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61/911,749 4 December 2013 (04.12.2013) US(71) Applicant (for all designated States except US): **MERCK SHARP & DOHME CORP.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(72) Inventor; and

(71) Applicant (for US only): **MANDAL, Mihir, B.** [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033 (US).

(72) Inventor; and

(71) Applicant (for NZ, US only): **ZHU, Zhaoning** [US/GB]; 65 Julius Hill, Warfield Berkshire RG42 3UN (GB).(74) Common Representative: **MERCK SHARP & DOHME CORP.**; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

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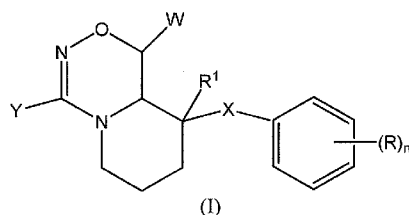
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(54) Title: GAMMA SECRETASE MODULATORS



(I)

(57) **Abstract:** Disclosed herein are compounds of Formula (I) or a pharmaceutically acceptable salt thereof, wherein each of the substituents is given the definition as set forth in the specification and claims. Also disclosed are pharmaceutical compositions containing the compound of Formula (I) and use of the compound in the treatment of neurodegenerative diseases or conditions such as Alzheimer's disease.

TITLE OF THE INVENTION

GAMMA SECRETASE MODULATORS

5 BACKGROUND OF THE INVENTION

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

A β protein, which is a metabolite of amyloid precursor protein (hereinafter referred to as APP), is considered to be greatly involved in degeneration and loss of
15 neurons as well as onset of demential conditions (for example, see Klein W L, et al *Proceeding National Academy of Science USA*, Sep. 2, 2003, 100(18), p. 10417-22), suggesting a molecular basis for reversible memory loss.

Nitsch R M, and 16 others, *Antibodies against β -amyloid slow cognitive decline in Alzheimer's disease*, Neuron, May 22, 2003, 38(4), p. 547-554) suggest that the main
20 components of A β protein are A β 40 consisting of 40 amino acids and A β 42 having two additional amino acids at the C-terminal. The A β 40 and A β 42 tend to aggregate (for example, see Jarrell J T et al, *The carboxy terminus of the β amyloid protein is critical for the seeding of amyloid formation: implications for the pathogenesis of Alzheimer's disease*, Biochemistry, May 11, 1993, 32(18), p. 4693-4697) and constitute the main
25 components of senile plaques (for example, (Glenner GG, et al, *Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein*, Biochemical and Biophysical Research Communications, May 16, 1984, 120(3), p. 885-90. See also Masters C L, et al, *Amyloid plaque core protein in Alzheimer's disease and Down's syndrome*, Proceeding National Academy of Science
30 USA, June 1985, 82(12), p. 4245-4249.).

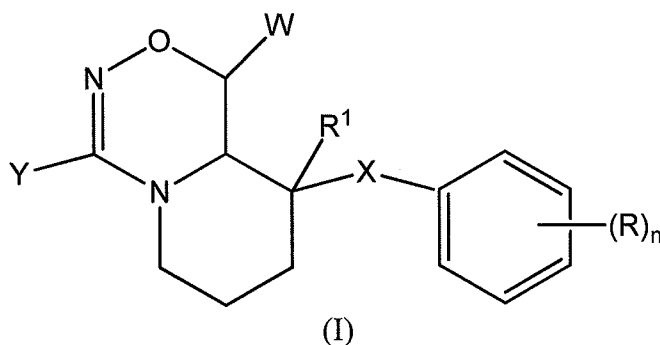
Furthermore, it is known that mutations of APP and presenelin genes, which are observed in familial Alzheimer's disease, increase production of A β 40 and A β 42 (for example, see Gouras G K, et al, *Intraneuronal A β 142 accumulation in human brain*, American Journal of Pathology, January 2000, 156(1), p. 15-20. Also, see Scheuner D, et al, Nature Medicine, August 1996, 2(8), p. 864-870; and Forman M S, et al, *Differential effects of the Swedish mutant amyloid precursor protein on β -amyloid accumulation and secretion in neurons and nonneuronal cells*, Journal of Biological Chemistry, Dec. 19, 1997, 272(51), p. 32247-32253.). Therefore, compounds which reduce production of A β 40 and A β 42 are expected to be agents for controlling progress of Alzheimer's disease or for preventing the disease.

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

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

SUMMARY OF THE INVENTION

This invention is directed to compounds of the Formula (I):



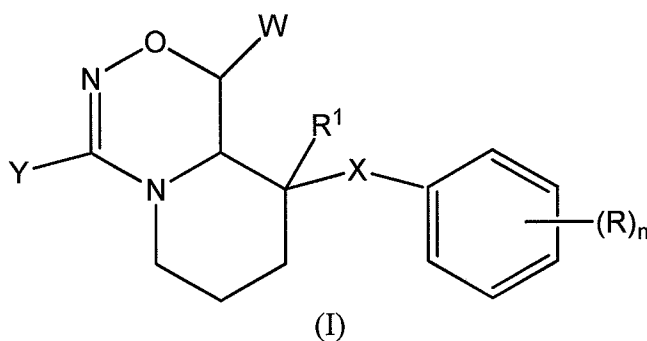
or a pharmaceutically acceptable salt thereof, wherein R, R¹, W, Y and n are defined below.

Compounds of this invention are modulators of gamma secretase, which by definition will block the γ -secretase activity to cleave the amyloid precursor protein (APP) to produce A β 42 without altering the production of total A β .

In an embodiment, the present invention provides for pharmaceutical compositions comprising at least one compound of Formula (I). In another embodiment, the present invention provides for methods for modulating gamma secretase activity comprising administering a therapeutically effective amount of at least one compound of Formula (I) to a patient afflicted with a disease or condition amenable to treatment by modulation of gamma secretase, e.g., Alzheimer's disease.

DETAILED DESCRIPTION OF THE INVENTION

This invention is directed to compounds of the Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein X is a bond, -S-, -S(O)₂-, -NH-, -O-, -CH₂-, -C(O)- or -CH(OH)-;

R is halogen;

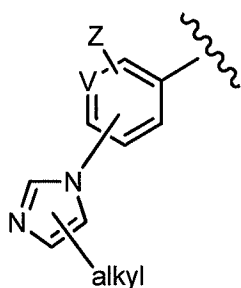
R¹ is hydrogen, -OH or C1-C3 alkyl optionally substituted with 1 to 3 halogen;

n is 0-3;

W is alkyl or alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1 to 3

halogen; and

Y is



, wherein V is $-C-$ or $-N-$, preferably $-C-$, and Z is halo, alkyl or alkoxy wherein the alkyl or alkoxy is optionally substituted with 1 to 3 halogen.

