd. aqueous $NaHCO_3$ solution (25 mL), dried (Na_2SO_4), and evaporated to give of a foam (151.5 mg). A methanolic solution (2 mL) of the foam was treated with 1 N NaOH (2 mL) and stirring was continued for 1 h at room temperature. The mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 15 mL). The combined extracts were washed with brine (1 x 20 mL), dried (Na_2SO_4), and evaporated to give the title compound (119.2 mg); ESI LCMS: 576.0 $[M+H]^+$.

Preparations 11-14

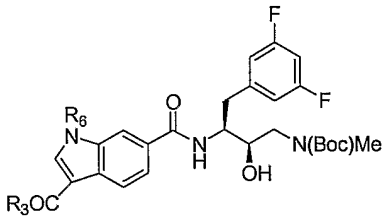
The compounds of Preparations 11-14 were prepared according to the procedure of Preparation 10 substituting the appropriate isophthalamic acid derivative for 5-bromo-N,N-dipropyl-isophthalamic acid.



Preparation	X_1	R_1	ESI LCMS
11	CH	Br	642.1 $[M+H]^+$
12	CH	2-oxazolyl	629.1 $[M+H]^+$
13	N	Me	577.0 $[M+H]^+$
14	CH	ethynyl	586.0 $[M+H]^+$

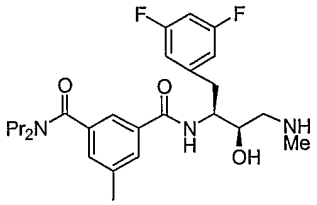
Preparations 15-17

The compounds of Preparations 15-17 were prepared according to the procedure of Preparation 10 substituting the appropriate indolecarboxylic acid for 5-bromo-N,N-dipropyl-isophthalamic acid.



Preparation	R_6	R_3	ESI LCMS
15	n-Bu	Me	572.0 $[M+H]^+$
16	n-Hex	Me	600.0 $[M+H]^+$
17	n-Bu	Et	586.0 $[M+H]^+$

Example 1



(1S, 2R) N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-5-methyl-N',N'-dipropyl-isophthalamide

Method 1

Step A: A mixture of the compound of Preparation 3 (50 mg, 0.08 mmol) and 2 M methylamine solution in THF (3 mL) was heated overnight at 50°C. The solvent was evaporated and replenished with 2 M methylamine solution in THF, and heating at 50°C was continued for 3 days. The solvent was evaporated and the residue was partitioned between sat'd. aqueous $NaHCO_3$ solution (20 mL) and EtOAc (20 ml). The separated aqueous layer was extracted with EtOAc (20 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated to give a brown oil (79 mg). Purification by flash chromatography eluting sequentially with $CHCl_3$, 3% MeOH/$CHCl_3$ and 6% MeOH/$CHCl_3$ afforded the methylamine displacement product as a brown oil (29.6 mg).

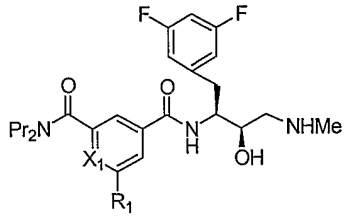
Step B: The above oil (25 mg) was dissolved in MeOH (1 mL), treated with 2M HCl solution (2 mL), and heated overnight at 50°C. The cooled mixture was diluted with 1 M HCl solution (10 ml) and washed with ether (5 ml). The acidic layer was basified with 1 N NaOH solution and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and evaporated, and the solid residue was triturated in hexane to afford of the title compound as a solid (17.6 mg); ESI LCMS: 476 $[M+H]^+$.

Method 2

The compound of Preparation 10 (25 mg) was diluted with 4 N HCl in dioxane solution (2 mL) and the mixture was stirred at room temperature for 1.5 h. The mixture was evaporated to give 24 mg of the title compound as the hydrochloride salt.

Examples 2-5

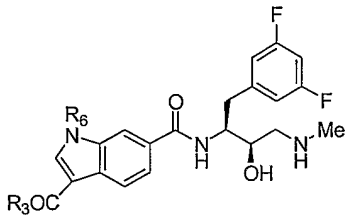
The compounds of Examples 2-5 were prepared according to the procedure of Example 1, Method 2 substituting the compounds of Preparations 11-14, respectively, for the compound of Preparation 10.



