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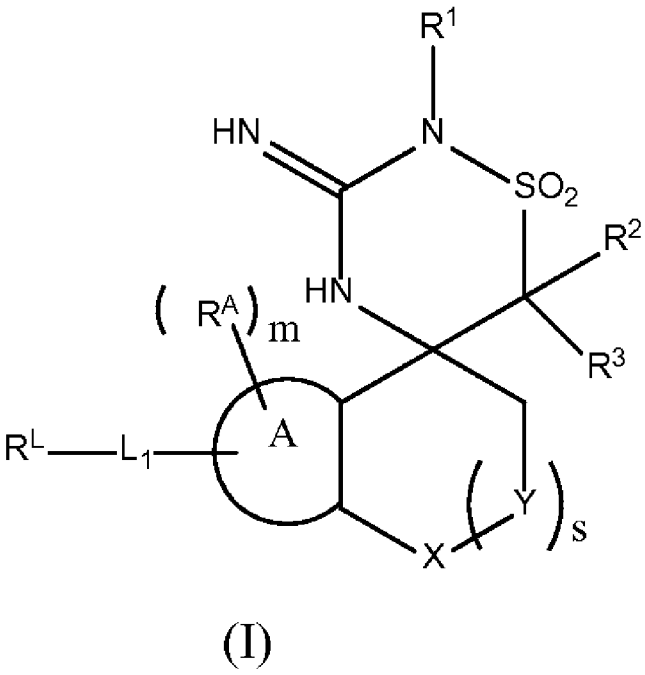
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[Continued on next page]

(54) Title: C5-SPIRO IMINOTHIADIAZINE DIOXIDES AS BACE INHIBITORS



(I)

(57) Abstract: In its many embodiments, the present invention provides certain C5-spiro iminothiadiazine dioxide compounds, including compounds Formula (I): (structurally represented) or tautomers thereof, and pharmaceutically acceptable salts of said compounds, wherein R1, R2, R3, X, Y, s, ring A, RA, m, -L1-, and RL are as defined herein. The novel compounds of the invention are useful as BACE inhibitors and/or for the treatment and prevention of various pathologies related thereto. Pharmaceutical compositions comprising one or more such compounds (alone and in combination with one or more other active agents), and methods for their preparation and use, including for the possible treatment of Alzheimer's disease, are also disclosed:

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MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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C5-SPIRO IMINOTHIADIAZINE DIOXIDES AS BACE INHIBITORS.

FIELD OF THE INVENTION

This invention provides certain C5-spiro iminothiadiazine dioxide compounds, and compositions comprising these compounds, as inhibitors of BACE, which may be useful for treating or preventing pathologies related thereto.

BACKGROUND

Amyloid beta peptide ("Aβ") is a primary component of β amyloid fibrils and plaques, which are regarded as having a role in an increasing number of pathologies. Examples of such pathologies include, but are not limited to, Alzheimer's disease, Down's syndrome, Parkinson's disease, memory loss (including memory loss associated with Alzheimer's disease and Parkinson's disease), attention deficit symptoms (including attention deficit symptoms associated with Alzheimer's disease ("AD"), Parkinson's disease, and Down's syndrome), dementia (including pre-senile dementia, senile dementia, dementia associated with Alzheimer's disease, Parkinson's disease, and Down's syndrome), progressive supranuclear palsy, cortical basal degeneration, neurodegeneration, olfactory impairment (including olfactory impairment associated with Alzheimer's disease, Parkinson's disease, and Down's syndrome), β-amyloid angiopathy (including cerebral amyloid angiopathy), hereditary cerebral hemorrhage, mild cognitive impairment ("MCI"), glaucoma, amyloidosis, type II diabetes, hemodialysis (β2 microglobulins and complications arising therefrom), neurodegenerative diseases such as scrapie, bovine spongiform encephalitis, Creutzfeld-Jakob disease, traumatic brain injury and the like.

Aβ peptides are short peptides which are made from the proteolytic break-down of the transmembrane protein called amyloid precursor protein ("APP"). Aβ peptides are made from the cleavage of APP by β-secretase activity at a position near the N-terminus of Aβ, and by gamma-secretase activity at a position near the C-terminus of Aβ. (APP is also cleaved by α-secretase activity, resulting in the secreted, non-amyloidogenic fragment known as soluble APPα.) Beta site APP Cleaving Enzyme ("BACE-1") is regarded as the primary aspartyl protease responsible for the production of Aβ by β-secretase activity. The inhibition of BACE-1 has been shown to inhibit the production of Aβ.

AD is estimated to afflict more than 20 million people worldwide and is believed to be the most common cause of dementia. AD is a disease characterized by degeneration and loss

of neurons and also by the formation of senile plaques and neurofibrillary tangles. Presently, treatment of Alzheimer's disease is limited to the treatment of its symptoms rather than the underlying causes. Symptom-improving agents approved for this purpose include, for example, N-methyl-D-aspartate receptor antagonists such as memantine (Namenda®, Forest Pharmaceuticals, Inc.), cholinesterase inhibitors such as donepezil (Aricept®, Pfizer), rivastigmine (Exelon®, Novartis), galantamine (Razadyne Reminyl®), and tacrine (Cognex®).

In AD, Aβ peptides, formed through β-secretase and *gamma*-secretase activity, can form tertiary structures that aggregate to form amyloid fibrils. Aβ peptides have also been shown to form Aβ oligomers (sometimes referred to as "Aβ aggregates" or "Abeta oligomers"). Aβ oligomers are small multimeric structures composed of 2 to 12 Aβ peptides that are structurally distinct from Aβ fibrils. Amyloid fibrils can deposit outside neurons in dense formations known as senile plaques, neuritic plaques, or diffuse plaques in regions of the brain important to memory and cognition. Aβ oligomers are cytotoxic when injected in the brains of rats or in cell culture. This Aβ plaque formation and deposition and/or Aβ oligomer formation, and the resultant neuronal death and cognitive impairment, are among the hallmarks of AD pathophysiology. Other hallmarks of AD pathophysiology include intracellular neurofibrillary tangles comprised of abnormally phosphorylated tau protein, and neuroinflammation.

Evidence suggests that Aβ, Aβ fibrils, aggregates, oligomers, and/or plaque play a causal role in AD pathophysiology. (Ohno et al., Neurobiology of Disease, No. 26 (2007), 134-145). Mutations in the genes for APP and presenilins 1/2 (PS1/2) are known to cause familial AD and an increase in the production of the 42-amino acid form of Aβ is regarded as causative. Aβ has been shown to be neurotoxic in culture and in vivo. For example, when injected into the brains of aged primates, fibrillar Aβ causes neuronal cell death around the injection site. Other direct and circumstantial evidence of the role of Aβ in Alzheimer etiology has also been published.

BACE-1 has become an accepted therapeutic target for the treatment of Alzheimer's disease. For example, McConlogue et al., J. Bio. Chem., Vol. 282, No. 36 (Sept. 2007), have shown that partial reductions of BACE-1 enzyme activity and concomitant reductions of Aβ levels lead to a dramatic inhibition of Aβ-driven AD-like pathology, making β-secretase a target for therapeutic intervention in AD. Ohno et al. Neurobiology of Disease, No. 26 (2007),

134-145, report that genetic deletion of BACE-1 in 5XFAD mice abrogates Aβ generation, blocks amyloid deposition, prevents neuron loss found in the cerebral cortex and subiculum (brain regions manifesting the most severe amyloidosis in 5XFAD mice), and rescues memory deficits in 5XFAD mice. The group also reports that Aβ is ultimately responsible for neuron death in AD and concludes that BACE-1 inhibition has been validated as an approach for the treatment of AD. Roberds et al., Human Mol. Genetics, 2001, Vol. 10, No. 12, 1317-1324, established that inhibition or loss of β-secretase activity produces no profound phenotypic defects while inducing a concomitant reduction in Aβ. Luo et al., Nature Neuroscience, Vol. 4, No. 3, March 2001, report that mice deficient in BACE-1 have normal phenotype and abolished β-amyloid generation.

More recently, Jonsson, et al. have reported in Nature, Vol. 488, pp. 96-99 (Aug. 2012), that a coding mutation (A673T) in the APP gene protects against Alzheimer's disease and cognitive decline in the elderly without Alzheimer's disease. More specifically, the A allele of rs63750847, a single nucleotide polymorphism (SNP), results in an alanine to threonine substitution at position 673 in APP (A673T). This SNP was found to be significantly more common in a healthy elderly control group than in an Alzheimer's disease group. The A673T substitution is adjacent to the aspartyl protease *beta*-site in APP, and results in an approximately 40% reduction in the formation of amyloidogenic peptides in a heterologous cell expression system *in vitro*. Jonsson, et al. report that an APP-derived peptide substrate containing the A673T mutation is processed 50% less efficiently by purified human BACE1 enzyme when compared to a wild-type peptide. Jonsson et al. indicate that the strong protective effect of the APP-A673T substitution against Alzheimer's disease provides proof of principle for the hypothesis that reducing the *beta*-cleavage of APP may protect against the disease.

BACE-1 has also been identified or implicated as a therapeutic target for a number of other diverse pathologies in which Aβ or Aβ fragments have been identified to play a causative role. One such example is in the treatment of AD-type symptoms of patients with Down's syndrome. The gene encoding APP is found on chromosome 21, which is also the chromosome found as an extra copy in Down's syndrome. Down's syndrome patients tend to acquire AD at an early age, with almost all those over 40 years of age showing Alzheimer's-type pathology. This is thought to be due to the extra copy of the APP gene found in these patients, which leads to overexpression of APP and therefore to increased levels of Aβ causing

the prevalence of AD seen in this population. Furthermore, Down's patients who have a duplication of a small region of chromosome 21 that does not include the APP gene do not develop AD pathology. Thus, it is thought that inhibitors of BACE-1 could be useful in reducing Alzheimer's type pathology in Down's syndrome patients.

Another example is in the treatment of glaucoma (Guo et al., PNAS, Vol. 104, No. 33, August 14, 2007). Glaucoma is a retinal disease of the eye and a major cause of irreversible blindness worldwide. Guo et al. report that Aβ colocalizes with apoptotic retinal ganglion cells (RGCs) in experimental glaucoma and induces significant RGC cell loss in vivo in a dose- and time-dependent manner. The group report having demonstrated that targeting different components of the Aβ formation and aggregation pathway, including inhibition of β-secretase alone and together with other approaches, can effectively reduce glaucomatous RGC apoptosis in vivo. Thus, the reduction of Aβ production by the inhibition of BACE-1 could be useful, alone or in combination with other approaches, for the treatment of glaucoma.

Another example is in the treatment of olfactory impairment. Getchell et al., Neurobiology of Aging, 24 (2003), 663-673, have observed that the olfactory epithelium, a neuroepithelium that lines the posterior-dorsal region of the nasal cavity, exhibits many of the same pathological changes found in the brains of AD patients, including deposits of Aβ, the presence of hyperphosphorylated tau protein, and dystrophic neurites among others. Other evidence in this connection has been reported by Bacon AW, et al., Ann NY Acad Sci 2002; 855:723–31; Crino PB, Martin JA, Hill WD, et al., Ann Otol Rhinol Laryngol, 1995;104:655–61; Davies DC, et al., Neurobiol Aging, 1993;14:353-7; Devanand DP, et al., Am J Psychiatr, 2000;157:1399-405; and Doty RL, et al., Brain Res Bull, 1987;18:597–600. It is reasonable to suggest that addressing such changes by reduction of Aβ by inhibition of BACE-1 could help to restore olfactory sensitivity in patients with AD.

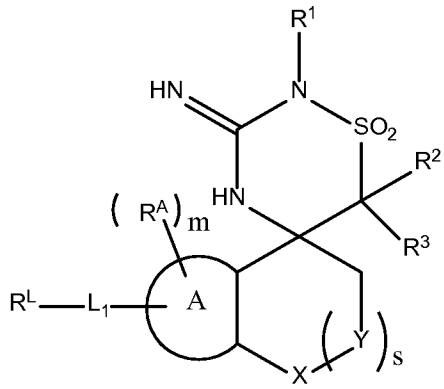
For compounds which are inhibitors of BACE-2, another example is in the treatment of type-II diabetes, including diabetes associated with amyloidogenesis. BACE-2 is expressed in the pancreas. BACE-2 immunoreactivity has been reported in secretory granules of beta cells, co-stored with insulin and IAPP, but lacking in the other endocrine and exocrine cell types. Stoffel et al., WO2010/063718, disclose the use of BACE-2 inhibitors in the treatment of metabolic diseases such as Type-II diabetes. The presence of BACE-2 in secretory granules of beta cells suggests that it may play a role in diabetes-associated amyloidogenesis. (Finzi, G. Franzi, et al., Ultrastruct Pathol. 2008 Nov-Dec;32(6):246-51.)

Other diverse pathologies characterized by the formation and deposition of Aβ or fragments thereof, and/or by the presence of amyloid fibrils, oligomers, and/or plaques, include neurodegenerative diseases such as scrapie, bovine spongiform encephalitis, traumatic brain injury ("TBI"), Creutzfeld-Jakob disease and the like, type II diabetes (which is characterized by the localized accumulation of cytotoxic amyloid fibrils in the insulin producing cells of the pancreas), and amyloid angiopathy. In this regard reference can be made to the patent literature. For example, Kong et al., US2008/0015180, disclose methods and compositions for treating amyloidosis with agents that inhibit Aβ peptide formation. As another example, Loane, et al. report the targeting of amyloid precursor protein secretases as therapeutic targets for traumatic brain injury. (Loane et al., "Amyloid precursor protein secretases as therapeutic targets for traumatic brain injury", Nature Medicine, Advance Online Publication, published online March 15, 2009.) Still other diverse pathologies characterized by the inappropriate formation and deposition of Aβ or fragments thereof, and/or by the presence of amyloid fibrils, and/or for which inhibitor(s) of BACE-1 is expected to be of therapeutic value are discussed further hereinbelow.

SUMMARY OF THE INVENTION

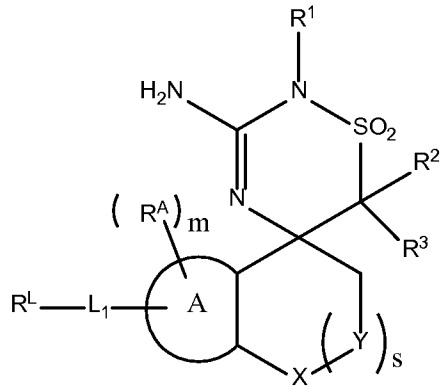
The present invention provides certain C5-spiro iminothiadiazine dioxide compounds, which are collectively or individually referred to herein as "compound(s) of the invention," as described herein. The compounds of the invention are useful as inhibitors of BACE-1 and/or BACE-2.

In one embodiment, the compounds of the invention have the structural Formula (I):



(I)

or a tautomer thereof having the structural Formula (I'):



(I')

or pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of H, alkyl, heteroalkyl, cycloalkyl, and -alkyl-cycloalkyl, wherein each said alkyl, heteroalkyl, cycloalkyl, and -alkyl-cycloalkyl, is optionally substituted with one or more halogen;

R^2 is selected from the group consisting of H, halogen, alkyl, heteroalkyl, cycloalkyl, and -alkyl-cycloalkyl, wherein each said alkyl, heteroalkyl, cycloalkyl, and -alkyl-cycloalkyl is optionally substituted with one or more halogen;

R^3 is selected from the group consisting of H, halogen, alkyl, heteroalkyl, cycloalkyl, and -alkyl-cycloalkyl, wherein each said alkyl, heteroalkyl, cycloalkyl, and -alkyl-cycloalkyl is optionally substituted with one or more halogen;

s is 0 or 1;

when s is 0, then Y is absent and X is selected from the group consisting of $-C(R^{1X})_2-$, -O-, -S-, -S(O)-, and $-S(O)_2-$, and

when s is 1, then X is selected from the group consisting of $-C(R^{1X})_2-$, -O-, -S-, -S(O)-, and $-S(O)_2-$, and Y is $-C(R^{1Y})_2-$,

or, alternatively, when s is 1, then X is $-C(R^{1X})_2-$ and Y is selected from the group consisting of $-C(R^{1Y})_2-$, -O-, -S-, -S(O)-, and $-S(O)_2-$;

each R^{1X} (when present) is independently selected from the group consisting of: H, halogen, alkyl, heteroalkyl, and cycloalkyl,

wherein said alkyl, heteroalkyl, and cycloalkyl are each optionally independently unsubstituted or substituted with one or more halogen;

each R^{1Y} (when present) is independently selected from the group consisting of: H, halogen, alkyl, heteroalkyl, and cycloalkyl,

wherein said alkyl, heteroalkyl, and cycloalkyl are each optionally independently unsubstituted or substituted with one or more halogen;

ring A is selected from the group consisting of aryl and heteroaryl;

m is 0 or more;

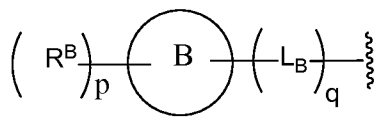
each R^A (when present) is independently selected from the group consisting of: halogen, -OH, -CN, $-SF_5$, $-OSF_5$, $-Si(R^{5A})_3$, $-N(R^{6A})_2$, $-OR^{6A}$, $-SR^{6A}$, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, and -alkyl-heterocycloalkyl,

wherein said alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, and -alkyl-heterocycloalkyl of R^A are each optionally independently unsubstituted or substituted with one or more groups independently selected from R^8;

n is 0 or 1;

$-L_1-$ represents a bond or a divalent moiety selected from the group consisting of -alkyl-, -haloalkyl-, -heteroalkyl-, -alkenyl-, -alkynyl-, -NHC(O)-, -C(O)NH-, -C(S)NH-, -NHC(S)-, -NH-, $-NHS(O)_2-$, $-S(O)_2NH-$, $-O-CH_2-$, $-CH_2-O-$, $-NHCH_2-$, and $-CH_2NH-$;

R^L is selected from the group consisting of alkyl and heteroalkyl, wherein said alkyl and heteroalkyl of R^L are each optionally unsubstituted or substituted with one or more halogen;

or, alternatively, R^L is a moiety having the formula 

,

wherein q is 0 or 1;