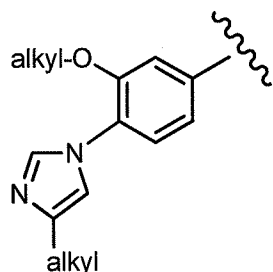
The compounds of the invention are modulators, which by definition will block the γ -secretase activity to cleave APP to produce $A\beta_{42}$ without altering the production of total $A\beta$, and thus are believed to be useful in providing treatment of conditions or diseases which can be treated by modulation of gamma-secretase activity, for example, Alzheimer's disease, Down's Syndrome, mild cognitive impairment, glaucoma, cerebral amyloid angiopathy, stroke, dementia, microgliosis, brain inflammation, traumatic brain injury and olfactory function loss.

In one embodiment of the compounds of Formula (I), n is 0, 1, 2 or 3.

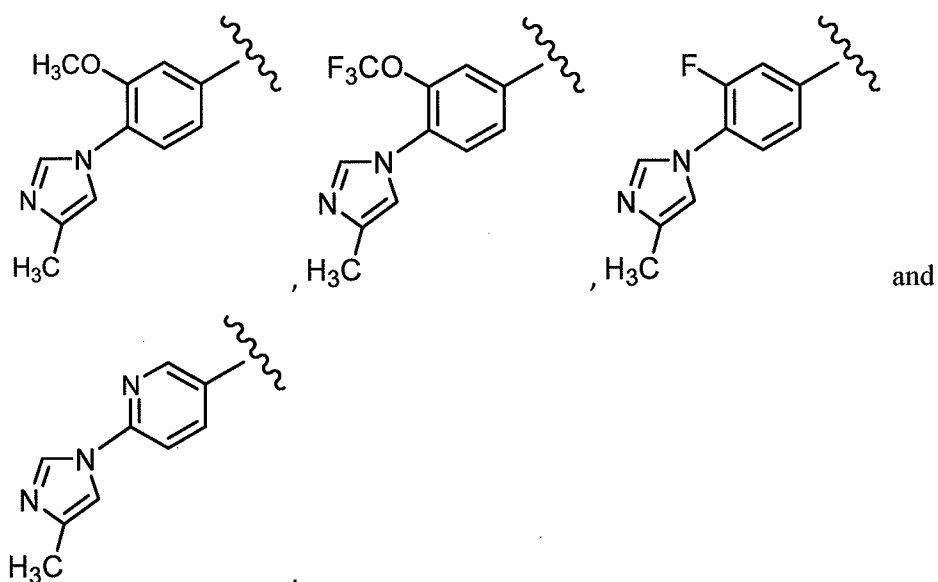
In another embodiment of the compounds of Formula (I), n is 2.

In another embodiment of the compounds of Formula (I), R is fluoro.

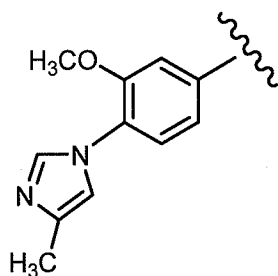
In another embodiment of the compounds of Formula (I), Y is



In another embodiment of the compounds of Formula (I), Y is selected from the group consisting of:

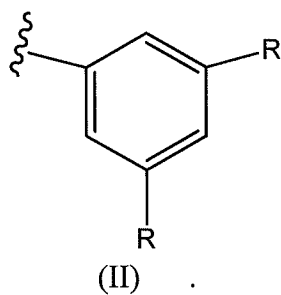


In another embodiment of the compounds of Formula (I), Y is



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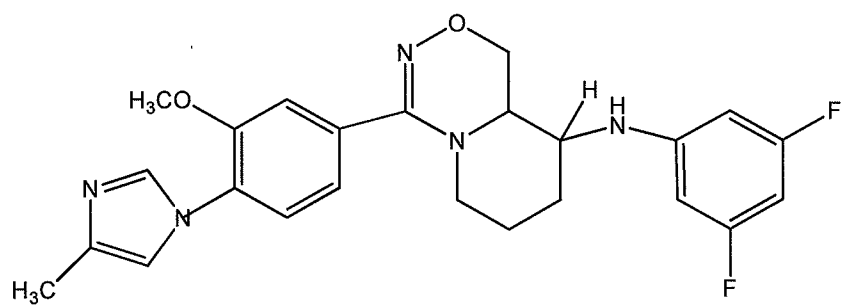
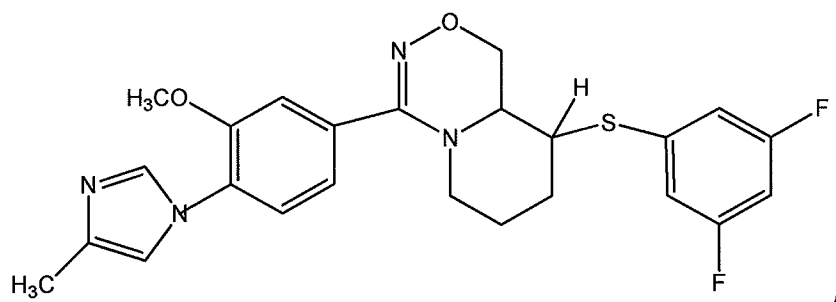
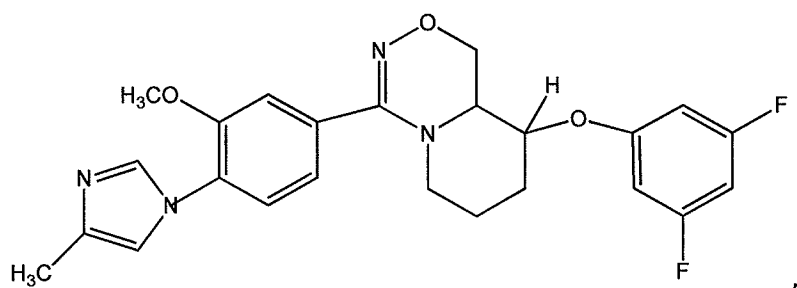
In another embodiment of the compounds of Formula (I), when n is 2, the R groups are bound to the phenyl moiety as shown in Formula (II):