Example	X_1	R_1	ESI LCMS
2	CH	Br	541.8 $[M+H]^+$
3	CH	2-oxazolyl	529.0 $[M+H]^+$
4	N	Me	477.0 $[M+H]^+$
5	CH	ethynyl	486.0 $[M+H]^+$

Examples 6-8

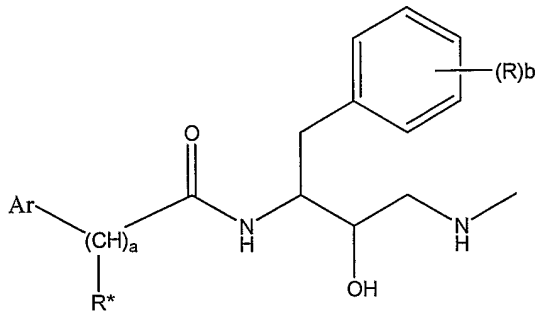
The compounds of Examples 6-8 were prepared according to the procedure of Example 3 substituting the compounds of Preparations 15-17, respectively, for the compound of Preparation 11.



Example	R_6	R_3	ESI LCMS
6	n-Bu	Me	472.0 $[M+H]^+$
7	n-Hex	Me	500.0 $[M+H]^+$
8	n-Bu	Et	486.0 $[M+H]^+$

CLAIMS

1. A compound of Formula I:



(I)

wherein:

a = 0, 1, 2, or 3;

b = 0, 1, 2, or 3;

each R is independently halogen, OH, CN, SH, NH_2, C_{1-6}alkyl, C_{1-6}alkoxy, $S(C_{1-6}alkyl)$, $NH(C_{1-6}alkyl)$, $N(C_{1-6}alkyl)(C_{1-6}alkyl)$, $NHC(=O)O(C_{1-6}alkyl)$, $NHSO_2(C_{1-6}alkyl)$, $C(=O)NH(C_{1-6}alkyl)$, $C(=O)N(C_{1-6}alkyl)(C_{1-6}alkyl)$, C_{6-10}aryl, (5 to 12 member)heteroaryl, wherein each alkyl group aforesaid may be independently optionally substituted with up to three F, OH or C_{1-3}alkoxy groups;

R* is H, C_{1-6}alkyl, $-(CH_2)_{0-5}(C_6-C_{10}aryl)$, $-(CH_2)_{0-5}$(5 to 12 member)heteroaryl;and

Ar is selected from (A), (B), (C), (D), (E) or (F):

(A) C_{6-10}aryl, (5 to 12 member)heteroaryl, (C_{6-10}aryl)-W-(C_{6-10}aryl), (C_{6-10}aryl)-W-(5 to 12 member)heteroaryl, (C_{6-10}aryl)-W-(5 to 7 member)heterocycloalkyl, (5 to 12 member)heteroaryl-W-(C_{6-10}aryl), (5 to 12 member)heteroaryl-W-(5 to 12 member)heteroaryl, (5 to 12 member)heteroaryl-W-(5 to 7 member)heterocycloalkyl, (5 to 7 member)heterocycloalkyl-W-(C_{6-10}aryl), (5 to 7 member)heterocycloalkyl-W-(5 to 12 member)heteroaryl, (5 to 7 member)heterocycloalkyl-W-(5 to 7 member)heterocycloalkyl, wherein W is selected from $-(CH_2)_{0-4}$-, -O-, -C(=O)-, $-S(=O)_{0-2}$-, $-N(R_{N-5})$-;

(B) $-C(=O)(C_{1-10}alkyl)$ where alkyl is optionally independently substituted with up to three substitutents ("SB") selected from: OH; C_{1-6}alkoxy; C_{1-6}thioalkoxy; $C(=O)OR_{N-8}$; $-C(=O)NR_{N-2}R_{N-3}$; $-C(=O)R_{N-4}$; $-SO_2(C_{1-8}alkyl)$; $-SO_2NR_{N-2}R_{N-3}$; $-NHC(=O)(C_{1-6}alkyl)$; $-NHC(=O)OR_{N-8}$; $-NR_{N-2}R_{N-3}$; $-R_{N-4}$; $-OC(=O)(C_{1-6}alkyl)$; $-O-C(=O)NR_{N-8}R_{N-8}$ where each R_{N-8} is the same or different; $-O(C_{1-6}alkyl)C(=O)OH$; -O-(C_{1-6}alkyl optionally substituted with up to three halogens); $-NHSO_2(C_{1-6}$ alkyl); F; Cl;