$-L_B-$ (when present) is a divalent moiety selected from the group consisting of lower alkyl and lower heteroalkyl, wherein each said lower alkyl and lower heteroalkyl is optionally substituted with one or more halogen;

ring B is selected from the group consisting of aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

p is 0 or more; and

each R^B (when present) is independently selected from the group consisting of: halogen, oxo, -OH, -CN, $-SF_5$, $-OSF_5$, $-Si(R^{5B})_3$, $-N(R^{6B})_2$, $-NR^{7B}C(O)R^{6B}$, $–NR^7S(O)_2R^{6B}$, $-NR^{7B}S(O)_2N(R^{6B})_2$, $–NR^{7B}C(O)N(R^{6B})_2$, $-NR^{7B}C(O)OR^{6B}$, $-C(O)R^{6B}$, $-C(O)OR^{6B}$, $-C(O)N(R^{6B})_2$, $-S(O)R^{6B}$, $-S(O)_2R^{6B}$, $-S(O)_2N(R^{6B})_2$, $-OR^{6B}$, $-SR^{6B}$, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, –alkyl-heterocycloalkyl, aryl, -alkyl-aryl, heteroaryl, and -alkyl-heteroaryl,

wherein said alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, –alkyl-heterocycloalkyl, aryl, -alkyl-aryl, heteroaryl, and -alkyl-heteroaryl of R^B are each optionally independently unsubstituted or substituted with one or more groups independently selected from R^9;

each R^{5X}, R^{5Y}, R^{5A}, R^{5B}, and R^{5C} (when present) is independently selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, -alkyl-heterocycloalkyl,

wherein each said alkyl, heteroalkyl, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, -alkyl-heterocycloalkyl of R^{5X}, R^{5Y}, R^{5A}, R^{5B}, and R^{5C} is unsubstituted or substituted with one or more halogen;

each R^{6X}, R^{6Y}, R^{6A} and R^{6C} (when present) is independently selected from the group consisting of H, alkyl, -alkyl-OH, alkenyl, alkynyl, heteroalkyl, -heteroalkyl-OH, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, and -alkyl-heterocycloalkyl,

wherein each said alkyl, -alkyl-OH, alkenyl, alkynyl, heteroalkyl, -heteroalkyl-OH, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, -alkyl-heterocycloalkyl, aryl, -alkyl-aryl, heteroaryl, and -alkyl-heteroaryl of R^{6X}, R^{6Y}, R^{6A} and R^{6C} is unsubstituted or substituted with one or more groups independently selected from halogen, alkyl, cycloalkyl, heteroalkyl, haloalkyl, alkoxy, heteroalkoxy, and haloalkoxy;

each R^{6B} (when present) is independently selected from the group consisting of H, alkyl, -alkyl-OH, alkenyl, alkynyl, heteroalkyl, -heteroalkyl-OH, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, -alkyl-heterocycloalkyl, aryl, -alkyl-aryl, heteroaryl, and -alkyl-heteroaryl,

wherein each said alkyl, -alkyl-OH, alkenyl, alkynyl, heteroalkyl, -heteroalkyl-OH, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, -alkyl-heterocycloalkyl, aryl, -alkyl-

aryl, heteroaryl, and -alkyl-heteroaryl of R^{6B} is unsubstituted or substituted with one or more groups independently selected from halogen, alkyl, cycloalkyl, heteroalkyl, haloalkyl, alkoxy, heteroalkoxy, and haloalkoxy;

each R^{7X}, R^{7Y}, R^{7A}, R^{7B}, and R^{7C} (when present) is independently selected from the group consisting of H, alkyl, heteroalkyl, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, and -alkyl-heterocycloalkyl,

wherein each said alkyl, heteroalkyl, -heteroalkyl-OH, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, and -alkyl-heterocycloalkyl of R^{7X}, R^{7Y}, R^{7A}, R^{7B}, and R^{7C} is unsubstituted or substituted with one or more halogen;

each R^8 (when present) is independently selected from the group consisting of halogen, lower alkyl, lower heteroalkyl, lower alkoxy, lower cycloalkyl, and lower heterocycloalkyl, wherein each said lower alkyl, lower heteroalkyl, lower alkoxy, lower cycloalkyl, and lower heterocycloalkyl of R^8 is optionally substituted with halogen; and

each R^9 (when present) is independently selected from the group consisting of halogen, -OH, -CN, $-SF_5$, $-OSF_5$, alkyl, -alkyl-OH, heteroalkyl, -heteroalkyl-OH, alkoxy, -O-heteroalkyl, cycloalkyl, -alkyl-cycloalkyl, -O-cycloalkyl, -O-alkyl-cycloalkyl, -heterocycloalkyl, -alkyl-heterocycloalkyl, -O-heterocycloalkyl and -O-alkyl-heterocycloalkyl, wherein each said alkyl, -alkyl-OH, heteroalkyl, -heteroalkyl-OH, alkoxy, -O-heteroalkyl, cycloalkyl, -alkyl-cycloalkyl, -O-cycloalkyl, -O-alkyl-cycloalkyl, -heterocycloalkyl, -alkyl-heterocycloalkyl, -O-heterocycloalkyl and -O-alkyl-heterocycloalkyl are optionally substituted with one or more halogen.

In other embodiments, the invention provides compositions, including pharmaceutical compositions, comprising one or more compounds of the invention (e.g., one compound of the invention), or a tautomer thereof, or a pharmaceutically acceptable salt or solvate of said compound(s) and/or said tautomer(s), optionally together with one or more additional therapeutic agents, optionally in an acceptable (e.g., pharmaceutically acceptable) carrier or diluent.

In other embodiments, the invention provides various methods of treating, preventing, ameliorating, and/or delaying the onset of an Aβ pathology and/or a symptom or symptoms thereof, comprising administering a composition comprising an effective amount of one or more compounds of the invention, or a tautomer thereof, or pharmaceutically acceptable salt or solvate of said compound(s) and/or said tautomer(s), to a patient in need thereof. Such

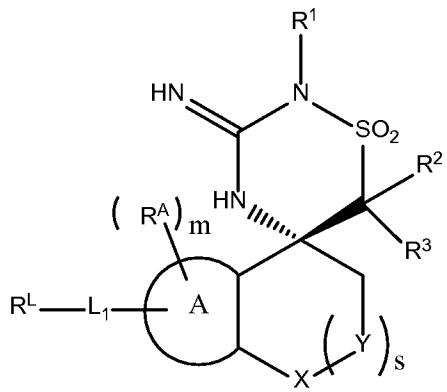
methods optionally additionally comprise administering an effective amount of one or more additional therapeutic agents, simultaneously or sequentially, suitable for treating the patient being treated.

These and other embodiments of the invention, which are described in detail below or will become readily apparent to those of ordinary skill in the art, are included within the scope of the invention.

DETAILED DESCRIPTION

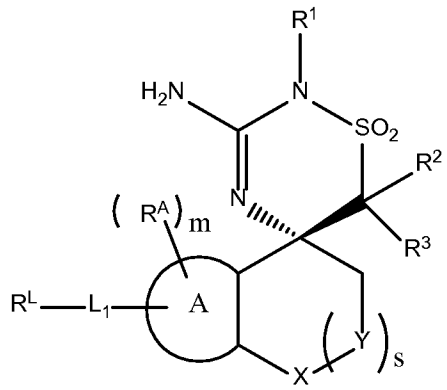
For each of the following embodiments, any variable not explicitly defined in the embodiment is as defined in Formula (I) or (IA). In each of the embodiments described herein, each variable is selected independently of the other unless otherwise noted.

In one embodiment, the compounds of the invention have the structural Formula (IA):



(IA)

or a tautomer thereof having the structural Formula (I'):



(IA')

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined in Formula (I).

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^1 is selected from the group consisting of H, methyl, ethyl, cyclopropyl, -CH_2-cyclopropyl, and -$CH_2CH_2OCH_3$.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^1 is selected from the group consisting of H and methyl.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^1 is methyl.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^2 is selected from the group consisting of H, fluoro, methyl, ethyl, propyl, butyl, cyclopropyl, -CH_2-cyclopropyl, and -CH_2OCH_3.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^2 is selected from the group consisting of H and methyl.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^2 is H.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^3 is selected from the group consisting of H, fluoro, methyl, ethyl, propyl, butyl, cyclopropyl, -CH_2-cyclopropyl, and -CH_2OCH_3.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^3 is selected from the group consisting of H and methyl.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^3 is H.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^2 is selected from the group consisting of of H, fluoro, methyl, ethyl, propyl, butyl, cyclopropyl, -CH_2-cyclopropyl, and -CH_2OCH_3; and R^3 is H.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^2 is selected from the group consisting of H and methyl; and R^3 is H.

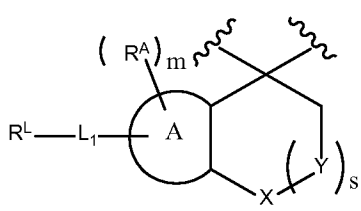
In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^2 is H; and R^3 is H.

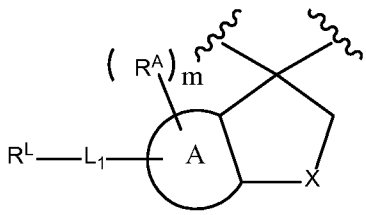
In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^1 is methyl; R^2 is H; and R^3 is H.

In some embodiments, s is 0 and Y is absent. In these embodiments, the moiety:



has the formula:



.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

s is 0;

Y is absent; and

X is selected from the group consisting of $-C(R^{1X})_2-$ and -O-,

wherein each R^{1X} (when present) is independently selected from the group consisting of H, halogen, lower alkyl, and lower heteroalkyl, wherein said lower alkyl and lower heteroalkyl are each optionally independently unsubstituted or substituted with one or more halogen.

In an alternative of the immediately preceding embodiment, each R^{1X} (when present) is independently selected from the group consisting of H, fluoro, methyl, ethyl, $-CF_3$, $-CHF_2$, and $-CH_2F$.

In another alternative of the immediately preceding embodiment, each R^{1X} (when present) is H.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

s is 1;

X is selected from the group consisting of $-C(R^{1X})_2-$, and -O-;

Y is $-C(R^{1Y})_2-$;

R^{1X} (when present) is independently selected from the group consisting of H, halogen, lower alkyl, and lower heteroalkyl, wherein said lower alkyl and lower heteroalkyl are each optionally independently unsubstituted or substituted with one or more halogen; and

R^{1Y} is H.

In an alternative of the immediately preceding embodiment, each R^{1X} (when present) is selected from the group consisting of H, methyl, ethyl, $-CF_3$, $-CHF_2$, and $-CH_2F$.

In another alternative of the immediately preceding embodiment, each R^{1X} (when present) is H.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

s is 1;

X is $–C(R^{1X})_2$-; and

Y is selected from the group consisting of $-C(R^{1Y})_2$- and -O-;

each R^{1X} is independently selected from the group consisting of H, halogen, lower alkyl, and lower heteroalkyl, wherein said lower alkyl and lower heteroalkyl are each optionally independently unsubstituted or substituted with one or more halogen; and

each R^{1Y} (when present) is H.

In an alternative of the immediately preceding embodiment, each R^{1X} (when present) is selected from the group consisting of H, methyl, ethyl, $-CF_3$, $-CHF_2$, and $-CH_2F$.

In another alternative of the immediately preceding embodiment, each R^{1X} is H.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

X is -O-; and

Y is $-C(R^{1Y})_2$-,

wherein each R^{1Y} is independently selected from the group consisting of H, lower alkyl, and lower heteroalkyl, wherein said lower alkyl and lower heteroalkyl are each optionally independently unsubstituted or substituted with one or more halogen.

In an alternative of the immediately preceding embodiment, each R^{1Y} is selected from the group consisting of H, methyl, ethyl, $-CF_3$, $-CHF_2$, and $-CH_2F$.

In another alternative of the immediately preceding embodiment, each R^{1Y} is H.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

X is - $C(R^{1X})_2$-; and

Y is -O-,

wherein each R^{1X} is independently selected from the group consisting of H, lower alkyl, and lower heteroalkyl, wherein said lower alkyl and lower heteroalkyl are each optionally independently unsubstituted or substituted with one or more halogen.

In an alternative of the immediately preceding embodiment, each R^{1X} is selected from the group consisting of H, methyl, ethyl, $-CF_3$, $-CHF_2$, and $-CH_2F$.

In another alternative of the immediately preceding embodiment, each R^{1X} is H.

The following alternatives of ring A are applicable to any of the embodiments described hereinabove.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

ring A is selected from the group consisting of phenyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, thienyl, and triazinyl.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

ring A is selected from the group consisting of phenyl, pyridyl, pyrimidinyl, pyrazinyl, and thienyl.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

ring A is selected from the group consisting of phenyl, pyridyl, and thienyl.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

ring A is selected from the group consisting of phenyl and pyridyl.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

ring A is phenyl.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

each R^A (when present) is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-NHCH_3$, $-N(CH_3)_2$, $-OCH_3$, $-OCH_2CH_3$, -O-cyclopropyl, $-O-CH_2$-cyclopropyl, $-CH_2OCH_3$, $-S(CH_3)$, methyl, ethyl, cyclopropyl, $-CH_2$-cyclopropyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, and $-OCHF_2$.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

each R^A (when present) is independently selected from the group consisting of fluoro, chloro, bromo, -CN, $-OCH_3$, $-CH_2OCH_3$, methyl, cyclopropyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, and $-OCHF_2$.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

each R^A (when present) is independently selected from the group consisting of fluoro, chloro, -CN, $-OCH_3$, $-CH_2OCH_3$, methyl, cyclopropyl, $-CF_3$, $-CHF_2$, and $-CH_2F$.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

ring A is selected from the group consisting of phenyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, thienyl, and triazinyl;

m is 0, 1, or 2; and

each R^A (when present) is independently selected from the group consisting of halogen, -CN, -SF_5, -$NHCH_3$, -$N(CH_3)_2$, -OCH_3, -OCH_2CH_3, -O-cyclopropyl, -O-CH_2-cyclopropyl, -CH_2OCH_3, -$S(CH_3)$, methyl, ethyl, cyclopropyl, -CH_2-cyclopropyl, -CF_3, -CHF_2, -CH_2F, -OCF_3, and -$OCHF_2$.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

ring A is selected from the group consisting of phenyl, pyridyl, pyrimidinyl, pyrazinyl, and thienyl;

m is 0 or 1; and

each R^A (when present) is independently selected from the group consisting of fluoro, chloro, bromo, -CN, -OCH_3, -CH_2OCH_3, methyl, cyclopropyl, -CF_3, -CHF_2, -CH_2F, -OCF_3, and -$OCHF_2$.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

ring A is selected from the group consisting of phenyl, pyridyl, and thienyl;

m is 0 or 1; and

each R^A (when present) is independently selected from the group consisting of fluoro, chloro, -CN, -OCH_3, -CH_2OCH_3, methyl, cyclopropyl, -CF_3, -CHF_2, and -CH_2F.

It shall be understood that the phrase "m is 0 or more" means m is an integer from 0 up to the number that corresponds to the maximum number of substitutable hydrogen atoms of the ring to which R^A is shown attached.

Thus, in embodiments wherein ring A is a moiety having 4 substitutable hydrogen atoms, m is 0, 1, 2, 3, or 4. In an alternative of such embodiments wherein ring A is a moiety having 4 substitutable hydrogen atoms, m is 0, 1, 2, or 3. In an alternative of such embodiments wherein ring A is a moiety having 4 substitutable hydrogen atoms, m is 0, 1, or 2. In an alternative of such embodiments wherein ring A is a moiety having 3 substitutable hydrogen atoms, m is 0 or 1. In alternative of such embodiments wherein ring A is a moiety having 3 substitutable hydrogen atoms, m is 0.

In embodiments wherein ring A is a moiety having 3 substitutable hydrogen atoms, m is 0, 1, 2, or 3. In an alternative of such embodiments wherein ring A is a moiety having 3 substitutable hydrogen atoms, m is 0, 1, or 2. In an alternative of such embodiments wherein

ring A is a moiety having 3 substitutable hydrogen atoms, m is 0 or 1. In alternative of such embodiments wherein ring A is a moiety having 3 substitutable hydrogen atoms, m is 0.

In embodiments wherein ring A is a moiety having 2 substitutable hydrogen atoms, m is 0, 1, or 2. In an alternative of such embodiments wherein ring A is a moiety having 2 substitutable hydrogen atoms, m is 0 or 1. In alternative of such embodiments wherein ring A is a moiety having 2 substitutable hydrogen atoms, m is 0.

In embodiments wherein ring A is a moiety having 1 substitutable hydrogen atom, m is 0 or 1. In an alternative of such embodiments wherein ring A is a moiety having 1 substitutable hydrogen atoms, m is 0.

The following alternatives of R^L are applicable to any of the embodiments described hereinabove.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^L is selected from the group consisting of lower alkyl and lower heteroalkyl, wherein said lower alkyl and lower heteroalkyl of R^L are each optionally unsubstituted or substituted with one or more halogen.

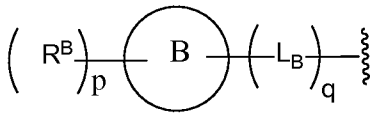
In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^L is selected from the group consisting of methyl, ethyl, propyl, butyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CF_3$, $-CF_2CH_3$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, $-CH_2SCH_3$, $-CH_2SCH_2CH_3$, $-CH_2CH_2SCH_3$, $-CH_2N(CH_3)_2$, $-CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2OCF_3$, and $-CH_2OCHF_2$.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'): R^L is selected from the group consisting of methyl, ethyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CF_3$, $-CF_2CH_3$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2SCH_3$, $-CH_2N(CH_3)_2$, $-CH_2OCF_3$, and $-CH_2OCHF_2$.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'): R^L is selected from the group consisting of methyl, ethyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CF_3$, $-CF_2CH_3$, $-CH_2OCH_3$, CH_2OCF_3, and $-CH_2OCHF_2$.

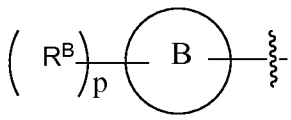
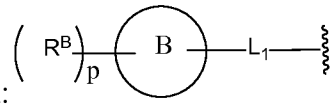
In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^L is a moiety having the formula 

,

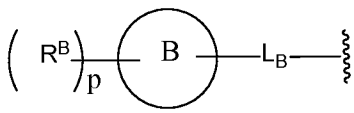
wherein q, L_B, ring B, p, and R^B are each as defined in Formula (I).

In some embodiments, in each of Formulas (I), (I'), (IA), and (IA'):

q is 0. In such embodiments, $-L_B-$ is absent; R^L is a moiety having the formula ; and ring B and $-L_1-$ are directly connected as shown: .

In some embodiments in each of Formulas (I), (I'), (IA), and (IA'):

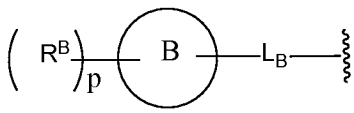
q is 1; and

R^L is a moiety having the formula , wherein:

$-L_B-$ is a divalent moiety selected from the group consisting of $-CH_2-$, $-CF_2-$, $-CH_2CH_2-$, $-CH_2O-$, and $-CF_2O-$.

In some embodiments in each of Formulas (I), (I'), (IA), and (IA'):

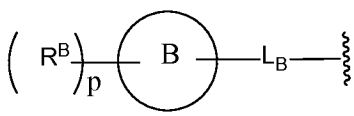
q is 1; and

R^L is a moiety having the formula , wherein:

$-L_B-$ is a divalent moiety selected from the group consisting of $-CH_2-$, $-CF_2-$, and $-CH_2CH_2-$.

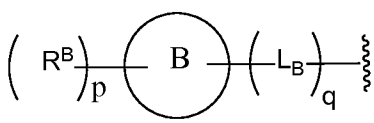
In some embodiments in each of Formulas (I), (I'), (IA), and (IA'):

q is 1; and

R^L is a moiety having the formula , wherein:

$-L_B-$ is $-CH_2-$.