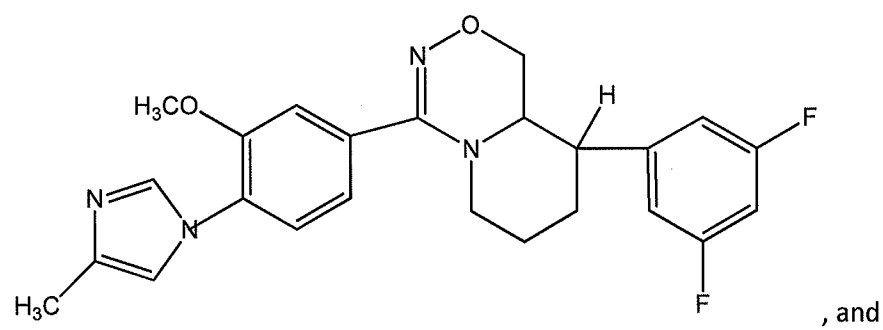
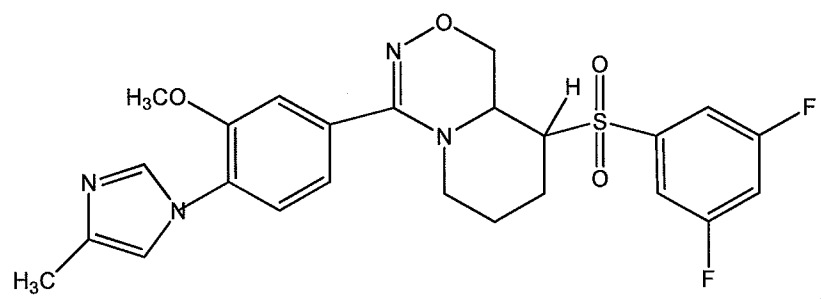
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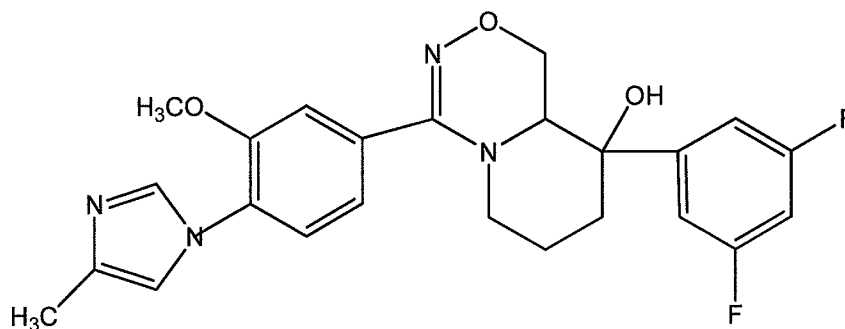
In another embodiment, the present invention is directed to a compound which is selected from the group consisting of:

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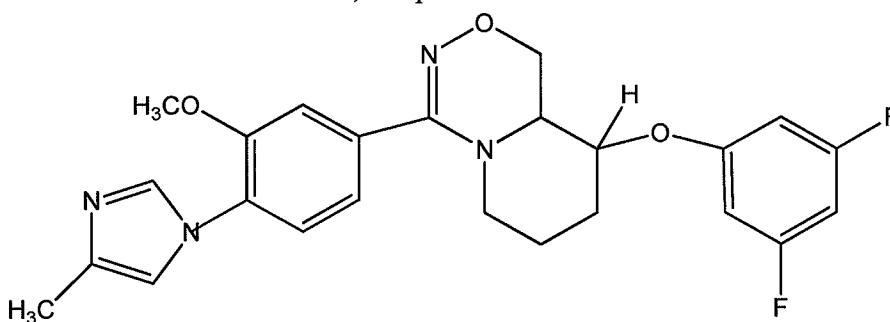
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or a pharmaceutically acceptable salt thereof.

5 In another embodiment, the present invention is directed to a compound which is:



or a pharmaceutically acceptable salt thereof.

The compounds of Formula (I) may form salts, which are also within the scope of this invention. Reference to a compound of Formula (I) herein is understood to include
 10 reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula (I) may be formed, for example, by reacting a
 15 compound of Formula (I) with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates,
 20 camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates,

propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like.

Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl et al, Camille G. (eds.) Handbook of Pharmaceutical Salts. Properties, Selection and Use. (2002) Zurich: Wiley-VCH; S. Berge et al, Journal of Pharmaceutical Sciences (1977) 66(1) 1-19; P. Gould, International J. of Pharmaceutics (1986) 33 201-217; Anderson et al, The Practice of Medicinal Chemistry (1996), Academic Press, New York; and in The Orange Book (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

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

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor that, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula (I) or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems (1987) 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, (1987) Edward B. Roche, ed., American

Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanولات, methanولات, and the like. A "hydrate" is a solvate wherein the solvent molecule(s) is/are H₂O.

Compounds of Formula (I), and salts, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

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

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

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

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

"At least one" means there is at least one, and examples include 1, 2 or 3, or 1 or 2, or 1.

"One or more" means the same as "at least one."

"Patient" means an animal, such as a mammal, e.g., a human being, and is preferably a human being.

"Alkyl" means an aliphatic hydrocarbon group, which may be straight or branched and comprising about 1 to about 6 carbon atoms in the chain or about 1 to about 2 or 3 carbon atoms in the chain. Branched means that one or more lower alkyl groups

such as methyl, ethyl or propyl, are attached to a linear alkyl chain. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl. "Halogen" or "Halo" means fluorine, chlorine, bromine, or iodine. Fluorine, chlorine and bromine are preferred.

5 "Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the production and/or deposition of amyloid protein, and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

Representative compounds of the invention include but are not limited to the compounds
10 and Examples described herein.

The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula (I) can modulate gamma-secretase, the compounds are therefore useful in the treatment or prevention of neurodegenerative diseases, e.g., Alzheimer's disease and other neurodegenerative diseases or conditions as described
15 below.

Pharmaceutical compositions can comprise at least one compound of Formula (I) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier. For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid.

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

Liquid form preparations include solutions, suspensions and emulsions. Water or
30 water-propylene glycol solutions for parenteral injection or addition of sweeteners and

opacifiers for oral solutions, suspensions and emulsions are examples. Liquid form preparations may also include solutions for intranasal administration.

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

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

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

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

The term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention
20 and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit
25 such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

The quantity of active compound in a unit dose of preparation may be varied or
30 adjusted from about 0.1 mg to about 1000 mg, preferably from about 0.1 mg to about 750 mg, more preferably from about 0.1 mg to about 500 mg, and most preferably from about

0.1 mg to about 250 mg, according to the particular application. The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 0.1 mg/day to about 1000 mg/day, in one to four divided doses.

As indicated above, the compounds of the invention are useful in the treatment of Alzheimer's disease. Accordingly, in another embodiment of this invention a method of treating Alzheimer's disease is provided comprising administering to a patient in need thereof a therapeutically effective amount of at least one compound of Formula (I) or a pharmaceutically acceptable salt thereof.