(C) $-C(=O)(C_{1-6}alkyl)O(C_{1-6}alkyl)$ where each alkyl is optionally independently substituted with up to three substituents SB as defined above in (A);

(D) –C(=O)(C_{1-6}alkyl)S(C_{1-6}alkyl) where each alkyl is optionally independently substituted with up to three of substituents SB as defined above in (A);

(E) –C(=O)CH(-$(CH_2)_{0-2}$-O-R_{N-10})-$(CH_2)_{0-2}$–(C_{6-10}aryl), or –C(=O)CH(-$CH_2)_{6-2}$-O-R_{N-10}-$(CH_2)_{6-2}$-(9 to 12 member)heteroary or

(F) –C(=O)(C_{3-8}cycloalkyl) where said cycloalkyl is optionally independently substituted with up to two substituents selected from: -$(CH_2)_{0-4}$OH; -$(CH_2)_{0-4}$$C_{1-6}$alkoxy; -$(CH_2)_{0-4}$$C_{1-6}$thioalkoxy; -$(CH_2)_{0-4}$C(=O)-O-$R_{N-8}$; -$(CH_2)_{0-4}$C(=O)-$NR_{N-2}R_{N-3}$; -$(CH_2)_{0-4}$C(=O)-$R_{N-4}$; -$(CH_2)_{0-4}$$SO_2$-($C_{1-6}$alkyl); -$(CH_2)_{0-4}$$SO_2$-$NR_{N-2}R_{N-3}$; -$(CH_2)_{0-4}$NH-C(=O)-($C_{1-6}$alkyl); -NH-C(=O)-O-$R_{N-8}$; -$(CH_2)_{0-4}$$NR_{N-2}R_{N-3}$; -$(CH_2)_{0-4}$$R_{N-4}$; -O-C(=O)-($C_{1-6}$alkyl); -O-C(=O)-$NR_{N-8}R_{N-8}$ where each R_{N-8} is the same or different; -O-(C_{1-6}alkyl)-C(=O)OH; -O-(C_{1-6}alkyl, wherein said alkyl is optionally substituted with up to three halogens); -$NHSO_2$(C_{1-6}alkyl); F; Cl;

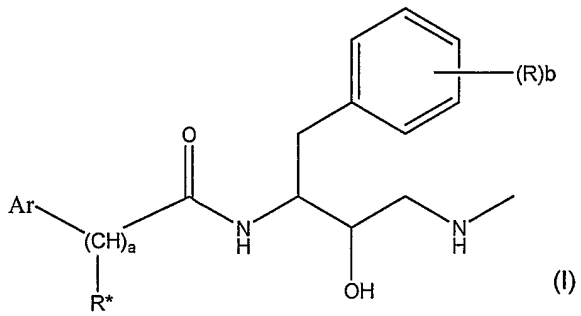
R_{N-2} and R_{N-3} are each independently selected from the group (a) H; (b) C_{1-6}alkyl optionally substituted with one substituent selected from: OH or NH_2; (c) C_{1-6}alkyl optionally substituted with up to three halogen; (d) C_{3-7}cycloalkyl; (e) -(C_{1-2}alkyl)(C_{3-7}cycloalkyl); (f) -(C_{1-6}alkyl)O(C_{1-3}alkyl); (g) C_{2-6}alkenyl with one or two double bonds; (h) C_{2-6}alkynyl with one or two triple bonds; (i) C_{1-6}alkyl chain with one double bond and one triple bond; (j) C_{6-10}aryl; or (k) (5 to 12 member)heteroaryl;

R_{N-4} is 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_{1-6}alkyl;

R_{N-5} is (a) C_{1-6}alkyl, (b) -$(CH_2)_{0-2}$(C_{6-10}aryl), (c) C_{2-6}alkenyl containing one or two double bonds, (d) C_{2-6}alkynyl containing one or two triple bonds, (e) C_{3-7}cycloalkyl, (f) -$(CH_2)_{0-2}$(5 to 12 member)heteroaryl; and

R_{N-8} is H, C_{1-6}alkyl, or phenyl.