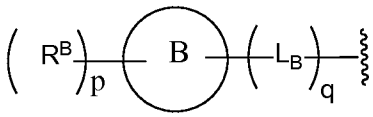
In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^L is a moiety having the formula , wherein:

ring B is selected from the group consisting of azetidinyl, benzimidazolyl, benzoisothiazolyl, benzoisoxazolyl, benzothiazolyl, benzoxazolyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropyl, dihydroindenyl, dihydrooxazolyl, furanyl, imidazolyl,

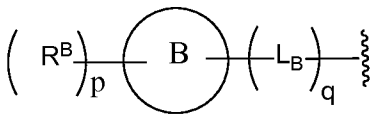
imidazopyridinyl, imidazopyrimidinyl, indenyl, indolyl, isothiazolyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolyl, oxetanyl, phenyl, piperazinyl, piperidinyl, pyrazinyl, pyrazolyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrazolopyridinyl, pyrrolidinyl, pyrrolyl, pyrrolopyridinyl, pyrrolopyrimidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, thienylpyridine, thiomorpholinyl, thiomorpholinyl dioxide, and triazolyl.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^L is a moiety having the formula , wherein:

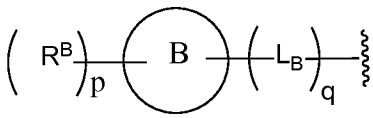
ring B is selected from the group consisting of cyclobutyl, cyclopropyl, furanyl, imidazopyridinyl, indolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, oxetanyl, phenyl, pyrazinyl, pyrazolyl, pyrazolopyridinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, tetrahydrofuranyl, tetrahydropyranyl, thiadiazolyl, thiazolyl, and thienyl.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^L is a moiety having the formula , wherein:

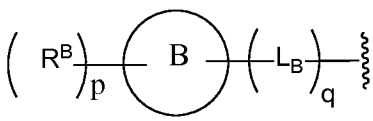
ring B is selected from the group consisting of furanyl, imidazopyridinyl, indolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, phenyl, pyrazinyl, pyrazolopyridinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, and thienyl.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^L is a moiety having the formula , wherein:

ring B is selected from the group consisting of imidazopyridinyl, isoxazolyl, oxadiazoyl, oxazolyl, phenyl, pyrazolopyridinyl, pyridinyl, pyrazinyl, pyrimidinyl,pyrazolyl, thiadiazolyl and thiazolyl.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

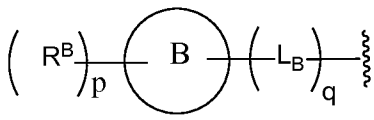
R^L is a moiety having the formula , wherein:

each R^B group (when present) is independently selected from the group consisting of halogen, oxo, -OH, -CN, $-SF_5$, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-N(CH_3)C(O)CH_3$,

-$NHS(O)_2CH_3$, -$N(CH_3)S(O)_2CH_3$, -$C(O)OCH_3$, -$C(O)OCH_2CH_3$, -$C(O)N(CH_3)_2$, -$C(O)NHCH_3$, -$S(O)_2CH_3$, -$S(O)_2N(CH_3)_2$, - $S(O)_2NHCH_3$, -OCH_3, -OCH_2CH_3, -O-cyclopropyl, -O-CH_2-cyclopropyl, $—OCH_2—C\equiv C—H$, $—OCH_2—C\equiv C—CH_3$, -$S(CH_3)$, methyl, ethyl, propyl, cyclopropyl, -CH_2-cyclopropyl, -CH_2OCH_3, -$CH_2OCH_2CH_3$, $—C\equiv CH$, $—C\equiv C—CH_3$, -CF_3, -CHF_2, -CH_2F, -OCF_3, -OCH_2CF_3, -$OCHF_2$, -OCH_2F, -OCH_2CH_2F, phenyl, pyridyl, oxadiazoyl, isoxazolyl, oxazolyl, and pyrrolyl,

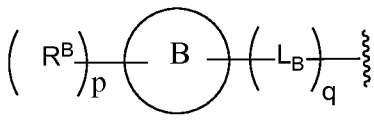
wherein each said phenyl, pyridyl, oxadiazoyl, isoxazolyl, oxazolyl, and pyrrolyl is optionally substituted with from 1 to 3 substituents independently selected from the group consisting of F, Cl, -CN, -CH_3, -OCH_3, and -CF_3.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^L is a moiety having the formula , wherein:

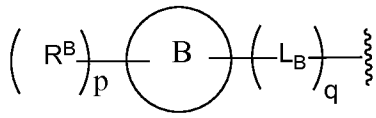
each R^B group (when present) is independently selected from the group consisting of fluoro, chloro, bromo, -OH, -CN, -SF_5, -NH_2, -$NH(CH_3)$, -$N(CH_3)_2$, -$NHC(O)CH_3$, -$N(CH_3)C(O)CH_3$, -$NHS(O)_2CH_3$, -$N(CH_3)S(O)_2CH_3$, -$C(O)OCH_3$, -$C(O)OCH_2CH_3$, -$C(O)N(CH_3)_2$, -$C(O)NHCH_3$, -$S(O)_2CH_3$, -$S(O)_2N(CH_3)_2$, - $S(O)_2NHCH_3$, -OCH_3, -OCH_2CH_3, -O-cyclopropyl, -O-CH_2-cyclopropyl, $—OCH_2—C\equiv C—H$, $—OCH_2—C\equiv C—CH_3$, -$S(CH_3)$, methyl, ethyl, propyl, cyclopropyl, -CH_2-cyclopropyl, -CH_2OCH_3, -$CH_2OCH_2CH_3$, $—C\equiv CH$, $—C\equiv C—CH_3$, -CF_3, -CHF_2, -CH_2F, -OCF_3, -OCH_2CF_3, -$OCHF_2$, -OCH_2F, and -OCH_2CH_2F.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^L is a moiety having the formula , wherein:

each R^B group (when present) is independently selected from the group consisting of fluoro, chloro, bromo, -CN, -$S(O)_2CH_3$, -OCH_3, -O-cyclopropyl, -O-CH_2-cyclopropyl, $—OCH_2—C\equiv C—H$, $—OCH_2—C\equiv C—CH_3$, methyl, cyclopropyl, -CH_2-cyclopropyl, -CH_2OCH_3, $—C\equiv CH$, $—C\equiv C—CH_3$, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, and -OCH_2CH_2F.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^L is a moiety having the formula , wherein:

q is 0 or 1;

$-L_B-$ (when present) is a divalent moiety selected from the group consisting of $-CH_2-$, $-CF_2-$, $-CH_2CH_2-$, $-CH_2O-$, and $-CF_2O-$;

ring B is selected from the group consisting of azetidinyl, benzimidazolyl, benzoisothiazolyl, benzoisoxazolyl, benzothiazolyl, benzoxazolyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropyl, dihydroindenyl, dihydrooxazolyl, furanyl, imidazolyl, imidazopyridinyl, imidazopyrimidinyl, indenyl, indolyl, isothiazolyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolyl, oxetanyl, phenyl, piperazinyl, piperidinyl, pyrazinyl, pyrazolyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrazolopyridinyl, pyrrolidinyl, pyrrolyl, pyrrolopyridinyl, pyrrolopyrimidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, thienylpyridine, thiomorpholinyl, thiomorpholinyl dioxide, and triazolyl;

p is 0 or more; and

each R^B group (when present) is independently selected from the group consisting of halogen, oxo, -OH, -CN, $-SF_5$, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-N(CH_3)C(O)CH_3$, $-NHS(O)_2CH_3$, $-N(CH_3)S(O)_2CH_3$, $-C(O)OCH_3$, $-C(O)OCH_2CH_3$, $-C(O)N(CH_3)_2$, $-C(O)NHCH_3$, $-S(O)_2CH_3$, $-S(O)_2N(CH_3)_2$, $-S(O)_2NHCH_3$, $-OCH_3$, $-OCH_2CH_3$, -O-cyclopropyl, $-O-CH_2$-cyclopropyl, $—OCH_2—C\equiv C—H$, $—OCH_2—C\equiv C—CH_3$, $-S(CH_3)$, methyl, ethyl, propyl, cyclopropyl, $-CH_2$-cyclopropyl, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $—C\equiv CH$, $—C\equiv C—CH_3$, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCH_2CF_3$, $-OCHF_2$, $-OCH_2F$, $-OCH_2CH_2F$, phenyl, pyridyl, oxadiazoyl, isoxazolyl, oxazolyl, and pyrrolyl,

wherein each said phenyl, pyridyl, oxadiazoyl, isoxazolyl, oxazolyl, and pyrrolyl is optionally substituted with from 1 to 3 substituents independently selected from the group consisting of F, Cl, CN, $-CH_3$, $-OCH_3$, and $-CF_3$.

In an alternative of the immediately preceding embodiment, q is 0.

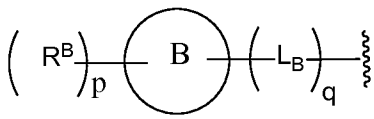
In another alternative of the immediately preceding embodiment, q is 1; and

$-L_B-$ is a divalent moiety selected from the group consisting of $-CH_2-$, $-CF_2-$, and $-CH_2CH_2-$.

In another alternative of the immediately preceding embodiment, q is 1; and

-L_B- is -CH_2-.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

R^L is a moiety having the formula , wherein:

q is 0 or 1;

-L_B- (when present) is a divalent moiety selected from the group consisting of -CH_2-, -CF_2-, -CH_2CH_2-, -CH_2O-, and -CF_2O-;

ring B is selected from the group consisting of cyclobutyl, cyclopropyl, furanyl, imidazopyridinyl, indolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, oxetanyl, phenyl, pyrazinyl, pyrazolyl, pyrazolopyridinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, tetrahydrofuranyl, tetrahydropyranyl, thiadiazolyl, thiazolyl, and thienyl;

p is 0 or more; and

each R^B group (when present) is independently selected from the group consisting of fluoro, chloro, bromo, -OH, -CN, -SF_5, -NH_2, -$NH(CH_3)$, -$N(CH_3)_2$, -$NHC(O)CH_3$, -$N(CH_3)C(O)CH_3$, -$NHS(O)_2CH_3$, -$N(CH_3)S(O)_2CH_3$, -$C(O)OCH_3$, -$C(O)OCH_2CH_3$, -$C(O)N(CH_3)_2$, -$C(O)NHCH_3$, -$S(O)_2CH_3$, -$S(O)_2N(CH_3)_2$, - $S(O)_2NHCH_3$, -OCH_3, -OCH_2CH_3, -O-cyclopropyl, -O-CH_2-cyclopropyl, $—OCH_2—C\equiv C—H$, $—OCH_2—C\equiv C—CH_3$, -$S(CH_3)$, methyl, ethyl, propyl, cyclopropyl, -CH_2-cyclopropyl, -CH_2OCH_3, -$CH_2OCH_2CH_3$, $—C\equiv CH$, $—C\equiv C—CH_3$, -CF_3, -CHF_2, -CH_2F, -OCF_3, -OCH_2CF_3, -$OCHF_2$, -OCH_2F, and -OCH_2CH_2F.

In an alternative of the immediately preceding embodiment, q is 0.

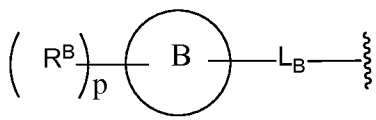
In another alternative of the immediately preceding embodiment, q is 1; and

-L_B- is a divalent moiety selected from the group consisting of -CH_2-, -CF_2-, and -CH_2CH_2-.

In another alternative of the immediately preceding embodiment, q is 1; and

-L_B- is -CH_2-.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

q is 1; and R^L is a moiety having the formula , wherein:

$-L_B-$ is a divalent moiety selected from the group consisting of $-CH_2-$, $-CF_2-$, and $-CH_2CH_2-$;

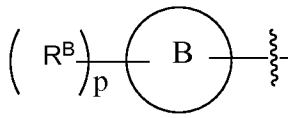
ring B is selected from the group consisting of furanyl, imidazopyridinyl, indolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, phenyl, pyrazinyl, pyrazolopyridinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, and thienyl;

p is 0 or more; and

each R^B group (when present) is independently selected from the group consisting of fluoro, chloro, bromo, -CN, $-S(O)_2CH_3$, $-OCH_3$, -O-cyclopropyl, $-O-CH_2$-cyclopropyl, $—OCH_2—C\equiv C—H$, $—OCH_2—C\equiv C—CH_3$, methyl, cyclopropyl, $-CH_2$-cyclopropyl, $-CH_2OCH_3$, $—C\equiv C—CH_3$, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-OCH_2CH_2F$.

In an alternative of the immediately preceding embodiment, $-L_B-$ is $-CH_2-$.

In one embodiment, in each of Formulas (I), (I'), (IA), and (IA'):

q is 0; and R^L is a moiety having the formula 

, wherein:

ring B is selected from the group consisting of imidazopyridinyl, isoxazolyl, oxadiazoyl, oxazolyl, phenyl, pyrazolopyridinyl, pyridinyl, pyrazinyl, pyrimidinyl,pyrazolyl, thiadiazolyl and thiazolyl;

p is 0 or more; and

each R^B group (when present) is independently selected from the group consisting of fluoro, chloro, bromo, -CN, $-S(O)_2CH_3$, $-OCH_3$, -O-cyclopropyl, $-O-CH_2$-cyclopropyl, $—OCH_2—C\equiv C—H$, $—OCH_2—C\equiv C—CH_3$, methyl, cyclopropyl, $-CH_2$-cyclopropyl, $-CH_2OCH_3$, $—C\equiv CH$, $—C\equiv C—CH_3$, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-OCH_2CH_2F$.

It shall be understood that the phrase "p is 0 or more" means p is an integer from 0 up to the number that corresponds to the maximum number of substitutable hydrogen atoms of the ring to which R^B is shown attached.

Thus, in embodiments wherein ring B is a moiety having 4 substitutable hydrogen atoms, p is 0, 1, 2, 3, or 4. In an alternative of such embodiments wherein ring B is a moiety having 4 substitutable hydrogen atoms, p is 0, 1, 2, or 3. In an alternative of such embodiments wherein ring B is a moiety having 4 substitutable hydrogen atoms, p is 0, 1, or 2. In an alternative of such embodiments wherein ring B is a moiety having 3 substitutable

hydrogen atoms, p is 0 or 1. In alternative of such embodiments wherein ring B is a moiety having 3 substitutable hydrogen atoms, p is 0.

In embodiments wherein ring B is a moiety having 3 substitutable hydrogen atoms, p is 0, 1, 2, or 3. In an alternative of such embodiments wherein ring B is a moiety having 3 substitutable hydrogen atoms, p is 0, 1, or 2. In an alternative of such embodiments wherein ring B is a moiety having 3 substitutable hydrogen atoms, p is 0 or 1. In alternative of such embodiments wherein ring B is a moiety having 3 substitutable hydrogen atoms, p is 0.

In embodiments wherein ring B is a moiety having 2 substitutable hydrogen atoms, p is 0, 1, or 2. In an alternative of such embodiments wherein ring B is a moiety having 2 substitutable hydrogen atoms, p is 0 or 1. In alternative of such embodiments wherein ring B is a moiety having 2 substitutable hydrogen atoms, p is 0.

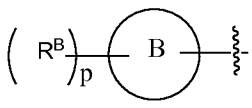
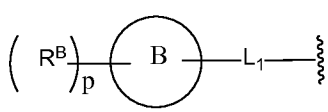
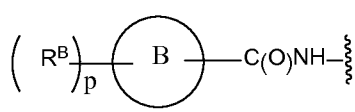
In embodiments wherein ring B is a moiety having 1 substitutable hydrogen atom, p is 0 or 1. In an alternative of such embodiments wherein ring B is a moiety having 1 substitutable hydrogen atoms, p is 0.

In an alternative of each of the embodiments described herein, $-L_1-$ is selected from the group consisting of -C(O)NH-, -NHC(O)-, -C(S)NH-, -NHC(S)-, -NH-, -O-CH_2-, -CH_2-O-, -NHCH_2-, and -CH_2NH-.

In another alternative of each of the embodiments described herein, $-L_1-$ is selected from the group consisting of -C(O)NH-, -NHC(O)-, -C(S)NH-, -NHC(S)-, -NH-, -O-CH_2-, and -CH_2-O-.

In another alternative of each of the embodiments described herein, $-L_1-$ is selected from the group consisting of -C(O)NH-, and -NHC(O)-.

In another alternative of each of the embodiments described herein, $-L_1-$ is -C(O)NH-.

As noted above, $-L_1-$ (and $-L_B-$ when present) represents a divalent moiety. The orientation of such divalent moieties in the formula is the same as the orientation of the moiety as written. Thus, when $-L_1-$ is a -C(O)NH- group, the moiety R^L-L_1- has the formula: R^L-C(O)NH-. For example, when R^L is the moiety  and $-L_1-$ is a -C(O)NH- group, the moiety  has the formula: .

Specific non-limiting examples of compounds of the invention are shown in the tables of examples below. While only one tautomeric form of each compound is shown in the tables, it shall be understood that all tautomeric forms of the compounds are contemplated as being within the scope of the non-limiting examples.

In another embodiment, 1 to 3 carbon atoms of the compounds of the invention may be replaced with 1 to 3 silicon atoms so long as all valency requirements are satisfied.

In another embodiment, there is provided a composition comprising a compound of the invention and a pharmaceutically acceptable carrier or diluent.

Another embodiment provides a composition comprising a compound of the invention, either as the sole active agent, or optionally in combination with one or more additional therapeutic agents, and a pharmaceutically acceptable carrier or diluent. Non-limiting examples of additional therapeutic agents which may be useful in combination with the compounds of the invention include those selected from the group consisting of: (a) drugs that may be useful for the treatment of Alzheimer's disease and/or drugs that may be useful for treating one or more symptoms of Alzheimer's disease, (b) drugs that may be useful for inhibiting the synthesis Aβ, (c) drugs that may be useful for treating neurodegenerative diseases, and (d) drugs that may be useful for the treatment of type II diabetes and/or one or more symptoms or associated pathologies thereof.

Non-limiting examples of additional therapeutic agents which may be useful in combination with the compounds of the invention include drugs that may be useful for the treatment, prevention, delay of onset, amelioration of any pathology associated with Aβ and/or a symptom thereof. Non-limiting examples of pathologies associated with Aβ include: Alzheimer's Disease, Down's syndrome, Parkinson's disease, memory loss, memory loss associated with Alzheimer's disease, memory loss associated with Parkinson's disease, attention deficit symptoms, attention deficit symptoms associated with Alzheimer's disease ("AD"), Parkinson's disease, and/orDown's syndrome, dementia, stroke, microgliosis and brain inflammation, pre-senile dementia, senile dementia, dementia associated with Alzheimer's disease, Parkinson's disease, and/or Down's syndrome, progressive supranuclear palsy, cortical basal degeneration, neurodegeneration, olfactory impairment, olfactory impairment associated with Alzheimer's disease, Parkinson's disease, and/or Down's syndrome, β-amyloid angiopathy, cerebral amyloid angiopathy, hereditary cerebral hemorrhage, mild cognitive impairment ("MCI"), glaucoma, amyloidosis, type II diabetes,

hemodialysis complications (from β_2 microglobulins and complications arising therefrom in hemodialysis patients), scrapie, bovine spongiform encephalitis, and Creutzfeld-Jakob disease, comprising administering to said patient at least one compound of the invention, or a tautomer or isomer thereof, or pharmaceutically acceptable salt or solvate of said compound or said tautomer, in an amount effective to inhibit or treat said pathology or pathologies.

Non-limiting examples of additional therapeutic agents for that may be useful in combination with compounds of the invention include: muscarinic antagonists (e.g., m_1 agonists (such as acetylcholine, oxotremorine, carbachol, or McNa343), or m_2 antagonists (such as atropine, dicycloverine, tolterodine, oxybutynin, ipratropium, methoctramine, tripitamine, or gallamine)); cholinesterase inhibitors (e.g., acetyl- and/or butyrylchlolinesterase inhibitors such as donepezil (Aricept®, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 H -inden-1-one hydrochloride), galantamine (Razadyne®), and rivastigimine (Exelon®); N-methyl-D-aspartate receptor antagonists (e.g., Namenda® (memantine HCl, available from Forrest Pharmaceuticals, Inc.); combinations of cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists; gamma secretase modulators; gamma secretase inhibitors; non-steroidal anti-inflammatory agents; anti-inflammatory agents that can reduce neuroinflammation; anti-amyloid antibodies (such as bapineuzemab, Wyeth/Elan); vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists or CB1 receptor antagonists; antibiotics; growth hormone secretagogues; histamine H3 antagonists; AMPA agonists; PDE4 inhibitors; $GABA_A$ inverse agonists; inhibitors of amyloid aggregation; glycogen synthase kinase beta inhibitors; promoters of alpha secretase activity; PDE-10 inhibitors; Tau kinase inhibitors (e.g., GSK3beta inhibitors, cdk5 inhibitors, or ERK inhibitors); Tau aggregation inhibitors (e.g., Rember®); RAGE inhibitors (e.g., TTP 488 (PF-4494700)); anti-Abeta vaccine; APP ligands; agents that upregulate insulin, cholesterol lowering agents such as HMG-CoA reductase inhibitors (for example, statins such as Atorvastatin, Fluvastatin, Lovastatin, Mevastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin) and/or cholesterol absorption inhibitors (such as Ezetimibe), or combinations of HMG-CoA reductase inhibitors and cholesterol absorption inhibitors (such as, for example, Vytorin®); fibrates (such as, for example, clofibrate, Clofibride, Etofibrate, and Aluminium Clofibrate); combinations of fibrates and cholesterol lowering agents and/or cholesterol absorption inhibitors; nicotinic receptor agonists; niacin; combinations of niacin and cholesterol absorption inhibitors and/or

cholesterol lowering agents (e.g., Simcor® (niacin/simvastatin, available from Abbott Laboratories, Inc.); LXR agonists; LRP mimics; H3 receptor antagonists; histone deacetylase inhibitors; hsp90 inhibitors; 5-HT4 agonists (e.g., PRX-03140 (Epix Pharmaceuticals)); 5-HT6 receptor antagonists; mGluR1 receptor modulators or antagonists; mGluR5 receptor modulators or antagonists; mGluR2/3 antagonists; Prostaglandin EP2 receptor antagonists; PAI-1 inhibitors; agents that can induce Abeta efflux such as gelsolin; Metal-protein attenuating compound (e.g, PBT2); and GPR3 modulators; and antihistamines such as Dimebolin (e.g., Dimebon®, Pfizer).