In another embodiment of the method of treating Alzheimer's disease, the method comprises administering to a patient in need thereof a therapeutically effective amount of at least one compound of Formula (I) or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of at least one drug selected from the group consisting of BACE inhibitors; muscarinic antagonists; cholinesterase inhibitors; gamma secretase inhibitors; gamma secretase modulators; HMG-CoA reductase inhibitors; non-steroidal anti-inflammatory agents; N-methyl-D-aspartate receptor antagonists; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; an antibiotic; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; GABAA inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity; PDE-10 inhibitors; Exelon (rivastigmine); Cognex (tacrine); Tau kinase; anti-Abeta vaccine; APP ligands; agents that upregulate insulin cholesterol lowering agents; cholesterol absorption inhibitors; fibrates; LXR agonists; LRP mimics; nicotinic receptor agonists; H3 receptor antagonists; histone deacetylase inhibitors; hsp90

inhibitors; m1 muscarinic receptor agonists; 5-HT₆ receptor antagonists; mGluR₁; mGluR₅; positive allosteric modulators or agonists; mGluR_{2/3} antagonists; anti-inflammatory agents that can reduce neuroinflammation; Prostaglandin EP₂ receptor antagonists; PAI-1 inhibitors; and agents that can induce Abeta efflux.

5 In another embodiment, a method of treating Alzheimer's disease is provided comprising administering a therapeutically effective amount of at least one compound of formula (I), in combination with a therapeutically effective amount of at least one cholinesterase inhibitor (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 H -inden-1-one hydrochloride, i.e, donepezil
10 hydrochloride, available as the Aricept® brand of donepezil hydrochloride), to a patient in need of treatment.

 The invention also provides for a method of inhibiting the deposition of amyloid beta protein in, on or around neurological tissue, the method comprising administering to a patient in need thereof a therapeutically effective amount of at least one compound of
15 the Formula (I) or a pharmaceutically acceptable salt thereof.

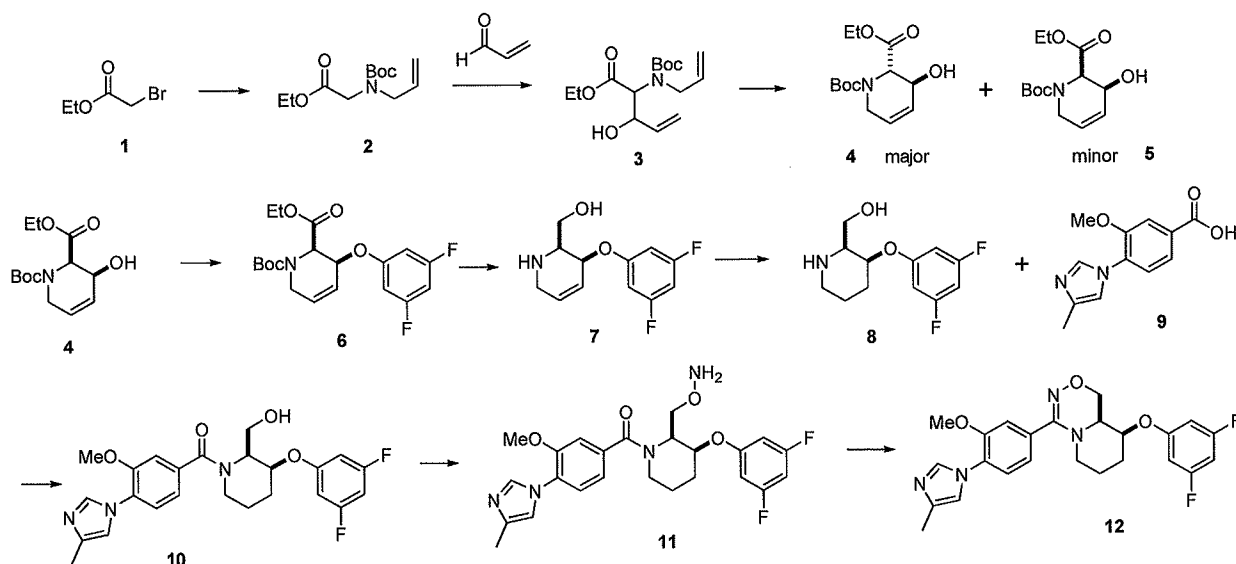
 As the compounds of Formula (I) modulate gamma secretase activity, the invention also provides for a method of modulating gamma secretase comprising administering to a patient in need thereof a therapeutically effective amount of at least one compound of the Formula (I) or a pharmaceutically acceptable salt thereof.

20 As the compounds of Formula (I) modulate gamma secretase activity, and thus inhibit amyloid beta production (Aβ₄₀ and Aβ₄₂ production), the invention also provides for a method of inhibiting amyloid beta production comprising administering to a patient in need thereof a therapeutically effective amount of at least one compound of the Formula (I) or a pharmaceutically acceptable salt thereof.

25 The compounds of Formula (I) are also useful in treating a neurodegenerative disease or condition selected from the group consisting of Down's Syndrome, mild cognitive impairment, glaucoma, cerebral amyloid angiopathy, stroke, dementia, microgliosis, brain inflammation, traumatic brain injury and olfactory function loss. The method of treatment comprises administering to a patient in need thereof a therapeutically
30 effective amount of at least one compound of the Formula (I) or a pharmaceutically acceptable salt thereof.

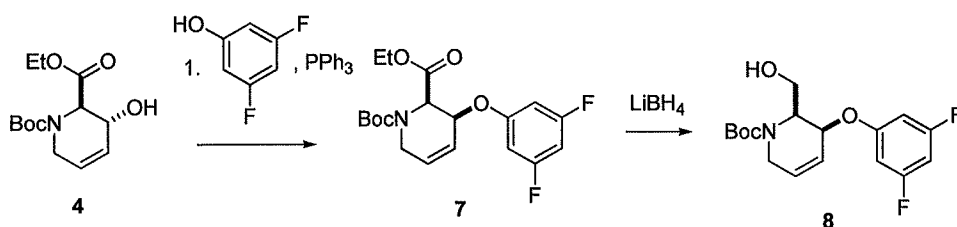
The invention disclosed herein is exemplified by the following preparations and examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art. Where NMR data are presented, ^1H spectra were obtained on either a Varian VXR-200 (200 MHz, ^1H), Varian Gemini-300 (300 MHz) or XL-400 (400 MHz) and are reported as ppm down field from Me_4Si with number of protons, multiplicities, and coupling constants in Hertz indicated parenthetically.

Experimental Procedures



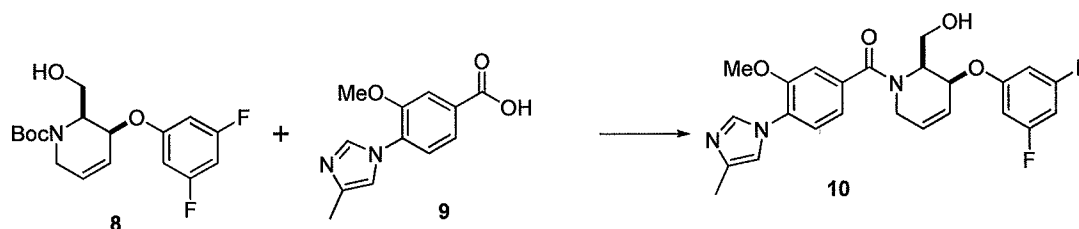
The intermediates **4** and **5** were prepared following literature procedures (e.g., Bioorganic & Medicinal Chemistry, 16(17), 8273-8286; 2008).