2. A compound of Formula I:



(I)

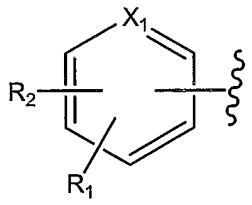
wherein:

a = 0, 1, 2, or 3;

b = 0, 1, 2, or 3;

each R is independently halogen, OH, C_{1-6}alkyl, CN, C_{1-6}alkoxy, C_{6-10}aryl, (5 to 12 member)heteroaryl, wherein said alkyl and alkoxy may each optionally independently be substituted with up to three halogen or OH groups;

R* is H, C_{1-6}alkyl, $-(CH_2)_{0-5}(C_{6-10}$aryl), $-(CH_2)_{0-5}$(5 to 12 member)heteroaryl, wherein said alkyl, aryl or heteroaryl may each optionally independently be substituted with up to three halogen, C_{1-6}alkoxy or OH groups; and Ar is selected from (i), (ii), (iii) or (iv), any of which Ar may be optionally substituted with an F at a ring carbon atom:



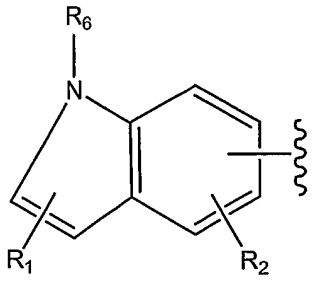
(i)

wherein:

X_1 is CH or N; R_1 is H, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, OH, CN, SH, C_{1-6}alkoxy, $S(C_{1-6})$alkyl, $-NR_3(C=O)_cR_4$, $-NR_3SO_2R_4$, $-(CH_2)_c(C=O)R_5$, $-(CH_2)_c(C=O)OR_5$, $-(S=O)R_5$, $-S(=O)_2R_5$, wherein c = 0 or 1, R_3, R_4 and R_5 are each independently H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl or $NR_3(Y)R_4$ wherein Y is CO or SO_2 and R_3 and R_4 together with the N and the C or S atoms of Y to which they are attached form a (5 to 7 member)heterocycloalkyl, and wherein any of said alkyl, cycloalkyl or heterocycloalkyl may be each be optionally independently substituted with up to three halogen, OH, C_{1-6}alkyl, C_{1-6}alkoxy, or CN groups;

R_2 is independently $-C(=O)R_3$, $-(C=O)_cNR_3R_4$, $-NR_3SO_2R_4$ or $-OR_5$ wherein c = 0 or 1, R_3, R_4, and R_5 are as defined above, or R_2 is $-NR_3SO_2R_4$ wherein R_3 and R_4 together with the N and S atoms to which they are attached form a (5 to 7 member)heterocycloalkyl and wherein any of said alkyl, cycloalkyl or heterocycloalkyl moieties of R_2 may each be optionally independently substituted with up to three halogen, OH, C_{1-6}alkyl, C_{1-6} alkoxy or CN groups;

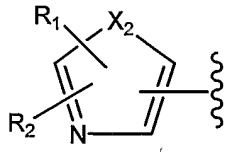
or R_1 and R_2 together with the C atoms to which they are attached form a fused C_{5-10} cycloalkyl, C_{5-10}aryl or (5 to 10 member)heteroaryl group wherein said fused cycloalkyl, aryl or heteroaryl group is optionally independently substituted with up to three groups selected from R_7 and R_8 wherein R_7 is C_{1-6} alkyl said alkyl optionally substituted with up to three F, OH, C_{1-3}alkoxy groups; and R_8 is $-(C=O)_dR_5$ wherein d = 0 or 1, and R_5 is as defined above;



(ii)

wherein:

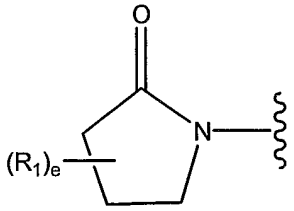
R_1 and R_2 are as defined above in (i); and R_6 is H, C_{1-6} alkyl, $-(CH_2)_{0-5}(C_{6-10}aryl)$, $-(CH_2)_{0-5}$(5 to 12 member) heteraryl, wherein said alkyl maybe optionally independently substituted with up to three halogen, C_{1-6}alkoxy or OH groups;



(iii)

wherein:

X_2 is NH, $N(C_{1-6}alkyl)$, O or S; and R_1 and R_2 are as defined above; or



(iv)

wherein:

e = 1 or 2; and each R_1 is independently as defined above, and wherein when Ar is (iv), a = 1.

3. The compound of Claim 2 wherein

a = 0;

b = 2;

each R is independently a halogen;

Ar is (i); and

R_2 is $-(C=O)_cNR_3R_4$.

4. The compound of Claim 4 wherein

R is F;

c = 1; and

R_3 and R_4 are each independently C_3alkyl;

R_1 is C_{1-6}alkyl, halogen, a (5 to 12 member)heteroaryl, or C_{2-12}alkynyl.