Another embodiment provides a method of preparing a pharmaceutical composition comprising the step of admixing at least one compound of the invention or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

Another embodiment provides a method of inhibiting β-secretase comprising exposing a population of cells expressing β-secretase to at least one compound of the invention, or a tautomer thereof, in an amount effective to inhibit β-secretase. In one such embodiment, said population of cells is *in vivo*. In another such embodiment, said population of cells is *ex vivo*. In another such embodiment, said population of cells is *in vitro*.

Additional embodiments in which the compounds of the invention may be useful include: a method of inhibiting β-secretase in a patient in need thereof. A method of inhibiting the formation of Aβ from APP in a patient in need thereof. A method of inhibiting the formation of Aβ plaque and/or Aβ fibrils and/or Aβ oligomers and/or senile plaques and/or neurofibrillary tangles and/or inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), in a patient in need thereof. Each such embodiment comprises administering at least one compound of the invention, or a tautomer thereof, or pharmaceutically acceptable salt of said compound or said tautomer, in a therapeutically effective amount to inhibit said pathology or condition in said patient.

Additional embodiments in which the compounds of the invention may be useful include: a method of treating, preventing, and/or delaying the onset of one or more pathologies associated with Aβ and/or one or more symptoms of one or more pathologies associated with Aβ. Non-limiting examples of pathologies which may be associated with Aβ include: Alzheimer's Disease, Down's syndrome, Parkinson's disease, memory loss, memory loss associated with Alzheimer's disease, memory loss associated with Parkinson's disease,

attention deficit symptoms, attention deficit symptoms associated with Alzheimer's disease ("AD"), Parkinson's disease, and/orDown's syndrome, dementia, stroke, microgliosis and brain inflammation, pre-senile dementia, senile dementia, dementia associated with Alzheimer's disease, Parkinson's disease, and/or Down's syndrome, progressive supranuclear palsy, cortical basal degeneration, neurodegeneration, olfactory impairment, olfactory impairment associated with Alzheimer's disease, Parkinson's disease, and/or Down's syndrome, β-amyloid angiopathy, cerebral amyloid angiopathy, hereditary cerebral hemorrhage, mild cognitive impairment ("MCI"), glaucoma, amyloidosis, type II diabetes, hemodialysis complications (from β_2 microglobulins and complications arising therefrom in hemodialysis patients), scrapie, bovine spongiform encephalitis, and Creutzfeld-Jakob disease, said method(s) comprising administering to said patient in need thereof at least one compound of the invention, or a tautomer thereof, or pharmaceutically acceptable salt of said compound or said tautomer, in an amount effective to inhibit said pathology or pathologies.

Another embodiment in which the compounds of the invention may be useful includes a method of treating Alzheimer's disease, wherein said method comprises administering an effective (i.e., therapeutically effective) amount of one or more compounds of the invention (or a tautomer thereof, or pharmaceutically acceptable salt of said compound or said tautomer), optionally in further combination with one or more additional therapeutic agents which may be effective to treat Alzheimer's disease or a disease or condition associated therewith, to a patient in need of treatment. In embodiments wherein one or more additional therapeutic agents are administered, such agents may be administered sequentially or together. Non-limiting examples of associated diseases or conditions, and non-limiting examples of suitable additional therapeutically active agents, are as described above.

Another embodiment in which the compounds of the invention may be useful includes a method of treating mild cognitive impairment ("MCI"), wherein said method comprises administering an effective (i.e., therapeutically effective) amount of one or more compounds of the invention (or a tautomer thereof, or pharmaceutically acceptable salt of said compound or said tautomer) to a patient in need of treatment. In one such embodiment, treatment is commenced prior to the onset of symptoms.

Another embodiment in which the compounds of the invention may be useful includes a method of preventing, or alternatively of delaying the onset, of mild cognitive impairment or, in a related embodiment, of preventing or alternatively of delaying the onset of Alzheimer's

disease. In such embodiments, treatment can be initiated prior to the onset of symptoms, in some embodiments significantly before (e.g., from several months to several years before) the onset of symptoms to a patient at risk for developing MCI or Alzheimer's disease. Thus, such methods comprise administering, prior to the onset of symptoms or clinical or biological evidence of MCI or Alzheimer's disease (e.g., from several months to several yeards before, an effective (i.e., therapeutically effective), and over a period of time and at a frequency of dose sufficient for the therapeutically effective degree of inhibition of the BACE enzyme over the period of treatment, an amount of one or more compounds of the invention (or a tautomer thereof, or pharmaceutically acceptable salt of said compound or said tautomer) to a patient in need of treatment.

Another embodiment in which the compounds of the invention may be useful includes a method of treating Down's syndrome, comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of the invention (or a tautomer thereof, or pharmaceutically acceptable salt or solvate of said compound or said tautomer) to a patient in need of treatment.

Another embodiment in which the compounds of the invention may be useful includes a kit comprising, in separate containers, in a single package, pharmaceutical compositions for use in combination, wherein one container comprises an effective amount of a compound of the invention (or a tautomer thereof, or pharmaceutically acceptable salt of said compound or said tautomer) in a pharmaceutically acceptable carrier, and another container (i.e., a second container) comprises an effective amount of another pharmaceutically active ingredient, the combined quantities of the compound of the invention and the other pharmaceutically active ingredient being effective to: (a) treat Alzheimer's disease, or (b) inhibit the deposition of amyloid protein in, on or around neurological tissue (e.g., the brain), or (c) treat neurodegenerative diseases, or (d) inhibit the activity of BACE-1 and/or BACE-2.

In various embodiments, the compositions and methods disclosed above and below wherein the compound(s) of the invention is a compound or compounds selected from the group consisting of the exemplary compounds of the invention described herein.

In another embodiment, the invention provides methods of treating a disease or pathology, wherein said disease or pathology is Alzheimer's disease, olfactory impairment associated with Alzheimer's disease, Down's syndrome, olfactory impairment associated with Down's syndrome, Parkinson's disease, olfactory impairment associated with Parkinson's

disease, stroke, microgliosis brain inflammation, pre-senile dementia, senile dementia, progressive supranuclear palsy, cortical basal degeneration, β-amyloid angiopathy, cerebral amyloid angiopathy, hereditary cerebral hemorrhage, mild cognitive impairment, glaucoma, amyloidosis, type II diabetes, diabetes-associated amyloidogenesis, scrapie, bovine spongiform encephalitis, traumatic brain injury, or Creutzfeld-Jakob disease, said method comprising administering a compound of the invention, or a pharmaceutically acceptable salt of said compound or said tautomer, to a patient in need thereof in an amount effective to treat said disease or pathology.

In another embodiment, the invention provides for the use of any of the compounds of the invention for use as a medicament, or in medicine, or in therapy.

In another embodiment, the invention provides for use of a compound of the invention for the manufacture of a medicament for the treatment of a disease or pathology, wherein said disease or pathology is Alzheimer's disease, olfactory impairment associated with Alzheimer's disease, Down's syndrome, olfactory impairment associated with Down's syndrome, Parkinson's disease, olfactory impairment associated with Parkinson's disease, stroke, microgliosis brain inflammation, pre-senile dementia, senile dementia, progressive supranuclear palsy, cortical basal degeneration, β-amyloid angiopathy, cerebral amyloid angiopathy, hereditary cerebral hemorrhage, mild cognitive impairment, glaucoma, amyloidosis, type II diabetes, diabetes-associated amyloidogenesis, scrapie, bovine spongiform encephalitis, traumatic brain injury, or Creutzfeld-Jakob disease.

DEFINITIONS

The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names and chemical structures may be used interchangeably to describe that same structure. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence the definition of "alkyl" applies to "alkyl" as well as the "alkyl" protion of "hydroxyalkyl", "haloalkyl", arylalkyl-, alkylaryl-, "alkoxy" etc.

It shall be understood that, in the various embodiments of the invention described herein, any variable not explicitly defined in the context of the embodiment is as defined in Formula (I). All valences not explicitly filled are assumed to be filled by hydrogen.

"Patient" includes both human and non-human animals. Non-human animals include those research animals and companion animals such as mice, primates, monkeys, great apes, canine (*e.g.,* dogs), and feline (*e.g.,* house cats).

"Pharmaceutical composition" (or "pharmaceutically acceptable composition") means a composition suitable for administration to a patient. Such compositions may contain the neat compound (or compounds) of the invention or mixtures thereof, or salts, solvates, prodrugs, isomers, or tautomers thereof, or they may contain one or more pharmaceutically acceptable carriers or diluents. 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 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 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.

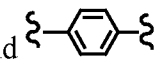
"Halogen" (or "halo") means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"Alkyl" means an aliphatic hydrocarbon group, which may be straight or branched, comprising 1 to about 10 carbon atoms. "Lower alkyl" means a straight or branched alkyl group comprising 1 to about 4 carbon atoms. 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, n-butyl, i-butyl, and t-butyl.

"Haloalkyl" means an alkyl as defined above wherein one or more hydrogen atoms on the alkyl is replaced by a halo group defined above.

"Heteroalkyl" means an alkyl moiety as defined above, which is substituted by one or more (e.g., one, two, or three) moieties independently selected from the group consisting of: -O-alkyl, -S-alkyl, -S(O)-alkyl, -$S(O)_2$-alkyl, -N(H)alkyl, and -$N(alkyl)_2$.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 10 carbon atoms in the straight or branched chain. Branched means that one or more lower alkyl groups such as methyl, ethyl propyl, ethenyl or propenyl are attached to a linear or branched alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkylene" means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. Non-limiting examples of alkylene include methylene, ethylene and propylene. More generally, the suffix "ene" on alkyl, aryl, hetercycloalkyl, etc. indicates a divalent moiety, e.g., $-CH_2CH_2-$ is ethylene, and  is para-phenylene.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 10 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, or lower alkenyl or lower alkynyl groups, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl.

"Alkenylene" means a difunctional group obtained by removal of a hydrogen from an alkenyl group that is defined above. Non-limiting examples of alkenylene include –CH=CH-, $-C(CH_3)=CH-$, and $–CH=CHCH_2-$.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl. "Monocyclic aryl" means phenyl.

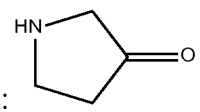
"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more substituents, which may be the same or different, as defined herein. The prefix aza, oxa or thia before the heteroaryl root name

means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. "Heteroaryl" may also include a heteroaryl as defined above fused to an aryl as defined above. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl (which alternatively may be referred to as thiophenyl), pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like. The term "monocyclic heteroaryl" refers to monocyclic versions of heteroaryl as described above and includes 4- to 7-membered monocyclic heteroaryl groups comprising from 1 to 4 ring heteroatoms, said ring heteroatoms being independently selected from the group consisting of N, O, and S, and oxides thereof. The point of attachment to the parent moiety is to any available ring carbon or ring heteroatom. Non-limiting examples of monocyclic heteroaryl moities include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, pyridoneyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, isoxazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl), imidazolyl, and triazinyl (e.g., 1,2,4-triazinyl), and oxides thereof.

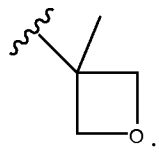
"Cycloalkyl" means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 3 to about 6 carbon atoms. The cycloalkyl can be optionally substituted with one or more substituents, which may be the same or different, as described herein. Monocyclic cycloalkyl refers to monocyclic versions of the cycloalkyl moieties described herein. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of multicyclic cycloalkyls include [1.1.1]-bicyclopentane, 1-decalinyl, norbornyl, adamantyl and the like.

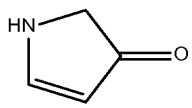
"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contain at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about

7 ring atoms. The cycloalkenyl can be optionally substituted with one or more substituents, which may be the same or different, as described herein. The term "monocyclic cycloalkenyl" refers to monocyclic versions of cycloalkenyl groups described herein and includes non-aromatic 3- to 7-membered monocyclic cycloalkyl groups which contains one or more carbon-carbon double bonds. Non-limiting examples include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohetpenyl, cyclohepta-1,3-dienyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

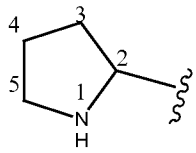
"Heterocycloalkyl" (or "heterocyclyl") means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more substituents, which may be the same or different, as described herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Thus, the term "oxide," when it appears in a definition of a variable in a general structure described herein, refers to the corresponding N-oxide, S-oxide, or S,S-dioxide. "Heterocyclyl" also includes rings wherein =O replaces two available hydrogens on the same carbon atom (i.e., heterocyclyl includes rings having a carbonyl group in the ring). Such =O groups may be referred to herein as "oxo." An example of such a moiety is pyrrolidinone (or pyrrolidone): 

. As used herein, the term "monocyclic heterocycloalkyl" refers monocyclic versions of the heterocycloalkyl moities decribed herein and include a 4- to 7-membered monocyclic heterocycloalkyl groups comprising from 1 to 4 ring heteroatoms, said ring heteroatoms being independently selected from the group consisting of N, N-oxide, O, S, S-oxide, S(O), and $S(O)_2$. The point of attachment to the parent moiety is to any available ring carbon or ring heteroatom. Non-limiting examples of monocyclic heterocycloalkyl groups include piperidyl, oxetanyl, pyrrolyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl,

tetrahydrothiophenyl, *beta* lactam, *gamma* lactam, *delta* lactam, *beta* lactone, *gamma* lactone, *delta lactone,* and pyrrolidinone, and oxides thereof. Non-limiting examples of lower alkyl-substituted oxetanyl include the moiety: .

"Heterocycloalkenyl" (or "heterocyclenyl") means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more substituents, which may be the same or different, as described herein. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable heterocyclenyl groups include 1,2,3,4-tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluorodihydrofuranyl, 7-oxabicyclo[2.2.1]heptenyl, dihydrothiophenyl, dihydrothiopyranyl, and the like. "Heterocyclenyl" also includes rings wherein =O replaces two available hydrogens on the same carbon atom (i.e., heterocyclyl includes rings having a carbonyl group in the ring). Example of such moiety is pyrrolidenone (or pyrrolone): . As used herein, the term "monocyclic heterocycloalkenyl" refers to monocyclic versions of the heterocycloalkenyl moities described herein and include 4- to 7-membered monocyclic heterocycloalkenyl groups comprising from 1 to 4 ring heteroatoms, said ring heteroatoms being independently selected from the group consisting of N, N-oxide, O, S, S-oxide, S(O), and $S(O)_2$. The point of attachment to the parent moiety is to any available ring carbon or ring heteroatom. Non-limiting examples of monocyclic heterocyloalkenyl groups include 1,2,3,4- tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-

dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluorodihydrofuranyl, dihydrothiophenyl, and dihydrothiopyranyl, and oxides thereof.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. 

, there is no -OH attached directly to carbons marked 2 and 5.

"Arylalkyl"(or "aralkyl") means an aryl-alkyl- group in which the aryl and alkyl are as previously described, except that in this context the "alkyl" portion of the "arylalkyl" (or "-alkyl-aryl") group refers to a straight or branched lower alkyl group. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl. The term (and similar terms) may be written as "arylalkyl-" (or as "–alkyl-aryl") to indicate the point of attachment to the parent moiety. Similarly, "heteroarylalkyl", "cycloalkylalkyl", "cycloalkenylalkyl", "heterocycloalkylalkyl", "heterocycloalkenylalkyl", etc., mean a heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, etc. as described herein bound to a parent moiety through an alkyl group. As indicated above, the "alkyl" group in this context represents a lower alkyl group, which may be straight or branched, or unsubstituted and/or substituted as described herein.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkylether" means a non-aromatic ring of 3 to 7 members comprising an oxygen atom and 2 to 7 carbon atoms. Ring carbon atoms can be substituted, provided that substituents adjacent to the ring oxygen do not include halo or substituents joined to the ring through an oxygen, nitrogen or sulfur atom.

"Cycloalkylalkyl" means a cycloalkyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkylalkyls include cyclohexylmethyl, adamantylmethyl, adamantylpropyl, and the like.

"Cycloalkenylalkyl" means a cycloalkenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkenylalkyls include cyclopentenylmethyl, cyclohexenylmethyl and the like.

"Heteroarylalkyl" means a heteroaryl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heteroaryls include 2-pyridinylmethyl, quinolinylmethyl and the like.

"Heterocyclylalkyl" (or "heterocycloalkylalkyl") means a heterocyclyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heterocyclylalkyls include piperidinylmethyl, piperazinylmethyl and the like.

"Heterocyclenylalkyl" means a heterocyclenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, *n*-propoxy, isopropoxy and *n*-butoxy. The bond to the parent moiety is through the ether oxygen.

"Alkyoxyalkyl" means a group derived from an alkoxy and alkyl as defined herein. The bond to the parent moiety is through the alkyl.

Any of the foregoing functional groups may be unsubstituted or substituted as described herein. The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution

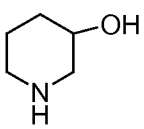
results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

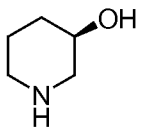
The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

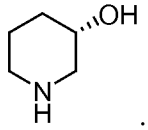
Substitution on a cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylfused cycloalkylalkyl- moiety or the like includes substitution on any ring portion and/or on the alkyl portion of the group.

When a variable appears more than once in a group, e.g., R^6 in $-N(R^6)_2$, or a variable appears more than once in a structure presented herein, the variables can be the same or different.

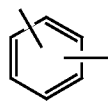
The line ——, as a bond generally indicates a mixture of, or either of, the possible isomers, e.g., containing (R)- and (S)- stereochemistry. For example:



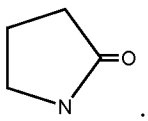
means containing both


and


.

The wavy line ∿∿∿, as used herein, indicates a point of attachment to the rest of the compound. Lines drawn into the ring systems, such as, for example: , indicate that the indicated line (bond) may be attached to any of the substitutable ring carbon atoms.

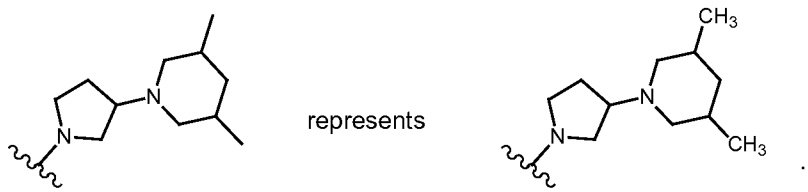
"Oxo" is defined as a oxygen atom that is double bonded to a ring carbon in a cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, or other ring described herein, e.g.,



.

In this specification, where there are multiple oxygen and/or sulfur atoms in a ring system, there cannot be any adjacent oxygen and/or sulfur present in said ring system.