Procedure A



To a solution of alcohol **6** (450 mg, 1.66 mmol, 1 equiv.) in 5 mL THF was added triphenyl phosphine (522 mg, 1.9 mmol, 1.2 equiv.), and the resulting solution was cooled to 0 °C. To this reaction mixture was added Diethyl azodicarboxylate (0.4 mL, 1.9 mmol, 1.2 equiv.) and the resulting mixture was stirred for 30 minutes at 0°C. The reaction mixture was slowly warmed to room temperature, and stirred at this temperature until the reaction completed. Subsequently, the reaction mixture was evaporated to dryness and purified using 10% ethyl acetate in hexanes to yield **7**. LiBH₄ was added to a solution of compound **7** (1.66 mmol) in a mixture of ether and methanol at 0°C and the resulting mixture was stirred for 30 minutes at 0°C. The reaction mixture was slowly warmed to room temperature, and stirred at this temperature until the reaction completed. Then the reaction mixture was quenched with excess of methanol, evaporated to dryness and purified using 30% ethyl acetate in hexanes to yield compound **8** in 60% yield. ¹H NMR d 6.44 (m, 3H), 5.85 (m, 1H), 5.76 (m, 1H), 5.10 (br-s, 1H), 4.93 (br-s, 0.5H), 4.78 (br-s, 0.5H), 4.36 (m, 0.5 H), 4.19 (m, 0.5H), 3.82 (m, 1H), 3.67 (m, 2H), 1.51 (m, 9H).

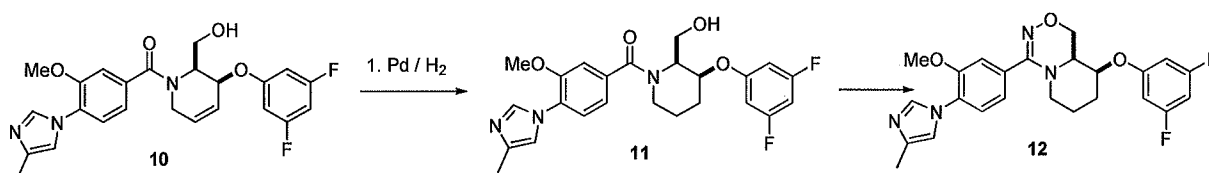
Procedure B



Trifluoro acetic acid (TFA, 0.5 mL) To a solution of alcohol (114 mg, 0.33 mmol) in 1mL dichloromethane was added and the resulting mixture was stirred for 30 minutes to remove the Boc (*N*-*tert*-butoxycarbonyl) protection from the amine functionality. Upon complete removal of the Boc group the reaction mixture was evaporated to dryness, and the excess of TFA was removed by co evaporating with toluene. To this crude amine salt in 1.6 mL *N,N*-dimethylformamide was added acid **9** (77 mg, 1 equiv.), *N*-

Hydroxybenzotriazole (54 mg, 0.4 mmol), DIEA (0.3 mL, 5 equiv.) followed by 3-(Ethyiminomethyleneamino)-*N,N*-dimethylpropan-1-amine (76 mg, 0.4 mmol)] and the resulting mixture was stirred for 18 hr. Upon completion of the reaction, the reaction mixture was diluted with water, extracted with ethyl acetate, dried with MgSO_4 ,
 5 evaporated and purified with 5% methanol in dichloromethane to yield compound **10** in 70% yield. ^1H NMR (CDCl_3) δ 7.74 (br-s, 0.4H), 7.49 (br-s, 0.7H), 7.23 (m, 2H), 7.13 (m, 1.4H), 6.89 (m, 1H), 6.56-6.24 (m, 3H), 6.0 (m, 0.8H), 5.81 (m, 1.3H), 5.50 (br-s, 0.3H), 5.13-5.01 (m, 1H), 4.78 (m, 0.84H), 4.76 (m, 0.7H), 3.98 (m, 1H), 3.87 (m, 5H), 2.27 (br-s, 3H).

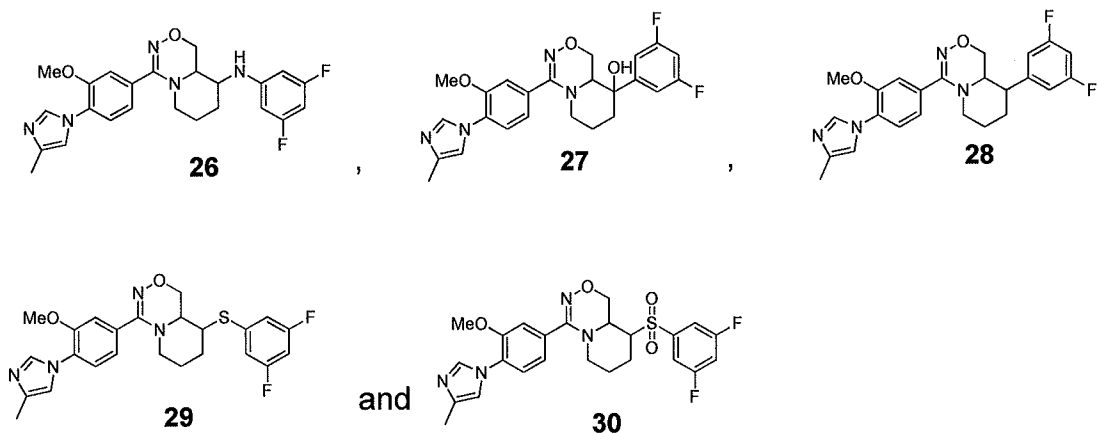
Procedure C



To a solution of compound **10** (200 mg) in 2 mL methanol was added palladium on carbon Pd/C (46 mg, 10% by wt.) and the resulting solution was stirred under hydrogen for 30 minutes. The reaction mixture was evaporated to dryness and purified with methanol in dichloromethane. Methanesulfonyl chloride (0.024 mL, 0.315 mmol, 2 equiv.) was added to this alcohol (72 mg, 0.157 mmol followed by triethyl amine (0.109 mL, 0.785 mmol) and the resulting mixture was stirred at $-20\text{ }^\circ\text{C}$ for 30 minutes before
 20 the addition of the *N*-hydroxy phthalimide (100 mg, 4 equiv.). The reaction mixture was slowly warmed to room temperature and stirred for 12 hr when LC/MS showed presence of no starting material. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate then with brine. The organic layer was dried with
 25 magnesium sulfate, concentrated and the crude material was treated with hydrazine to remove the phthalimide group. Upon heating this phthalimide removed product with phosphoric acid in toluene compound **12** was obtained. Compound **12** was purified using C18 reverse phase column using 0.05% trifluoroacetic acid in water and acetonitrile.