5. The compound of Claim 4 wherein

R_1 is methyl, bromine, oxazolyl, or ethynyl.

6. The compound of Claim 5 comprising

(1S, 2R) N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-5-methyl-N',N'-dipropyl-isophthalamide;

(1S, 2R) 5-Bromo-N-[1-(3,5-difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-N',N'-dipropyl-isophthalamide;

(1S, 2R) N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-5-oxazol-2-yl-N',N'-dipropyl-isophthalamide;

(1S, 2R) 6-Methyl-pyridine-2,4-dicarboxylic acid 4-{[1-(3,5-difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-amide} 2-dipropylamide; and

(1S, 2R) N-[1-(3,5-Difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-5-ethynyl-N',N'-dipropyl-isophthalamide.

7. The compound of Claim 2 wherein

a = 0;

b = 2;

R_2 is $-(C=O)_cNR_3R_4$;

each R is independently a halogen; and

Ar is (ii).

8. The compound of Claim 7 wherein

R is F;

c = 1;

R_1 is H;

R_3 and R_4 are each C_3alkyl; and

R_6 is C_{1-6}alkyl.

9. The compound of Claim 8 wherein

R_6 is C_2alkyl, C_4alkyl or C_6 alkyl.

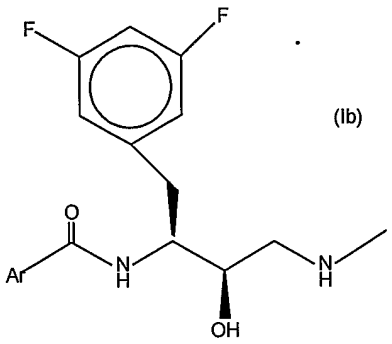
10. The compound of Claim 9 comprising

(1S, 2R) 3-Acetyl-1-butyl-1H-indole-6-carboxylic acid [1-(3,5-difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-amide;

(1S, 2R) 3-Acetyl-1-hexyl-1H-indole-6-carboxylic acid [1-(3,5-difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-amide; and

(1S, 2R) 1-Butyl-3-propionyl-1H-indole-6-carboxylic acid [1-(3,5-difluoro-benzyl)-2-hydroxy-3-methylamino-propyl]-amide.

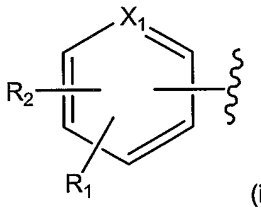
11. A compound of Formula (Ib):



(Ib)

wherein:

Ar is selected from (i), (ii) or (iii):



(i)

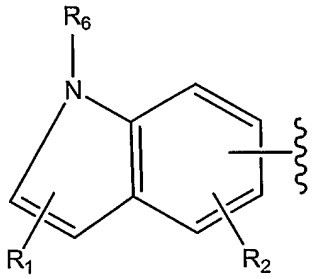
wherein:

X_1 is CH or N; R_1 is H, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, OH, CN, SH, C_{1-6}alkoxy, $S(C_{1-6})$alkyl, $-NR_3(C=O)_cR_4$, $-NR_3SO_2R_4$, $-(CH_2)_c(C=O)R_5$, $-(CH_2)_c(C=O)OR_5$, $-(S=O)R_5$, $-S(=O)_2R_5$, wherein c = 0 or 1, R_3, R_4 and R_5 are each independently H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl or $NR_3SO_2R_4$ wherein R_3 and R_4 together with the N and S atoms to which they are attached form a (5 to 7 member)heterocycloalkyl, and wherein any of said alkyl, cycloalkyl, or heterocycloalkyl may be each be optionally independently substituted with up to three halogen, OH, C_{1-6}alkyl, C_{1-6}alkoxy, or CN groups;

R_2 is independently $-C(=O)R_3$, $-(C=O)_cNR_3R_4$, $-NR_3SO_2R_4$ or $-OR_5$ wherein c = 0 or 1, and R_3, R_4, and R_5 are as defined above, or R_2 is $-NR_3SO_2R_4$ wherein R_3 and R_4 together with the N and S atoms to which they are attached form a (5 to 7 member) heterocycloalkyl and wherein any of said alkyl, cycloalkyl or heterocycloalkyl moieties of R_2 may each be optionally independently substituted with up to three halogen, OH, C_{1-6}alkyl, C_{1-6} alkoxy or CN groups;

or R_1 and R_2 together with the C atoms to which they are attached form a fused C_{3-6}cycloalkyl, C_{5-10}aryl or (5 to 10 member)heteroaryl group wherein said fused cycloalkyl, aryl or heteroaryl group is optionally independently substituted with up to three groups selected from R_7 and R_8 wherein R_7 is C_{1-6} alkyl said alkyl optionally substituted with up to