As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom, unless stated otherwise. For example:



In another embodiment, the compounds of the invention, and/or compositions comprising them, are present in isolated and/or purified form. The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound (or a tautomer thereof, or pharmaceutically acceptable salt of said compound or said tautomer) after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization and the like), in sufficient purity to be suitable for in vivo or medicinal use and/or characterizable by standard analytical techniques described herein or well known to the skilled artisan.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

Those skilled in the art will recognize those instances in which the compounds of the invention may be converted to prodrugs and/or solvates, another embodiment of the present invention. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs 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. The term "prodrug" means a compound (e.g, a drug precursor) that is transformed *in vivo* to yield a compound of the invention or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible

Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms where they exist. "Solvate" means a physical association of a compound of the 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 ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

"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 above-noted diseases and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

Those skilled in the art will recognize those instances in which the compounds of the invention may form salts. In such instances, another embodiment provides pharmaceutically acceptable salts of the compounds of the invention. Thus, reference to a compound of the invention herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes any of the following: acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of the invention contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also potentially useful. Salts of the compounds of the invention may be formed by methods known to those of ordinary skill in the art, for example, by reacting a compound of the invention 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 which may be useful include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, 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 as potentially useful alternatives to the free forms of the corresponding compounds for purposes of the invention.

Another embodiment which may be useful includes pharmaceutically acceptable esters of the compounds of the invention. Such esters may include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for

example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

As mentioned herein, under certain conditions the compounds of the invention may form tautomers. Such tautomers, when present, comprise another embodiment of the invention. It shall be understood that all tautomeric forms of such compounds are within the scope of the compounds of the invention. For example, all keto-enol and imine-enamine forms of the compounds, when present, are included in the invention.

The compounds of the invention may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of the invention incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Where various stereoisomers of the compounds of the invention are possible, another embodiment provides for diastereomeric mixtures and individual enantiomers of the compounds of the invention. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of the invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the compounds of the invention (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters 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 as embodiments within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). (For example, if a compound of the invention incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.).

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", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

Another embodiment which may be useful include isotopically-labelled compounds of the invention. Such compounds are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

In the compounds of the invention, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of the invention. For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds of the invention can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by

processes analogous to those described in the schemes and examples herein using appropriate isotopically-enriched reagents and/or intermediates.

Polymorphic forms of the compounds of the invention, and of the salts, solvates, esters and prodrugs of the compounds of the invention, are intended to be included in the present invention.

Another embodiment provides suitable dosages and dosage forms of the compounds of the invention. Suitable doses for administering compounds of the invention to patients may readily be determined by those skilled in the art, e.g., by an attending physician, pharmacist, or other skilled worker, and may vary according to patient health, age, weight, frequency of administration, use with other active ingredients, and/or indication for which the compounds are administered. Doses may range from about 0.001 to 500 mg/kg of body weight/day of the compound of the invention. In one embodiment, the dosage is from about 0.01 to about 25 mg/kg of body weight/day of a compound of the invention, or a pharmaceutically acceptable salt or solvate of said compound. In another embodiment, the quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application. In another embodiment, a typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 500 mg/day, preferably 1 mg/day to 200 mg/day, in two to four divided doses.

When used in combination with one or more additional therapeutic agents, the compounds of this invention may be administered together or sequentially. When administered sequentially, compounds of the invention may be administered before or after the one or more additional therapeutic agents, as determined by those skilled in the art or patient preference.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent or treatment within its dosage range.

Accordingly, another embodiment provides combinations comprising an amount of at least one compound of the invention, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and an effective amount of one or more additional agents described above.

Another embodiment provides for pharmaceutically acceptable compositions comprising a compound of the invention, either as the neat chemical or optionally further

comprising additional ingredients. For preparing pharmaceutical compositions from the compounds of the invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. 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 ingredient. 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 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.

Liquid form preparations include solutions, suspensions and emulsions. Non-limiting examples which may be useful include water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. 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, 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.

Another embodiment which may be useful includes compositions comprising a compound of the invention formulated for transdermal delivery. The 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.

Other embodiment which may be useful includes compositions comprising a compound of the invention formulated for subcutaneous delivery or for oral delivery. In some embodiments, it may be advantageous for the pharmaceutical preparation compring one or more compounds of the invention be prepared in a unit dosage form. In such forms, the preparation may be subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose. Each of the

foregoing alternatives, together with their corresponding methods of use, are considered as included in the various embodiments of the invention.

PREPARATIVE EXAMPLES

Compounds of the invention can be made using procedures known in the art. The following reaction schemes show typical procedures, but those skilled in the art will recognize that other procedures can also be suitable. Reactions may involve monitoring for consumption of starting material, and there are many methods for said monitoring, including but not limited to thin layer chromatography (TLC) and liquid chromatography mass spectrometry (LCMS), and those skilled in the art will recognize that where one method is specified, other non-limiting methods may be substituted.

Techniques, solvents and reagents may be referred to by their abbreviations as follows:

Acetic acid: AcOH
Acetonitrile: MeCN
Aqueous: aq.
Benzyl: Bn
tert-Butyl: t-Bu or tBu
Centimeters: cm
Dichloromethane: DCM
Diisopropylamine: iPr_2NH or DIPA
Diisopropylethylamine: DIEA or iPr_2NEt
Dimethylformamide: DMF
Dimethylsulfoxide: DMSO
Ether or diethyl ether: Et_2O
Ethanol: EtOH
Ethyl: Et
Ethyl acetate: AcOEt, EtOAc, or EA
Example: Ex.
Grams: g
Hexanes: hex
High performance liquid chromatography: HPLC
Inhibition: Inh.
Iron(III) acetylacetonate: $Fe(acac)_3$
Liquid chromatography mass Spectrometry: LCMS
Methanesulfonyl chloride: MsCl
Methanol: MeOH
Methyl iodide: MeI
Microliters: µl or µL
Milligrams: mg
Milliliters: mL
Millimoles: mmol
Minutes: min
n-Butyllithium: nBuLi or n-BuLi
Nuclear magnetic resonance spectroscopy: NMR
Para-methoxy benzyl: PMB
Petroleum ether: PE
Retention time: t_R or Ret. Time
Room temperature (ambient, about 25°C): rt or RT

tert-Butoxycarbonyl: t-Boc or Boc

Temperature: temp.

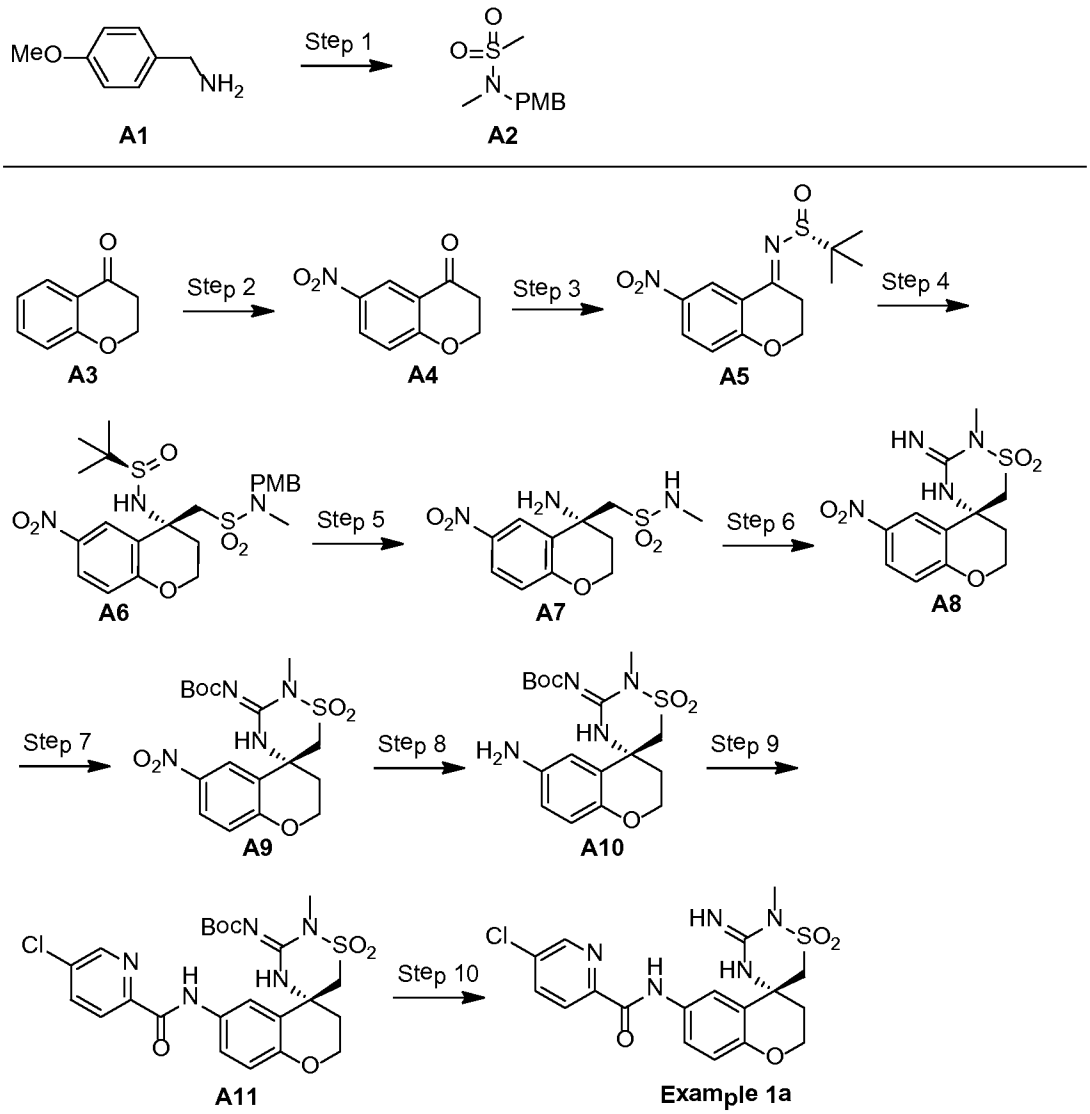
Tetrahydrofuran: THF

2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4-6-trioxide: T3P

Triethylamine: Et_3N or TEA

Trifluoroacetic acid: TFA

Method A:



Step 1:

To a stirred solution of compound **A1** (200 g, 1.46 mol) in pyridine (400 mL) was added MsCl (167 g, 1.46 mol) dropwise via an addition funnel at 0°C. After the addition was completed, the mixture was stirred at room temperature for 6 h. After that time, the reaction was concentrated under vacuum. To the residue was added CH_2Cl_2 (1 L) and the resulting mixture was washed with 1N $HCl_{(aq.)}$ (2 x 1 L), sat. $NaHCO_{3(aq.)}$ (2 x 1 L) and brine (500 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to afford crude product, which was washed with (petroleum ether/ethyl acetate, 2:1, 300 mL). The product was isolated by filtration and the solid was dried under vacuum. To a solution of the solid (220 g, 1.02 mol) in DMF (1100 mL) at 0°C was added Cs_2CO_3 (500 g, 1.53 mol) followed by the dropwise addition of CH_3I (188.6 g, 1.33 mol). The mixture was stirred at room

temperature overnight. The reaction was then poured into cold water which caused a solid to precipitate. The solid was removed via filtration and washed with water. The solid was then dissolved in CH_2Cl_2 (3 L), and the resulting solution was washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered and dried under vacuum to afford compound **A2**.

Step 2:

To a solution of 90% HNO_3 (2 mL) at -40 °C was added compound **A3** (500 mg, 3.4 mmol) dropwise over 15 min. The resulting solution was stirred at -40 °C for 30 min. The reaction was then slowly poured into ice water and the resultant mixture was extracted with dichloromethane (50 mL). The combined organic layers were washed successively with sat. $NaHCO_3$ (aq.), water and brine. The organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **A4**. ^{1}H NMR (DMSO-d_6, 300 MHz): 8.46 (d, *J*= 2.91 Hz, 1H), 8.37 (dd, *J*= 2.91 Hz, *J*= 9.15 Hz, 1H), 7.27 (d, *J*= 9.15 Hz, 1H), 4.70 (d, *J*= 6.36 Hz, 2H), 2.90 (d, *J*= 6.39 Hz, 2H). MS: ES/APCI-MS [M - H^+] m/z 192.2.

Step 3:

To a stirred solution of compound **A4** (1.0 g, 5.5 mmol) in tetrahydrofuran (10 mL) under nitrogen was added (*R*)-(+)-*t*-butyl sulfinamide (727 mg, 6.0 mmol) followed by $Ti(OEt)_4$ (1.6 mL, 6.8 mmol). The reaction mixture was heated to reflux for 18 h. After that time, the reaction mixture was cooled to RT and diluted with ice water. The mixture was filtered through a pad of celite. The filter pad was thoroughly washed with dichloromethane. The phases of the filtrate were separated. The organic layer was washed with water and brine then dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by column chromatography over silica gel (gradient 12-15% ethyl acetate in petroleum ether) to obtain compound **A5**. ^{1}H NMR (DMSO-d_6, 400 MHz): 8.65 (d, *J*= 2.88 Hz, 1H), 8.28 (dd, *J*= 2.88 Hz, *J*= 9.12 Hz, 1H), 7.22 (d, *J*= 9.16 Hz, 1H), 4.53-4.48 (m, 2H), 3.41-3.37 (m, 2H), 1.24 (s, 9H).

Step 4:

To a solution of compound **A2** (905 mg, 3.06 mmol) in tetrahydrofuran (15 mL) at -78 °C was added *n*-BuLi (1.8 mL, 4.4 mmol, 2.5 M in hexane) dropwise. The reaction mixture was stirred for 30 min at -78°C. To the mixture was then added a solution of compound **A5** (1 g, 4.4 mmol) in tetrahydrofuran (15 mL) and the mixture was stirred for 3.5 h at -78°C. The reaction mixture was quenched with saturated $NH_4Cl_{(aq.)}$ (20 mL) and the resulting mixture was warmed to RT. The mixture was then extracted with ethyl acetate. The combined organic

layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography over silica gel (gradient 15-20% ethyl acetate in petroleum ether) to yield compound **A6**. ^{1}H NMR (DMSO-d_6, 300 MHz): 8.17 (d, *J*= 2.67 Hz, 1H), 8.10-8.06 (m, 1H), 7.28-7.25 (m, 2H), 6.99-6.89 (m, 3H), 4.65-4.57 (m, 1H), 4.42-4.35 (m, 2H), 4.27-4.24 (m, 1H), 4.15-4.07 (m, 1H), 3.81 (s, 3H), 3.32-3.20 (m, 2H), 2.90-2.84 (m,1H), 2.82 (s, 3H), 1.29 (s, 9H). MS: ES/APCI-MS [M+H$^+$] m/z 526.2.

Step 5:

To a solution of the sulfinamide **A6** (1.0 g, 1.90 mmol) in dichloromethane (10 mL) was added a solution of HCl (4 M in dioxane. 3 mL). The resultant solution was stirred at room temperature for 1 h. After that time, the solution was concentrated *in vacuo*. The obtained residue was dissolved in trifluoroacetic acid (10 mL). To this mixture was added thioglycolic acid (1.73 mL, 23.8 mmol). The resultant mixture was stirred at room temperature overnight and concentrated. The residue was partitioned between DCM and $NaHCO_{3\ (aq.)}$ and the layers were separated. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude residue was purified by flash column chromatography over silica gel (gradient elution: 55-60% ethyl acetate in petroleum ether) to afford compound **A7**. ^{1}H NMR (DMSO-d_6, 300 MHz): 8.51 (d, *J*= 2.79 Hz, 1H), 8.01 (dd, *J*= 2.82 Hz, *J*= 9.06 Hz, 1H), 6.93 (d, *J*= 9.06 Hz, 1H), 4.40-4.36 (m, 2H), 4.08-4.06 (m, 1H), 3.63 (d, *J*= 14.46 Hz, 1H), 3.48 (d, *J*= 14.46 Hz, 1H), 3.15 (d, *J*= 5.19 Hz, 1H), 2.58 (s, 3H). MS: ES/APCI-MS [M+H$^+$] m/z 302.0.

Step 6:

To a slurry of the amine **A7** (340 mg 1.13 mmol) in n-butanol (5 mL) and acetonitrile (5 mL) was added cyanogen bromide (593 mg, 5.65 mmol). The resultant mixture was heated to reflux and stirred for 16 h. The mixture was then concentrated and purified by flash column chromatography over silica gel (gradient elution 80-90% ethyl acetate in petroleum ether) to afford compound **A8**.

Step 7:

To a solution of compound **A8** (180 mg, 0.553 mmol) in dichloromethane was added Boc_2O (0.18 mL, 0.828 mmol) and triethylamine (0.19 mL, 1.38 mmol). The resultant mixture was stirred at room temperature overnight. The mixture was then diluted with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over

anhydrous Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography over silica gel (gradient elution 15-25% ethyl acetate in petroleum ether) to afford compound **A9**. ^{1}H NMR (CD_3OD, 400 MHz): 8.45 (d, *J*= 2.40 Hz, 1H), 8.16 (dd, *J*= 2.48 Hz, *J*= 9.08 Hz, 1H), 7.03 (d, *J*= 9.12 Hz, 1H), 4.54-4.50 (m, 1H), 4.48-4.40 (m, 1H), 4.39-4.32 (m, 1H), 4.27-4.23 (m, 1H), 3.29 (s, 3H), 2.91-2.87 (m, 1H), 2.53-2.49 (m, 1H), 1.29 (s, 9H). MS: 98.46%; ES/APCI-MS [M+H$^+$] m/z 427.

Step 8.

A solution of compound **A9** (120 mg, 0.281 mmol) in methanol (2 mL) was degassed with nitrogen for 5 min. To the solution was added Pd/C (20% w/w, 50% H_2O, 25 mg). The resulting mixture was stirred at room temperature under a hydrogen balloon for 2 h. After that time, the reaction mixture was filtered through celite and concentrated. The crude residue was purified by flash column chromatography over silica gel (gradient elution 55-60% ethyl acetate in petroleum ether) to afford compound **A10**. ^{1}H NMR (CD_3OD, 400 MHz): 6.81 (d, *J*= 2.52 Hz, 1H), 6.71-6.66 (m, 2H), 4.29-4.23 (m, 2H), 4.15-4.10 (m, 2H), 3.17 (s, 3H), 2.80-2.74 (m, 1H), 2.44-2.41(m, 1H), 1.44 (s, 9H). MS: ES/APCI-MS [M+H$^+$] m/z 397.2.

Step 9:

To a solution of 5-chloropicolinic acid (71 mg, 0.621 mmol) in tetrahydrofuran (2 mL) at room temperature under nitrogen was added *N*,*N*-diisopropylethylamine (0.21 mL, 1.134 mmol) and 50% solution of T_3P in ethyl acetate (0.17 mL, 0.529 mmol). The reaction mixture was stirred at room temperature for 15 min. After that time, aniline **A10** (150 mg, 0.378 mmol) dissolved in THF (3 mL) was added slowly and the reaction mixture was stirred at room temperature for 3 h. Water was added to the reaction and the mixture was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude residue was purified by flash column chromatography over silica gel (gradient elution 22-25% ethyl acetate in petroleum ether) to afford **A11**. MS: ES/APCI-MS [M$^+$] m/z 536.0.