¹H NMR (CD₃OD) 9.21 (s, 1H), 7.71 (m, 1H), 7.63 (s, 1H), 7.35 (s, 1H), 7.33 (m, 1H), 6.7-6.5 (m, 4H), 4.75 (br-s, 1H), 4.34 (m, 1H), 4.13 (m, 1H), 4.0 (m, 4H), 3.6 (m, 1H), 3.2 (m, 1H), 2.43 (s, 3H), 2.25 (m, 1H), 2.0-1.8 (m, 2H), 1.6 (m, 1H).

5 Compounds **26**, **27**, **28**, **29** and **30** are prepared following the synthetic scheme and experimental procedures described herein.

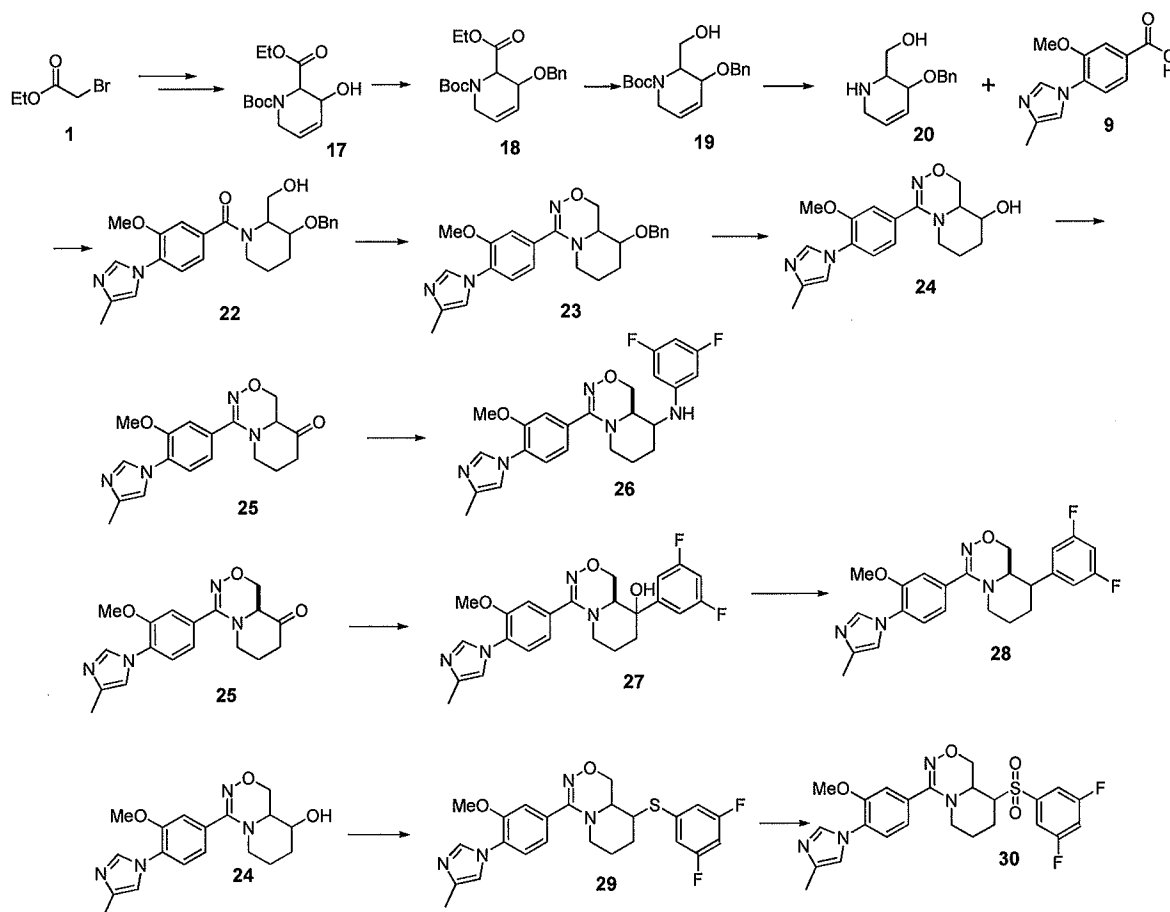


Compound **1** may be transformed to compound **17** following the literature procedure ((Bioorganic & Medicinal Chemistry, 16(17), 8273-8286; 2008) and the free hydroxyl group may be benzylated using benzyl bromide. Reduction of the ester of compound **18** would be carried out using LiBH₄ to yield compound **19**. Removal of the Boc followed by coupling with the acid **9** and reduction of the alkene moiety using Adam's catalyst (PtO₂) would provide compound **22**. Compound **22** can be converted to compound **23** following the protocol similar to **Procedure C**. BCl₃ mediated removal of the benzyl group followed by oxidation of the resulting alcohol can provide the ketone **25**.

Reductive amination with a variety of amines can provide compounds, for example compound **26**.

Addition of a variety of Grignard reagents, e.g., 3,5-difluorophenyl)magnesium bromide, (3,4,5-trifluorophenyl)magnesium bromide, to compound **25** provides compounds, for example compound **27**. Removal of the hydroxyl using triethyl silane and TFA provides compound **28**.

Mitsunobu reaction of compound **24** with 3,5-difluorobenzene thiol would provide compound **29** and oxidation with mCPBA would provide compound **30**.



5

Assay:

Secretase Reaction and A β Analysis in Whole Cells: HEK293 cells

overexpressing APP with Swedish and London mutations were treated with the specified
 10 compounds for 5 hour at 37 °C in 100 ml of DMEM medium containing 10% fetal
 bovine serum. At the end of the incubation, total A β , A β 40 and A β 42 were measured
 using electrochemiluminescence (ECL) based sandwich immunoassays. Total A β was
 determined using a pair of antibodies TAG-W02 and biotin-4G8, A β 40 was identified
 with antibody pairs TAG-G2-10 and biotin- 4G8, while A β 42 was identified with TAG-
 15 G2-11 and biotin-4G8. The ECL signal was measured using Sector Imager 2400 (Meso
 Scale Discovery, referred thereafter as MSD).

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

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

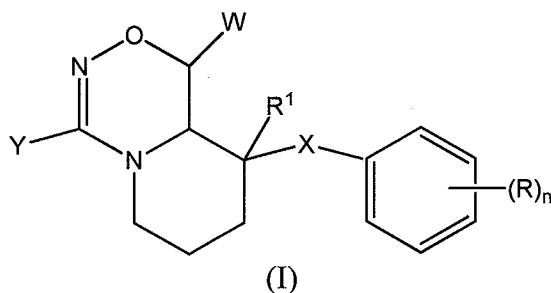
10 *MS analysis of A β profile:* To isolate A β products from conditioned media, cells expressing APP were grown to 90% confluence and re-fed with fresh media containing γ -secretase modulator. The conditioned media, harvested after 16 h of incubation, were incubated overnight with antibody W02 in RIPA buffer (20 mM Tris-HCl, pH7.4, 150 mM NaCl, 0.2% Twenn 20, 0.2% Triton 100 and 0.2% NP40). Protein A plus G agarose
15 (Calbiochem) was added to the reaction and the mixture was rocked at room temperature for another 2 h. The agarose beads were then collected by centrifugation and washed 3 times with RIPA buffer and twice with 20 mM Tris (pH 7.4). The immunoprecipitated peptides were eluted from the beads with 10 μ L of 10% acetonitrile/ 0.1% trifluoroacetic acid.