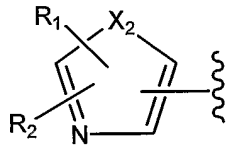
three F, OH, C_{1-3}alkoxy groups; and R_8 is $-(C=O)_dR_5$ wherein d = 0 or 1, and R_5 is as defined above;



(ii)

wherein:

R_1 and R_2 are as defined above in (i); and R_6 is H, C_{1-6} alkyl, $-(CH_2)_{0-5}(C_{6-10}$aryl), $-(CH_2)_{0-5}$(5 to 12 member) heteraryl, wherein said alkyl maybe optionally independently substituted with up to three halogen, C_{1-6}alkoxy or OH groups;



(iii)

wherein:

X_2 is NH, $N(C_{1-6}$alkyl), O or S; and R_1 and R_2 are as defined above.

12. A pharmaceutical composition comprising the compound of Claim 1, 2 or 11 and a pharmaceutically acceptable carrier.

13. A method of treating a CNS condition comprising administering to a patient in need of such treatment a therapeutically effective amount of the compound of Claim 1.

14. The method of Claim 13 wherein said CNS condition is a neurodegenerative condition.

15. The method of Claim 14 wherein said neurodegenerative condition is Alzheimer's Disease.

16. A method of treating a condition in which inhibition of beta-secretase is indicated comprising administering to a patient in need of such treatment a beta-secretase inhibiting amount of the compound of Claim 1, 2 or 11.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/002877

A. CLASSIFICATION OF SUBJECT MATTER
C07C233/37 C07C233/39 C07C233/40 C07C233/73 A61K31/165
A61K31/166

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/006423 A (ELAN PHARMACEUTICALS, INC; PHARMACIA & UPJOHN COMPANY; GAILUNAS, ANDRE) 23 January 2003 (2003-01-23) page 4, compound of general formula (I); page 6, line 3; page 11, lines 9 and 19; page 12, line 15; page 81, line 21 - page 82, line 8; claims	1-12
A	WO 2004/050619 A (GLAXO GROUP LIMITED; DEMONT, EMMANUEL, H; FALLER, ANDREW; MACPHERSON,) 17 June 2004 (2004-06-17) page 193, lines 29-40; claims	1-12
A	WO 02/02505 A (ELAN PHARMACEUTICALS, INC) 10 January 2002 (2002-01-10) page 5, compound of general formula (X); page 94, lines 18-22; page 95, line 19; claims	1-12

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 February 2006	15/02/2006

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/002877

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

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

Although claims 13-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

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

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

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

Remark on Protest

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2005/002877

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03006423 A	23-01-2003	BR 0211119 A	13-12-2005
		CA 2453503 A1	23-01-2003
		EP 1409450 A1	21-04-2004
		HR 20040069 A2	28-02-2005
		JP 2005504737 T	17-02-2005
WO 2004050619 A	17-06-2004	AU 2003292198 A1	23-06-2004
		BR 0317020 A	25-10-2005
		CA 2508325 A1	17-06-2004
		EP 1567488 A1	31-08-2005
WO 0202505 A	10-01-2002	AT 302751 T	15-09-2005
		AT 314343 T	15-01-2006
		AU 7168601 A	14-01-2002
		AU 7309401 A	14-01-2002
		AU 7311301 A	14-01-2002
		BR 0111980 A	06-05-2003
		CA 2410680 A1	10-01-2002
		CA 2410972 A1	10-01-2002
		CN 1443155 A	17-09-2003
		DE 60112942 D1	29-09-2005
		EP 1299349 A2	09-04-2003
		EP 1299352 A2	09-04-2003
		HK 1055721 A1	09-12-2005
		JP 2004502664 T	29-01-2004
		JP 2004502665 T	29-01-2004
		MX PA02012560 A	14-05-2003
		NZ 523005 A	26-11-2004
		WO 0202518 A2	10-01-2002
		WO 0202506 A2	10-01-2002
		ZA 200209991 A	03-05-2004
		ZA 200300327 A	25-03-2004