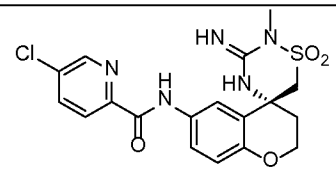
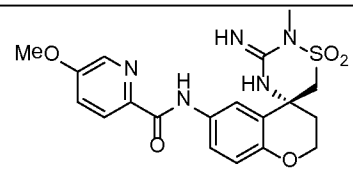
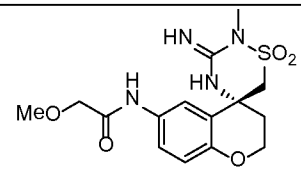
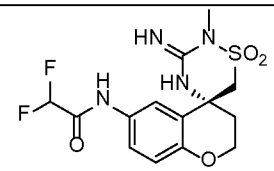
Step 10:

To a solution of compound **A11** (120 mg, 0.223 mmol) in DCM (2 mL) at 0^{o}C was added HCl (4M in dioxane, 2 mL). The reaction was warmed to RT and stirred for 2 h at which point the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography over silica gel (10-15% methanol in dichloromethane) to afford **Example 1a**. ^{1}H NMR (DMSO-d_6, 400 MHz): 10.48 (s, 1H), 10.23 (bs, 1H), 8.78 (s, 1H), 8.45 (bs, 1H),

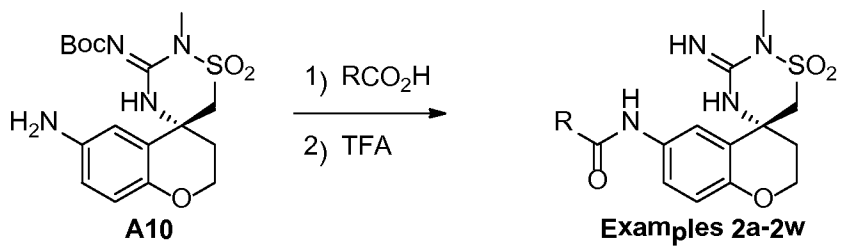
8.35-8.33(m, 1H), 8.22-8.20 (m, 1H), 7.97(d, *J*= 2.32 Hz, 1H), 7.86 (dd, *J*= 2.41 Hz, *J*= 8.92 Hz, 1H), 6.90(d, *J*= 8.92 Hz, 1H), 4.86-4.82 (m, 1H), 4.39-4.31 (m, 1H), 4.27-4.19 (m, 2H), 3.35 (s, 3H), 2.63-2.60 (m, 1H), 2.49-2.46(m, 1H). MS: ES/APCI-MS [M+H$^+$] m/z 436.0.

The examples in Table 1 were prepared using procedures similar to those described in Method A using the requisite carboxylic acid in step 9.

Table 1:

Ex. no.	Example	LCMS data			BACE1 K_i (nM)	BACE2 K_i (nM)
		m/z	t_R (min)	Conditions		
1a		436	2.30	1	70	17
1b		432	2.21	1	233	130
1c		369	1.81	1	2008	341
1d		375	1.87	1	2275	728

Method B:

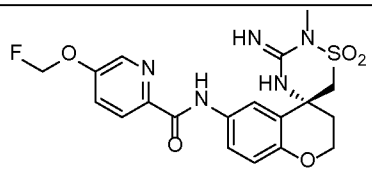
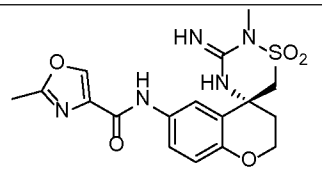
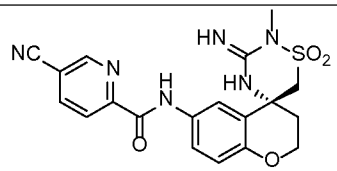
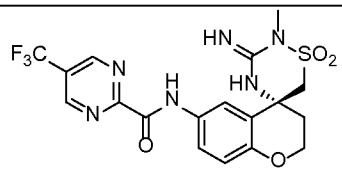
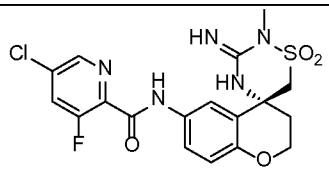
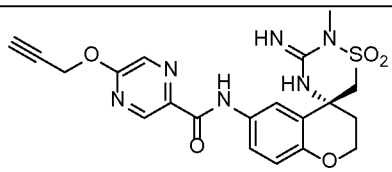


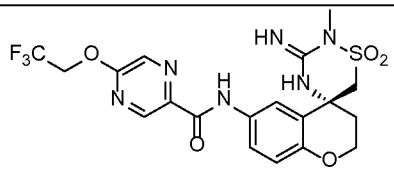
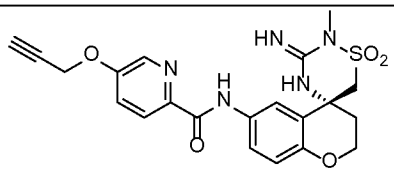
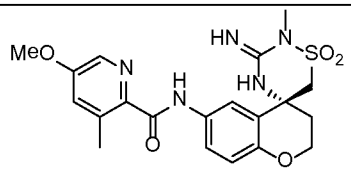
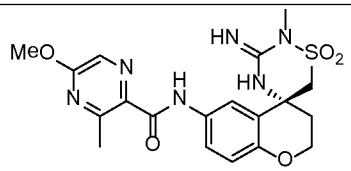
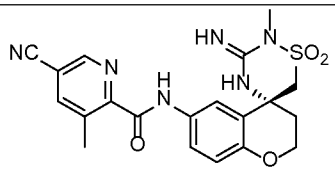
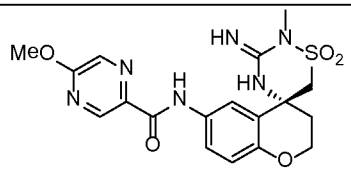
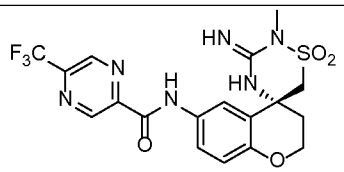
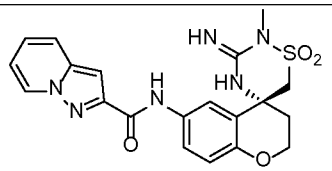
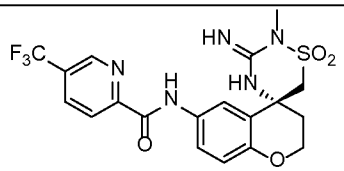
A10 **Examples 2a-2w**

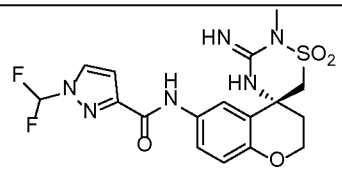
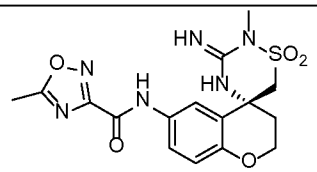
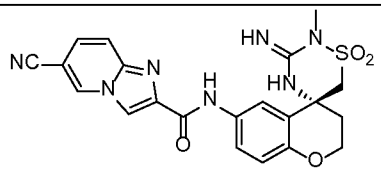
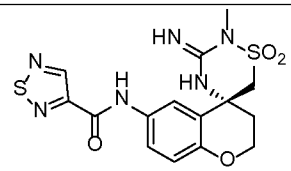
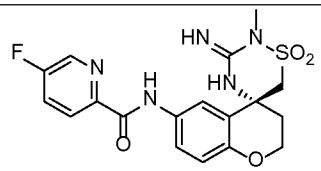
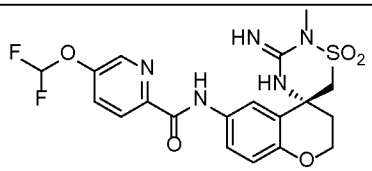
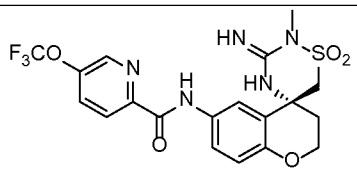
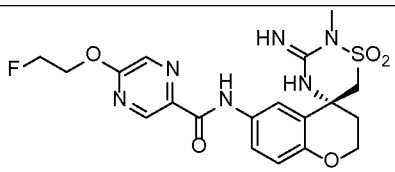
Parallel preparation of **Examples 2a-2w:** To a set of vials containing the requisite carboxylic acid (0.076 mmol) was added a solution of **A10** (25 mg, 0.063 mmol) in DCM (0.75 mL) followed by the addition of iPr_2NEt (0.033 mL, 0.19 mmol) and a solution of T3P (50% in

EtOAc, 0.075 mL, 0.13 mmol). The vials were capped and the mixtures were shaken at RT overnight. After that time, water (0.050 mL) and TFA (0.50 mL) were added to each vial. The mixtures were then shaken at RT for 3 hours. After that time, the mixtures were concentrated *in vacuo*. The crude residues were dissolved in DMSO (1 mL) and filtered. The crude products were purified by mass triggered HPLC using the following conditions: [column: Waters Sunfire C18, 5μm , 19x100 mm; solvent: gradient range 10% initial to 18-29% final MeCN (0.1% formic acid) in water (0.1% formic acid) 25 mL/min; 9-12 min run time] to afford **Examples 2a-2w**.

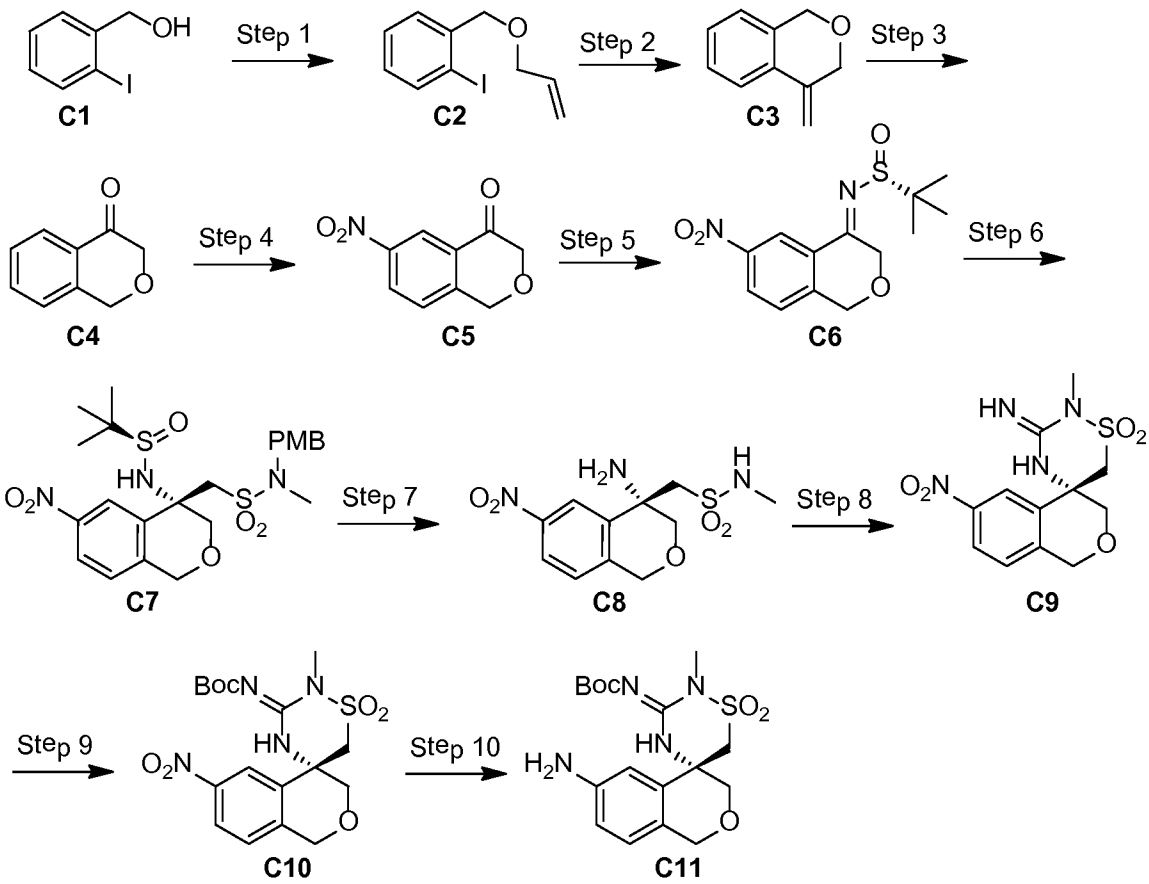
Table 2:

Ex. no.	Example	LCMS data			BACE1 K_i (nM)	BACE2 K_i (nM)
		m/z	t_R (min)	Conditions		
2a		450.12	0.82	2	91	59
2b		406.11	0.67	2	142	20
2c		427.11	0.76	2	26	51
2d		471.1	0.76	2	579	780
2e		454.07	0.82	2	49	9
2f		457.12	0.85	2	13	138

Ex. no.	Example	LCMS data			BACE1 K_i (nM)	BACE2 K_i (nM)
		m/z	t_R (min)	Conditions		
2g		501.11	0.96	2	70	699
2h		456.13	0.87	2	33	313
2i		446.14	0.87	2	168	29
2j		447.14	0.87	2	294	160
2k		441.13	0.80	2	15	26
2l		433.12	0.78	2	212	254
2m		471.1	0.88	2	303	1150
2n		441.13	0.79	2	1488	337
2o		470.1	0.94	2	77	283

Ex. no.	Example	LCMS data			BACE1 K_i (nM)	BACE2 K_i (nM)
		m/z	t_R (min)	Conditions		
2p		441.11	0.74	2	20	3
2q		407.11	0.63	2	367	31
2r		466.12	0.74	2	604	6912
2s		409.07	0.68	2	240	46
2t		420.11	0.79	2	205	31
2u		468.11	0.88	2	44	166
2v		486.1	0.97	2	52	261
2w		465.13	0.81	2	229	572

Method C:



Step 1:

NaH (1.8 g, 46.6 mmol) was added to a THF (60 mL) solution of 2-iodo-benzyl alcohol **C1** (7.3 g, 31.19 mmol) at 0°C, in small portions. After the complete addition of NaH, allyl bromide (3.9 mL, 46.73 mmol) was added. The mixture was stirred overnight at room temperature. The resultant heterogeneous mixture was quenched with a saturated cold $NH_4Cl_{(aq.)}$ solution and extracted with ethyl acetate. The combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by flash chromatography over silica gel using 5% ethyl acetate in petroleum ether as the eluent to yield **C2**. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.83 (dd, J = 7.6, 0.8 Hz, 1H), 7.47 (d, J = 6.4 Hz, 1H), 7.36 (dt, J = 7.6, 0.8 Hz, 1H), 6.99 (dt, J = 7.6, 1.6 Hz, 1H), 6.05–5.96 (m, 1H), 5.40–5.39 (m, 0.5 H), 5.35–5.34 (m, 0.5 H), 5.25 (dd, J = 10.4, 1.6 Hz, 1H), 4.51 (s, 2H), 4.14–4.12 (m, 2H).

Step 2:

Allyl ether **C2** (1.0 g, 3.65 mmol) was dissolved in a mixture of 15 ml of MeCN and 2.5 mL (18.2 mmol) of Et_3N. The mixture was vacuum degassed (3 cycles) followed by the addition of

$Pd(OAc)_2$ (40.88 mg, 0.182 mmol) and PPh_3 (95.73 mg, 0.365 mmol). The mixture was heated to 80°C for 2 h. The mixture was then cooled to room temperature and diluted with water. The mixture was extracted with ethyl acetate. The organic layer was washed sequentially with 1N $HCl_{(aq.)}$, sat. $NaHCO_{3(aq.)}$ and brine. The organic layer was then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography over silica gel using a gradient elution of 0-2% ethyl acetate in petroleum ether to provide **C3**. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.72–7.69 (m, 1H), 7.28–7.24 (m, 2H), 7.07–7.04 (m, 1H), 5.63 (s, 1H), 5.04 (s, 1H), 4.84 (s, 2H), 4.47 (s, 2H).

Step 3:

To a mixture of **C3** (3.0 g, 20.55 mmol) in dioxane-water (1:1, 40 mL) at 0°C was added $NaIO_4$ (13.1 g, 61.5 mmol). The reaction mixture was stirred for 10 min. After that time, a solution of OsO_4 (2.5 % in *t*-butanol, 0.104 g, 0.41 mmol) was added dropwise. The reaction was allowed to warm to RT and stirred overnight. After that time, water was added to the reaction flask and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography over silica gel eluting with 10% ethyl acetate in petroleum ether to afford **C4**. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, J = 7.7 Hz, 1H), 7.61–7.56 (m, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 4.91 (s, 2H), 4.39 (s, 2H).

Step 4:

To a cooled solution of 90% HNO_3 (47.6 mL) at -30°C, **C4** (7 g, 47.3 mmol) was added dropwise over 30 min. The resultant solution was stirred at -30°C for 5 h and then slowly poured onto ice. The reaction mixture was diluted by adding cold water and the mixture was extracted with dichloromethane. The combined organic layers were washed sequentially with sat. $NaHCO_{3(aq.)}$, water and brine. The organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography over silica gel using a gradient elution of 30-50% ethyl acetate in petroleum ether to afford **C5**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ. 8.88 (d, J = 2.4 Hz, 1H), 8.43 (dd, J = 8.4, 2.4 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 5.00 (s, 2H), 4.45 (s, 2H).

Step 5:

To a solution of **C5** (6 g, 31.09 mmol) in THF (80 mL) was added (R)-(+)-2-methyl-2-propanesulfinamide (6.77 g, 55.95 mmol) and $Ti(OEt)_4$, (12.76 g, 55.96 mmol). The resultant solution was heated to reflux for 1 h. After that time, the solution was cooled to RT and poured

into ice cold water. The mixture was filtered and the filter cake was washed with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography over silica gel eluting with 15% ethyl acetate in petroleum ether to afford **C6**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ. 8.88 (d, *J* = 2 Hz, 1H), 8.30 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 5.24 (d, *J* = 17.2 Hz, 1H), 5.05 (d, *J* = 17.2 Hz, 1H), 4.87 (d, *J* = 2.4 Hz, 2H), 1.38 (s, 9H).

Step 6:

To a solution of the sulfonamide **A2** (4.64 g, 20.26 mmol) in anhydrous THF (25 mL) at -78°C under an atmosphere of N_2 was added dropwise a solution of n- BuLi (2.5 M in hexane, 8.11 mL, 20.28 mmol). The resultant solution was stirred at -78°C for 1 h. After that time, a solution of the ketimine **C6** (3 g, 10.14 mmol) in THF (25 mL) precooled to -78°C in a separate round bottom flask was transferred via cannula to the solution above. The resultant solution was stirred at -78°C for 3.5 h. The reaction was the quenched with a saturated aqueous solution of NH_4Cl and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with water and brine then dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography over silica gel eluting with a gradient of 50-60% EtOAc in petroleum ether to afford **C7**.

Step 7:

To a solution of **C7** (3.0 g, 5.7 mmol) in dichloromethane (30 mL) was added a solution of HCl in dioxane (30 mL, 4.5 M) at 0 °C and the resultant solution was stirred at RT for 3 h. After that time, the reaction mixture was concentrated. To the residue was added TFA (30 mL) at 0 °C followed by the addition of thioglycolic acid (4.14 mL, 57.13 mmol). The reaction mixture was stirred RT for 16 h. The solution was then concentrated. The residue was partitioned between aq. $NaHCO_3$ (pH 8) and DCM. The layers were separated and the aqueous layer was extracted with DCM. The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified over silica gel eluting with 80% EtOAc in petroleum ether to afford **C8**

Step 8:

To slurry of **C8** (1.3 g, 3.98 mmol) in 1:1 mixture of acetonitrile and n-butanol (25 mL:25 mL) was added cyanogen bromide (2.11 g, 19.9 mmol). The resultant mixture was heated to reflux overnight. The reaction mixture was cooled to RT and the volatiles removed under reduced

pressure. The crude residue was washed with diethyl ether (3X) and the product **C9** was isolated via filtration.