20 The characteristics of γ -secretase activity described were confirmed using at least two experiments. Compound 12 was tested and had an A β 42 membrane IC50 of 354 nM. The Abtotal/AB42, IC50 ratio was 57.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modification and variations thereof will
25 be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound of the Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein X is a bond, -S-, -S(O)₂-, -NH-, -O-, -CH₂-, -C(O) or -CHOH ;

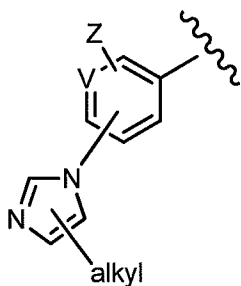
10 R is halogen;

R¹ is hydrogen, -OH or C1-C3 alkyl optionally substituted with 1 to 3 halogen;

n is 0-3;

W is alkyl or alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1 to 3 halogen; and

15 Y is



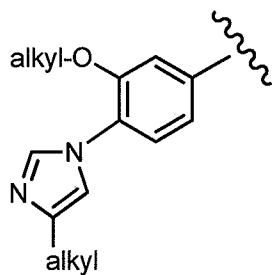
, wherein V is -C- or -N-, and Z is halo, alkyl or alkoxy wherein the alkyl or alkoxy is optionally substituted with 1 to 3 halogen; or a pharmaceutically acceptable salt thereof.

20

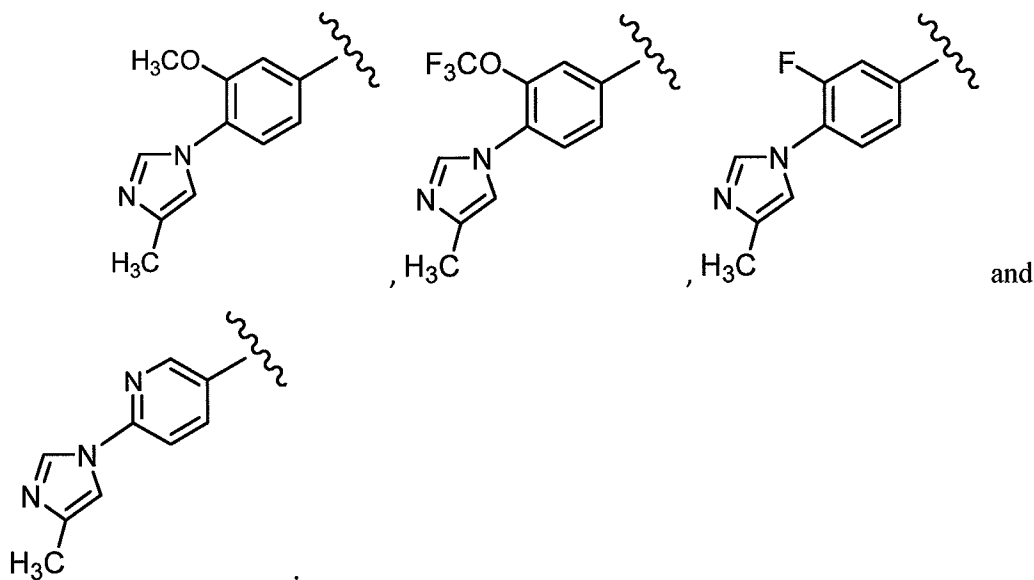
2. The compound of Claim 1 or a pharmaceutically acceptable salt thereof, wherein n is 2.

3. The compound of Claim 1 or a pharmaceutically acceptable salt thereof,
wherein R is fluoro.

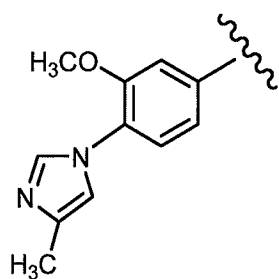
4. The compound of Claim 1 or a pharmaceutically acceptable salt thereof,
5 wherein Y is:



5. The compound of Claim 1 or a pharmaceutically acceptable salt thereof,
10 wherein Y is selected from the group consisting of:

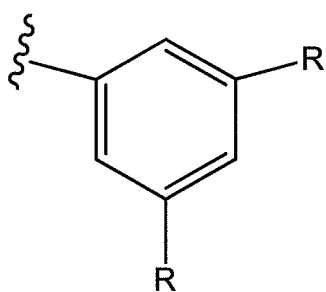


6. The compound of Claim 1 or a pharmaceutically acceptable salt thereof,
15 wherein Y is:



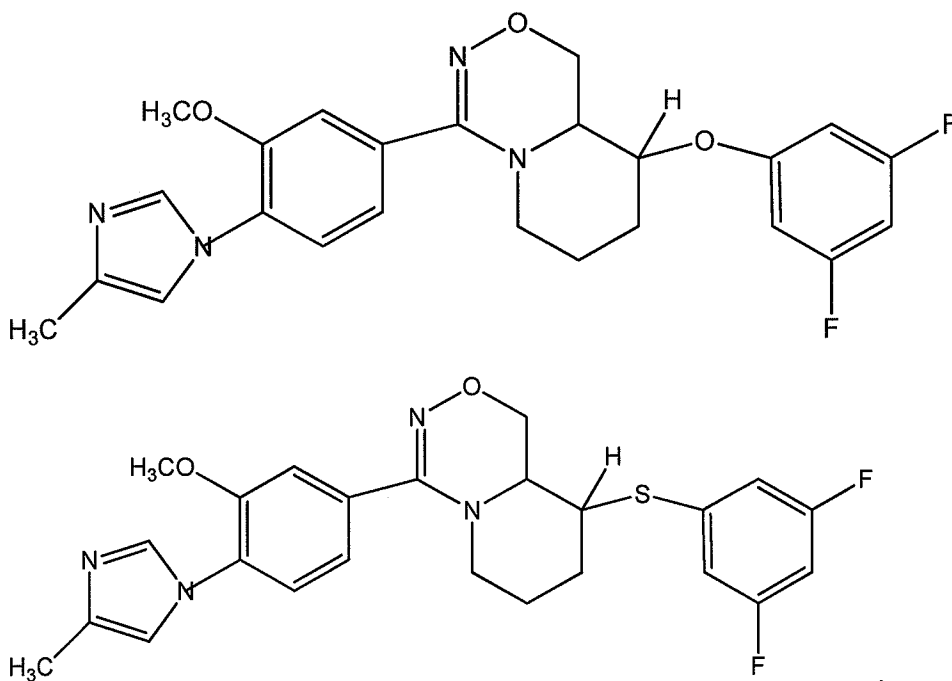
7. The compound of Claim 2 or a pharmaceutically acceptable salt thereof, wherein the R groups that are bound to the phenyl moiety are as shown in Formula (II):