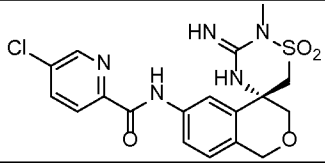
Step 9:

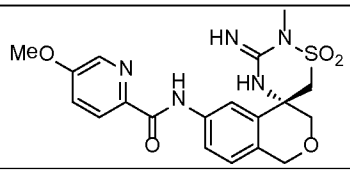
To a solution of **C9** (1.3 g, 3.99 mmol) in CH_2Cl_2 (25 mL) was added Boc_2O (2.6 mL, 11.93 mmol) and DIEA (3.0 mL, 19.88 mmol). The resultant solution was stirred at RT overnight. The volatiles were removed under reduced pressure and the crude residue was purified by flash chromatography over silica gel eluting with 20% EtOAc in petroleum ether to afford **C10**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ. 10.56 (s, 1H), 8.36 (d, *J* = 2.0 Hz, 1H), 8.21 (dd, *J* = 2.0 & 8.4 Hz, 1H), 7.28 (s, 1H), 5.01 – 4.86 (m, 2H), 4.20 (d, *J* = 14 Hz, 2H), 3.67 (dd, *J* = 1.6 & 11.6 Hz, 1H), 3.51 (dd, *J* = 1.6 & 14 Hz, 1H), 3.40 (s, 3H), 1.48 (s, 9H). m/z: 425.02 $(M-H; \text{negative mode})^-$

Step 10:

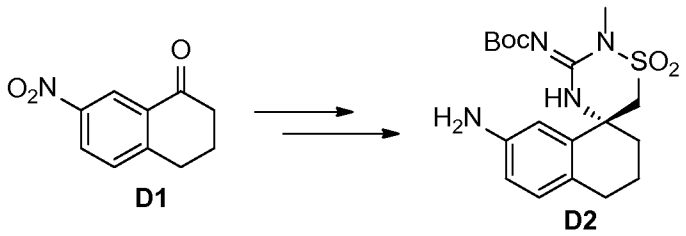
A solution of the **C10** (1.3 g, 3.05 mmol) in 1:1 mixture of methanol and ethanol (40 mL) was degassed by bubbling N_2 through the solution for 3 min. To this solution was added Pd/C (10% w/w, 400 mg.). The mixture was placed under an atmosphere of N_2. The atmosphere was evacuated and back-filled with hydrogen. The resulting mixture was stirred at RT under an atmosphere of hydrogen for 2 h. The mixture was then filtered through celite and concentrated. The crude residue was purified by flash chromatography over silica gel eluting with a gradient 20-30% EtOAc in petroleum ether to afford **C11**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ. 9.95 (s, 1H), 6.79–6.76 (m, 1H), 6.71 (s, 1H), 6.57–6.54 (m, 1H), 5.13 (s, 2H), 4.64–4.54 (m, 1H), 4.42–4.37 (m, 1H), 4.27–4.23 (m, 1H), 4.04–3.85 (m, 3H), 3.12 (s, 3H), 1.36 (s, 9H). m/z: 397.4 $(M+H)^+$

Table 3 The following examples were prepared from **C11** using the requisite carboxylic acid following procedures similar to those described in Method A, steps 9-10.

Ex. no.	Example	LCMS data			BACE1 K_i (nM)	BACE2 K_i (nM)
		m/z	t_R (min)	Conditions		
3a		436.3	2.30	1	272	58

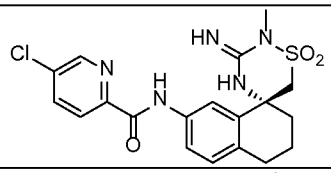
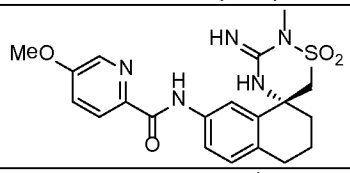
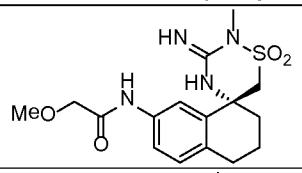
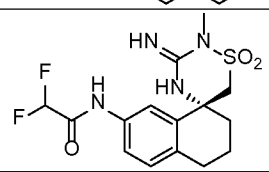
Ex. no.	Example	LCMS data			BACE1 K_i (nM)	BACE2 K_i (nM)
		m/z	t_R (min)	Conditions		
3b		432.2	2.24	1	1160	354

Method D:

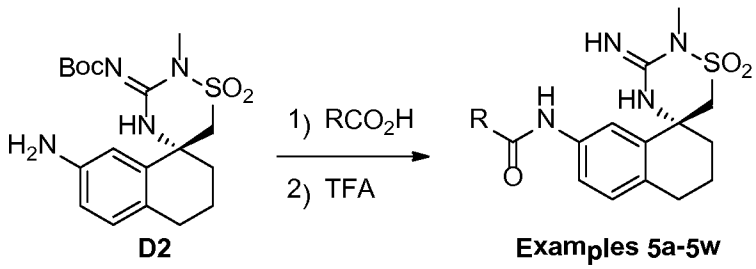


D1 was converted to **D2** using conditions similar to those described in Method B steps 5-11.

Table 4 The following examples were prepared from **D2** using the requisite carboxylic acid following procedures similar to those described in Method A, steps 9-10.

Ex. no.	Example	LCMS data			BACE1 K_i (nM)	BACE2 K_i (nM)
		m/z	t_R (min)	Conditions		
4a		434.2	2.40	1	58	15
4b		430.2	2.35	1	228	67
4c		367.2	1.99	1	2115	260
4d		373.2	2.07	1	2576	515

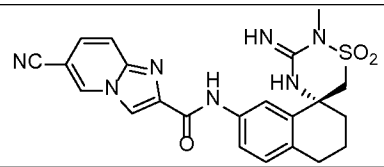
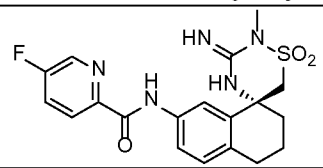
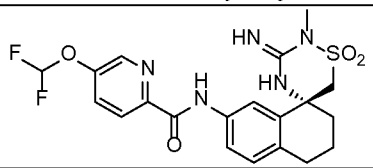
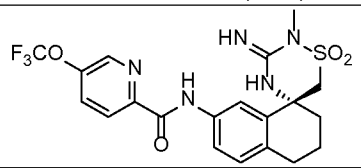
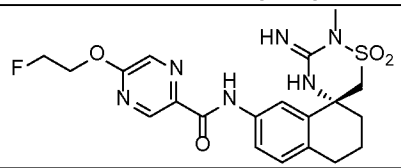
Method E:

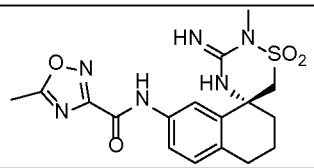
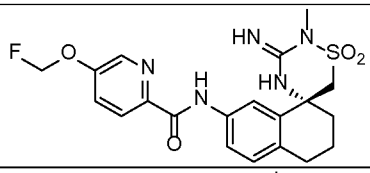
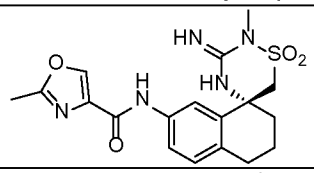
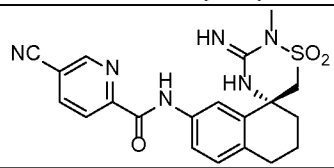
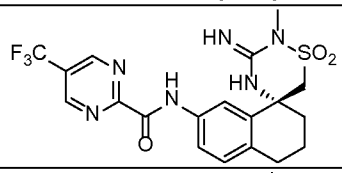
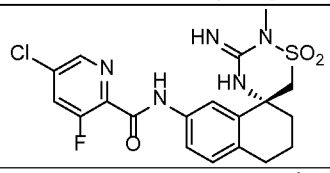
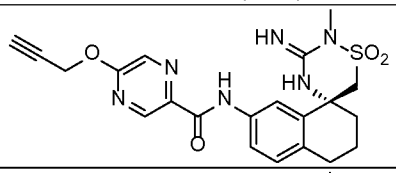
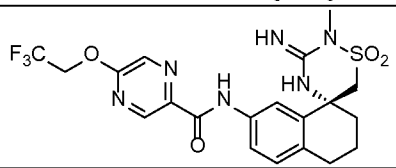
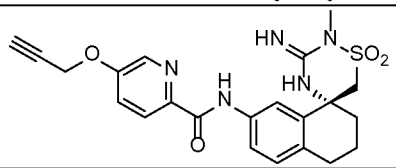
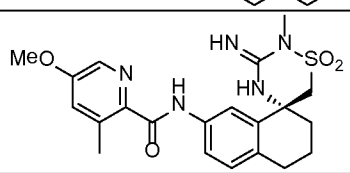


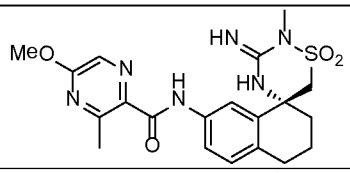
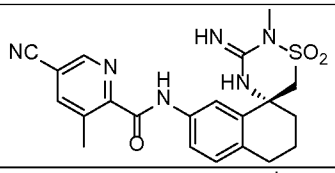
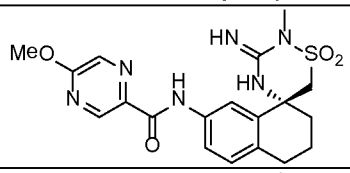
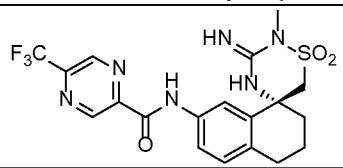
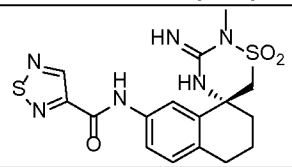
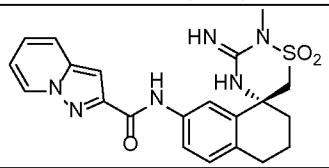
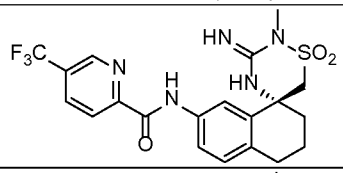
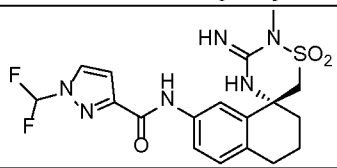
D2 Examples 5a-5w

Parallel preparation of **Examples 5a-5w:** These examples were prepared from **D2** and the requisite carboxylic acid using a procedure similar to that described in Method B. The crude products were purified by mass triggered HPLC using the following conditions: [column: Waters XBridge C18, 5µm , 19x100 mm; solvent: gradient range 15-30% initial to 50-65% final MeCN (0.1% NH_4OH) in water (0.1% NH_4OH) 50 mL/min; 8 min run time] to afford **Examples 5a-5w.**

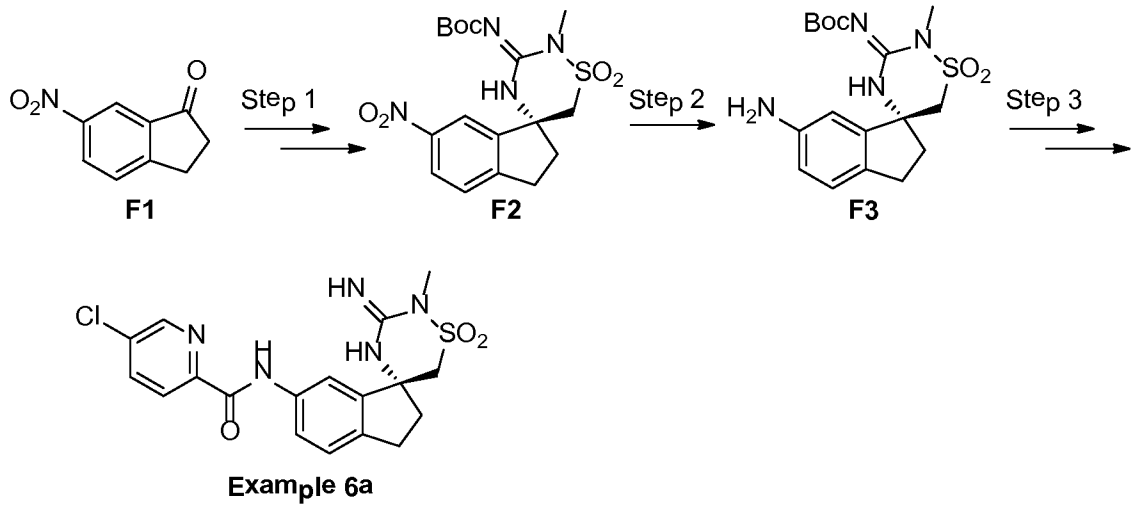
Table 5:

Ex. no.	Example	LCMS data			BACE1 K_i (nM)	BACE2 K_i (nM)
		m/z	t_R (min)	Conditions		
5a		464.14	0.81	2	636	1131
5b		418.13	0.86	2	192	28
5c		466.13	0.95	2	59	126
5d		484.12	1.03	2	55	219
5e		463.15	0.89	2	257	487

Ex. no.	Example	LCMS data			BACE1 K_i (nM)	BACE2 K_i (nM)
		m/z	t_R (min)	Conditions		
5f		405.13	0.71	2	314	16
5g		448.14	0.89	2	77	33
5h		404.13	0.75	2	108	11
5i		425.13	0.83	2	19	44
5j		469.12	0.83	2	468	423
5k		452.09	0.89	2	54	8
5l		455.14	0.91	2	11	77
5m		499.13	1.01	2	72	508
5n		454.15	0.93	2	42	221
5o		444.16	0.94	2	119	17

Ex. no.	Example	LCMS data			BACE1 K_i (nM)	BACE2 K_i (nM)
		m/z	t_R (min)	Conditions		
5p		445.16	0.94	2	224	123
5q		439.15	0.88	2	9	17
5r		431.14	0.85	2	144	177
5s		469.12	0.94	2	253	685
5t		407.09	0.76	2	264	56
5u		439.15	0.86	2	1336	385
5v		468.12	1.00	2	55	171
5w		439.13	0.82	2	20	3

Method F:

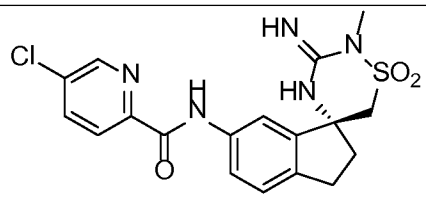


Step 1: Ketone **F1** was converted to intermediate **F2** using procedures similar to those described in Method C steps 5-8.

Step 2: To a mixture of compound **F2** (350 mg, 0.853 mmol) in methanol (6 mL) and water (2 mL) was added Zinc (278 mg, 4.27 mmol) and ammonium chloride (228 mg, 4.268 mmol). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then filtered through celite and the filter cake was washed with excess of 1:1 mixture of methanol and dichloromethane. The filtrate was and concentrated and the product was used without further purification. m/z: 381.2

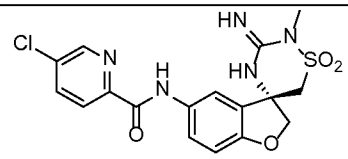
Step 3: Amine **F3** was converted to **Example 6a** following procedures similar to those described in Method A steps 9 and 10.

Table 6:

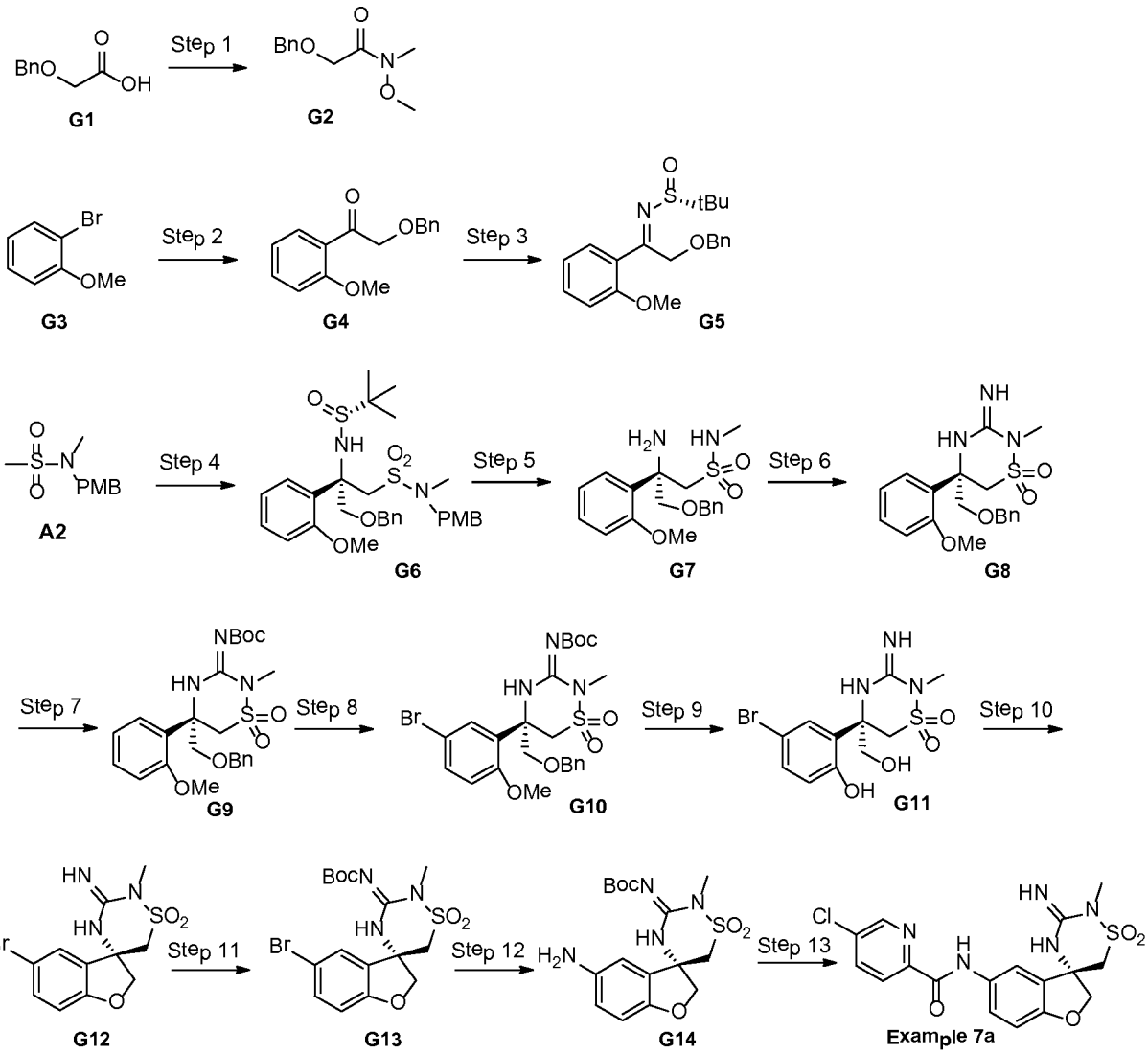
Ex. no.	Example	LCMS data		
		m/z	t_R (min)	Conditions
6a		420.4	2.33	1

The example in Table 7 is made using procedures described in Method G.

Table 7:

Ex. no.	Example
7a	

Method G:



Step 1: To a solution of 2-(benzyloxy)acetic acid **G1** (3.23 g, 19.5 mmol) in DCM (60 mL) was added EDCI (6.1 g, 29.2 mmol), followed by *N,O*-dimethylhydroxylamine hydrochloride (2.8 g, 29.2 mmol) and pyridine (10 mL). The mixture was stirred at 25 °C for 16 h, then

washed with 0.1 M aq. HCl, brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography (PE:EA = 10:1) to afford **G2**.

Step 2: Bromide **G3** can be treated with nBuLi to afford the aryl lithium intermediate in which **G2** can be added to afford ketone **G4**.

Steps 3-7: Ketone **G4** can be converted to compound **G9** following procedures similar to Method A steps 3-7.

Step 8. Compound **G9** can be treated with NBS and the like in the appropriate solvent to afford bromide **G10.**

Step 9. Treatment of **G10** with BBr_3 in the appropriate solvent and temperature can provide compound **G11**.