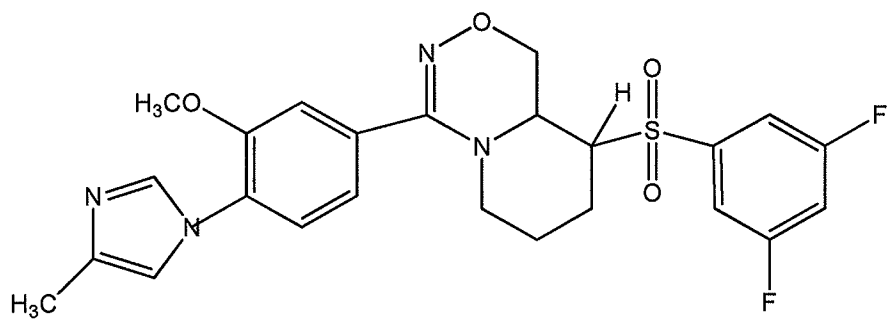
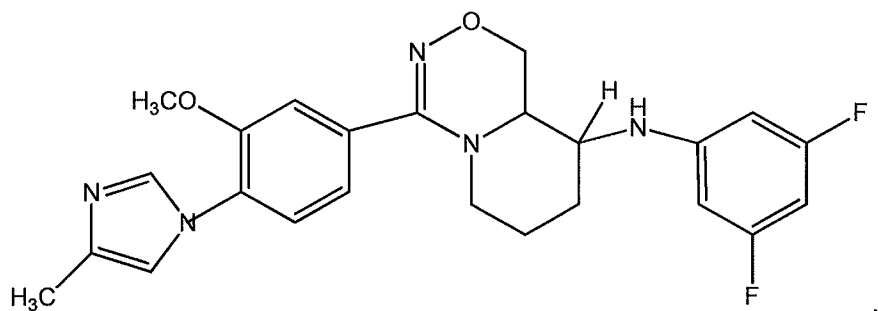
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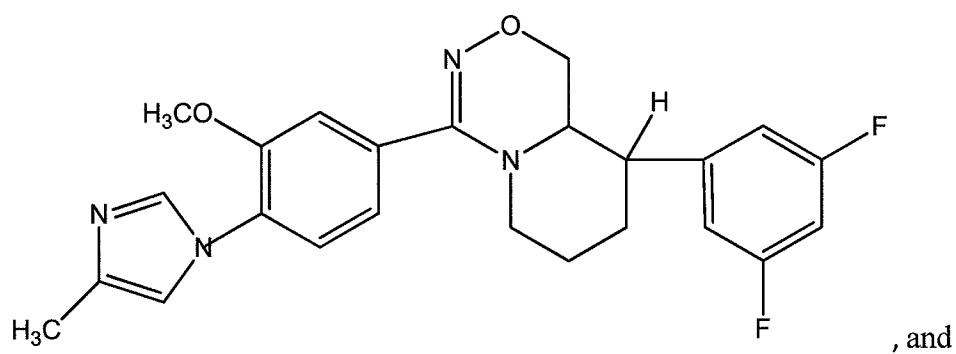
8. The compound of Claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

10

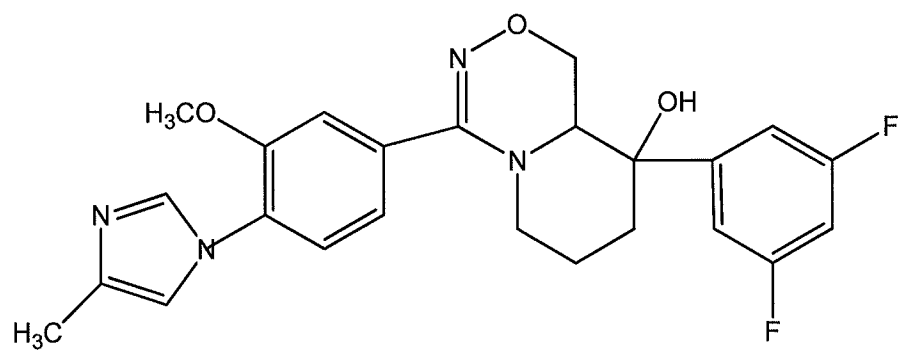




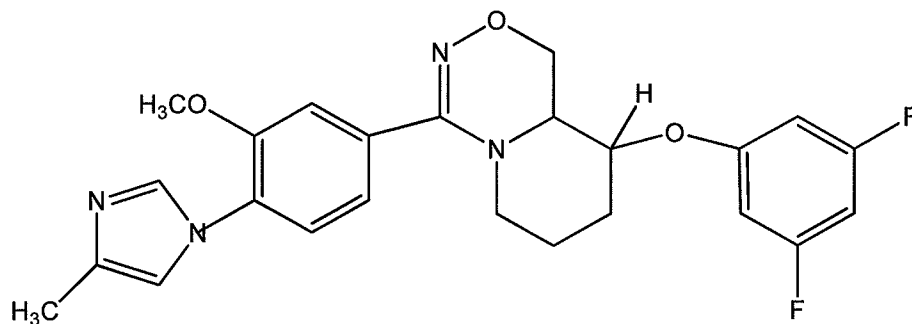
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, and



9. The compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is:



10. A pharmaceutical composition comprising the compound of any of Claims 1-8 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition comprising the compound of Claim 9 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

12. A method of treating Alzheimer's disease comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any of Claims 1-9 or a pharmaceutically acceptable salt thereof.

13. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, for use in the treatment of Alzheimer's disease.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/067988

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/40 (2015.01)

CPC - C07D 417/14 (2014.11)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61K 31/40, 31/4439; A61P 25/28 (2015.01)

CPC - A61K 31/40; C07D 417/14, 513/04 (2014.11) (keyword delimited)

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

USPC - 514/210.21, 230.5, 256; 544/238 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, STN, Google Patents, Google Scholar, PubChem

Search terms used: imidazole alzheimer's gamma secretase modulators

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2010/0256128 A1 (ZHU et al) 07 October 2010 (07.10.2010) entire document	1-13
A	US 6,096,745 A (POINDEXTER et al) 01 August 2000 (01.08.2000) entire document	1-13
A	US 6,887,872 B2 (LITERATI NAGY et al) 03 May 2005 (03.05.2005) entire document	1-13

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

* 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 application or patent 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

27 January 2015

Date of mailing of the international search report

06 MAR 2015

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Blaine R. Copenheaver

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774