Step 10: Compound **G11** can be treated under the appropriate conditions such as Mitsunobu or BBr_3 to afford the dihydrobenzofuran **G12**.

Step 11. Compound **G12** can be converted to **Example 7a** following the procedures similar to those described in Method A steps 7 and 9-10.

LCMS Conditions

Conditions 1: Column: Atlantis dC18 (50 x 4.6mm) 5.0 micron; Column temp: Ambient; Mobile phase: A: 0.1% Formic acid in water, B: 100% Acetonitrile; Gradient: From 0 to 3 min 95:5 to 5:95 (A:B), from 3-4 min 5:95 (A:B), from 4 to 4.5 min 5:95 to 95:5 (A:B), from 4.5 to 6 min 95:5 (A:B); Flow rate: 1.5mL/min; UV detection: 215 nm; Mass spectrometer: Agilent 6130 (Single) quadrupole.

Conditions 2: Waters Acquity UPLC/MS, Electrospray positive ion mode; Column: Waters Acquity UPLC BEH C18, 2.1x50 mm, 1.7 micron; Gradient elution 5:95 to 100:0 MeCN (0.1 % NH_4OH): water (0.1 % NH_4OH) over 1.4 min 0.8 mL/min; UV: 220 nm.

ASSAYS

Protocols that used to determine the recited potency values for the compounds of the invention are described below.

BACE1 HTRF FRET Assay

Reagents: Na^+-Acetate pH 5.0; 1% Brij-35; Glycerol; Dimethyl Sulfoxide (DMSO); Recombinant human soluble BACE1 catalytic domain (>95% pure); APP Swedish mutant peptide substrate (QSY7-APP^{swe}-Eu): QSY7-EISEVNLDAEFC-Europium-amide.

A homogeneous time-resolved FRET assay can be used to determine IC_{50} values for inhibitors of the soluble human BACE1 catalytic domain. This assay monitors the increase of 620 nm fluorescence that resulted from BACE1 cleavage of an APPswedish APP^{swe} mutant peptide FRET substrate (QSY7-EISEVNLDAEFC-Europium-amide). This substrate contains an N-terminal QSY7 moiety that serves as a quencher of the C-terminal Europium fluorophore (620nm Em). In the absence of enzyme activity, 620 nm fluorescence is low in the assay and increased linearly over 3 hours in the presence of uninhibited BACE1 enzyme. Inhibition of BACE1 cleavage of the QSY7-APP^{swe}-Eu substrate by inhibitors is manifested as a suppression of 620 nm fluorescence.

Varying concentrations of inhibitors at 3x the final desired concentration in a volume of 10ul are preincubated with purified human BACE1 catalytic domain (3 nM in 10 µl) for 30 minutes at 30° C in reaction buffer containing 20 mM Na-Acetate pH 5.0, 10% glycerol, 0.1% Brij-35 and 7.5% DSMO. Reactions are initiated by addition of 10 µl of 600 nM QSY7-APP^{swe}-Eu substrate (200 nM final) to give a final reaction volume of 30 µl in a 384 well Nunc HTRF plate. The reactions are incubated at 30° C for 1.5 hours. The 620nm fluorescence is then read on a Rubystar HTRF plate reader (BMG Labtechnologies) using a 50 millisecond delay followed by a 400 millisecond acquisition time window. Inhibitor IC_{50} values are derived from non-linear regression analysis of concentration response curves. K_i values are then calculated from IC_{50} values using the Cheng-Prusoff equation using a previously determined µm value of 8µM for the QSY7-APP^{swe}-Eu substrate at BACE1.

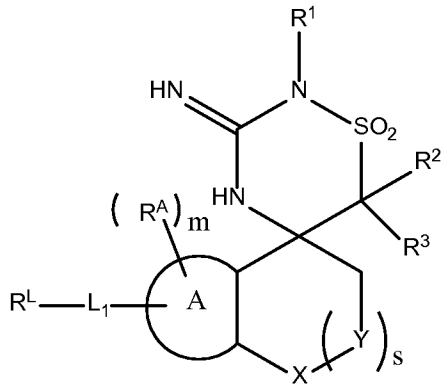
BACE-2 Assay

Inhibitor IC_{50s} at purified human autoBACE-2 are determined in a time-resolved endpoint proteolysis assay that measures hydrolysis of the QSY7-EISEVNLDAEFC-Eu-amide FRET peptide substrate (BACE-HTRF assay). BACE-mediated hydrolysis of this peptide results in an increase in relative fluorescence (RFU) at 620 nm after excitation with 320 nm light. Inhibitor compounds, prepared at 3x the desired final concentration in 1x BACE assay buffer (20 mM sodium acetate pH 5.0, 10% glycerol, 0.1% Brij-35) supplemented with 7.5% DMSO are pre-incubated with an equal volume of autoBACE-2 enzyme diluted in 1x BACE

assay buffer (final enzyme concentration 1 nM) in black 384-well NUNC plates for 30 minutes at 30°C. The assay is initiated by addition of an equal volume of the QSY7-EISEVNLDAEFC-Eu-amide substrate (200 nM final concentration, K_m=8 μM for 4 μM for autoBACE-2) prepared in 1x BACE assay buffer supplemented with 7.5% DMSO and incubated for 90 minutes at 30°C. DMSO is present at 5% final concentration in the assay. Following laser excitation of sample wells at 320 nm, the fluorescence signal at 620 nm is collected for 400 ms following a 50 μs delay on a RUBYstar HTRF plate reader (BMG Labtechnologies). Raw RFU data is normalized to maximum (1.0 nM BACE/DMSO) and minimum (no enzyme/DMSO) RFU values. IC_{50s} are determined by nonlinear regression analysis (sigmoidal dose response, variable slope) of percent inhibition data with minimum and maximum values set to 0 and 100 percent respectively. Similar IC_{50s} are obtained when using raw RFU data. The K_i values are calculated from the IC_{50} using the Cheng-Prusoff equation.

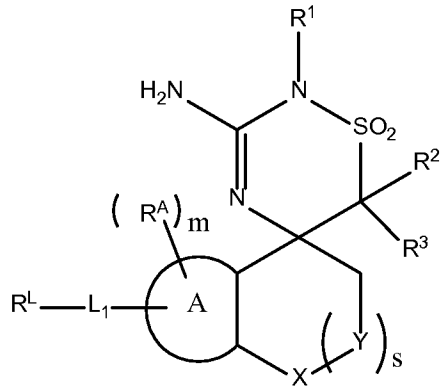
WE CLAIM:

Claim 1. A compound, or a pharmaceutically acceptable salt thereof, said compound having the structural Formula (I):



(I)

or a tautomer thereof having the structural Formula (I'):



(I')

or pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of H, alkyl, heteroalkyl, cycloalkyl, and -alkyl-cycloalkyl, wherein each said alkyl, heteroalkyl, cycloalkyl, and -alkyl-cycloalkyl, is optionally substituted with one or more halogen;

R^2 is selected from the group consisting of H, halogen, alkyl, heteroalkyl, cycloalkyl, and -alkyl-cycloalkyl, wherein each said alkyl, heteroalkyl, cycloalkyl, and -alkyl-cycloalkyl is optionally substituted with one or more halogen;

R^3 is selected from the group consisting of H, halogen, alkyl, heteroalkyl, cycloalkyl, and -alkyl-cycloalkyl, wherein each said alkyl, heteroalkyl, cycloalkyl, and -alkyl-cycloalkyl is optionally substituted with one or more halogen;

s is 0 or 1;

when s is 0, then Y is absent and X is selected from the group consisting of -$C(R^{1X})_2$-, -O-, -S-, -S(O)-, and -$S(O)_2$-, and

when s is 1, then X is selected from the group consisting of -$C(R^{1X})_2$-, -O-, -S-, -S(O)-, and -$S(O)_2$-, and Y is –$C(R^{1Y})_2$-,

or, alternatively, when s is 1, then X is –$C(R^{1X})_2$- and Y is selected from the group consisting of -$C(R^{1Y})_2$-, -O-, -S-, -S(O)-, and -$S(O)_2$-;

each R^{1X} (when present) is independently selected from the group consisting of: H, halogen, alkyl, heteroalkyl, and cycloalkyl,

wherein said alkyl, heteroalkyl, and cycloalkyl are each optionally independently unsubstituted or substituted with one or more halogen;

each R^{1Y} (when present) is independently selected from the group consisting of: H, halogen, alkyl, heteroalkyl, and cycloalkyl,

wherein said alkyl, heteroalkyl, and cycloalkyl are each optionally independently unsubstituted or substituted with one or more halogen;

ring A is selected from the group consisting of aryl and heteroaryl;

m is 0 or more;

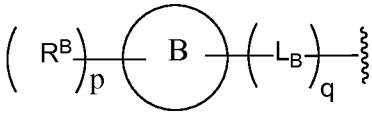
each R^A (when present) is independently selected from the group consisting of: halogen, -OH, -CN, -SF_5, -OSF_5, -$Si(R^{5A})_3$, -$N(R^{6A})_2$, -OR^{6A}, -SR^{6A}, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, and -alkyl-heterocycloalkyl,

wherein said alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, and -alkyl-heterocycloalkyl of R^A are each optionally independently unsubstituted or substituted with one or more groups independently selected from R^8;

n is 0 or 1;

–L_1- represents a bond or a divalent moiety selected from the group consisting of -alkyl-, -haloalkyl-, -heteroalkyl-, -alkenyl-, -alkynyl-, -NHC(O)-, -C(O)NH-, -C(S)NH-, -NHC(S)-, -NH-, -$NHS(O)_2$-, -$S(O)_2NH$-, -O-CH_2-, -CH_2-O-, -$NHCH_2$-, and -CH_2NH-;

R^L is selected from the group consisting of alkyl and heteroalkyl, wherein said alkyl and heteroalkyl of R^L are each optionally unsubstituted or substituted with one or more halogen;

or, alternatively, R^L is a moiety having the formula 

,

wherein q is 0 or 1;

-L_B- (when present) is a divalent moiety selected from the group consisting of lower alkyl and lower heteroalkyl, wherein each said lower alkyl and lower heteroalkyl is optionally substituted with one or more halogen;

ring B is selected from the group consisting of aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

p is 0 or more; and

each R^B (when present) is independently selected from the group consisting of: halogen, oxo, -OH, -CN, -SF_5, -OSF_5, -$Si(R^{5B})_3$, -$N(R^{6B})_2$, -$NR^{7B}C(O)R^{6B}$, –$NR^7S(O)_2R^{6B}$, -$NR^{7B}S(O)_2N(R^{6B})_2$, –$NR^{7B}C(O)N(R^{6B})_2$, -$NR^{7B}C(O)OR^{6B}$, -$C(O)R^{6B}$, -$C(O)OR^{6B}$, -$C(O)N(R^{6B})_2$, -$S(O)R^{6B}$, -$S(O)_2R^{6B}$, -$S(O)_2N(R^{6B})_2$, -OR^{6B}, -SR^{6B}, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, –alkyl-heterocycloalkyl, aryl, -alkyl-aryl, heteroaryl, and -alkyl-heteroaryl,

wherein said alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, –alkyl-heterocycloalkyl, aryl, -alkyl-aryl, heteroaryl, and -alkyl-heteroaryl of R^B are each optionally independently unsubstituted or substituted with one or more groups independently selected from R^9;

each R^{5X}, R^{5Y}, R^{5A}, R^{5B}, and R^{5C} (when present) is independently selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, -alkyl-heterocycloalkyl,

wherein each said alkyl, heteroalkyl, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, -alkyl-heterocycloalkyl of R^{5X}, R^{5Y}, R^{5A}, R^{5B}, and R^{5C} is unsubstituted or substituted with one or more halogen;

each R^{6X}, R^{6Y}, R^{6A} and R^{6C} (when present) is independently selected from the group consisting of H, alkyl, -alkyl-OH, alkenyl, alkynyl, heteroalkyl, -heteroalkyl-OH, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, and -alkyl-heterocycloalkyl,

wherein each said alkyl, -alkyl-OH, alkenyl, alkynyl, heteroalkyl, -heteroalkyl-OH, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, -alkyl-heterocycloalkyl, aryl, -alkyl-aryl, heteroaryl, and -alkyl-heteroaryl of R^{6X}, R^{6Y}, R^{6A} and R^{6C} is unsubstituted or substituted with one or more groups independently selected from halogen, alkyl, cycloalkyl, heteroalkyl, haloalkyl, alkoxy, heteroalkoxy, and haloalkoxy;

each R^{6B} (when present) is independently selected from the group consisting of H, alkyl, -alkyl-OH, alkenyl, alkynyl, heteroalkyl, -heteroalkyl-OH, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, -alkyl-heterocycloalkyl, aryl, -alkyl-aryl, heteroaryl, and -alkyl-heteroaryl,

wherein each said alkyl, -alkyl-OH, alkenyl, alkynyl, heteroalkyl, -heteroalkyl-OH, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, -alkyl-heterocycloalkyl, aryl, -alkyl-aryl, heteroaryl, and -alkyl-heteroaryl of R^{6B} is unsubstituted or substituted with one or more groups independently selected from halogen, alkyl, cycloalkyl, heteroalkyl, haloalkyl, alkoxy, heteroalkoxy, and haloalkoxy;

each R^{7X}, R^{7Y}, R^{7A}, R^{7B}, and R^{7C} (when present) is independently selected from the group consisting of H, alkyl, heteroalkyl, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, and -alkyl-heterocycloalkyl,

wherein each said alkyl, heteroalkyl, -heteroalkyl-OH, cycloalkyl, -alkyl-cycloalkyl, heterocycloalkyl, and -alkyl-heterocycloalkyl of R^{7X}, R^{7Y}, R^{7A}, R^{7B}, and R^{7C} is unsubstituted or substituted with one or more halogen;

each R^8 (when present) is independently selected from the group consisting of halogen, lower alkyl, lower heteroalkyl, lower alkoxy, lower cycloalkyl, and lower heterocycloalkyl, wherein each said lower alkyl, lower heteroalkyl, lower alkoxy, lower cycloalkyl, and lower heterocycloalkyl of R^8 is optionally substituted with halogen; and

each R^9 (when present) is independently selected from the group consisting of halogen, -OH, -CN, $-SF_5$, $-OSF_5$, alkyl, -alkyl-OH, heteroalkyl, -heteroalkyl-OH, alkoxy, -O-heteroalkyl, cycloalkyl, -alkyl-cycloalkyl, -O-cycloalkyl, -O-alkyl-cycloalkyl, -heterocycloalkyl, -alkyl-heterocycloalkyl, -O-heterocycloalkyl and -O-alkyl-heterocycloalkyl, wherein each said alkyl, -alkyl-OH, heteroalkyl, -heteroalkyl-OH, alkoxy, -O-heteroalkyl, cycloalkyl, -alkyl-cycloalkyl, -O-cycloalkyl, -O-alkyl-cycloalkyl, -heterocycloalkyl, -alkyl-heterocycloalkyl, -O-heterocycloalkyl and -O-alkyl-heterocycloalkyl are optionally substituted with one or more halogen.

Claim 2. A compound of claim 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, wherein:

R^1 is methyl;

R^2 is H; and

R^3 is H.

Claim 3. A compound of claim 2, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, wherein:

s is 1;

X is -O-; and

Y is $-C(R^{1Y})_2-$,

wherein each R^{1Y} is independently selected from the group consisting of H, lower alkyl, and lower heteroalkyl, wherein said lower alkyl and lower heteroalkyl are each optionally independently unsubstituted or substituted with one or more halogen.

Claim 4. A compound of claim 2, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, wherein:

s is 0;

Y is absent; and

X is selected from the group consisting of $-C(R^{1X})_2-$ and -O-,

wherein each R^{1X} (when present) is independently selected from the group consisting of H, halogen, lower alkyl, and lower heteroalkyl, wherein said lower alkyl and lower heteroalkyl are each optionally independently unsubstituted or substituted with one or more halogen.

Claim 5. A compound of claim 2, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, wherein:

s is 1;

X is $-C(R^{1X})_2-$; and

Y is selected from the group consisting of $-C(R^{1Y})_2-$ and -O-;

R^{1X} is independently selected from the group consisting of H, halogen, lower alkyl, and lower heteroalkyl, wherein said lower alkyl and lower heteroalkyl are each optionally independently unsubstituted or substituted with one or more halogen; and

R^{1Y} is H.

Claim 6. A compound of claim 2, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, wherein:

ring A is selected from the group consisting of phenyl, pyridyl, thienyl, pyrimidinyl, and pyrazinyl;

m is 0, 1, or 2; and

each R^A (when present) is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-NHCH_3$, $-N(CH_3)_2$, $-OCH_3$, $-OCH_2CH_3$, -O-cyclopropyl, -O-CH_2-cyclopropyl, $-CH_2OCH_3$, $-S(CH_3)$, methyl, ethyl, cyclopropyl, -CH_2-cyclopropyl, $-C\equiv C-CH_3$, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, and $-OCHF_2$.

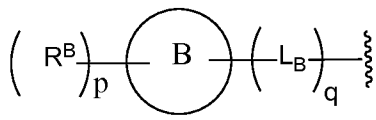
Claim 7. A compound of claim 6, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, wherein:

R^L is selected from the group consisting of lower alkyl and lower heteroalkyl, wherein said lower alkyl and lower heteroalkyl of R^L are each optionally unsubstituted or substituted with one or more halogen.

Claim 8. A compound of claim 7, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, wherein:

$-L_1-$ is -C(O)NH-.

Claim 9. A compound of claim 6, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, wherein:

R^L is a moiety having the formula 

, wherein:

q is 1;

$-L_B-$ (when present) is a divalent moiety selected from the group consisting of $-CH_2-$, $-CF_2-$, and $-CH_2CH_2-$;

ring B is selected from the group consisting of isoxazolyl, oxadiazoyl, oxazolyl, phenyl, pyridinyl, pyrazinyl, pyrimidinyl, and pyrazolyl;

p is 0 or more; and

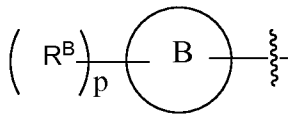
each R^B group (when present) is independently selected from the group consisting of fluoro, chloro, bromo, -CN, $-S(O)_2CH_3$, $-OCH_3$, -O-cyclopropyl, -O-CH_2-cyclopropyl,

—OCH_2–C≡C–H, —OCH_2–C≡C–CH_3, methyl, cyclopropyl, -CH_2-cyclopropyl, -CH_2OCH_3, —C≡CH, —C≡C–CH_3, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, and -OCH_2CH_2F.

Claim 10. A compound of claim 9, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, wherein:

-L_1- is -C(O)NH-.

Claim 11. A compound of claim 6, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, wherein:

q is 0; and R^L is a moiety having the formula 

, wherein:

ring B is selected from the group consisting of isoxazolyl, oxadiazoyl, oxazolyl, phenyl, pyridinyl, pyrazinyl, pyrimidinyl, and pyrazolyl;

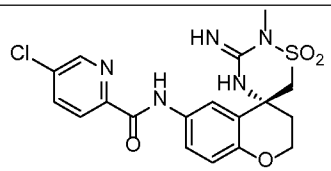
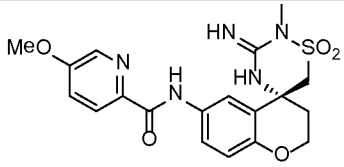
p is 0 or more; and

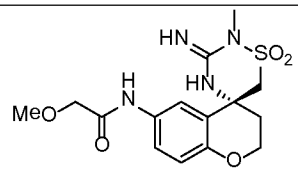
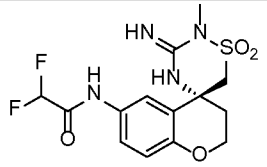
each R^B group (when present) is independently selected from the group consisting of fluoro, chloro, bromo, -CN, -$S(O)_2CH_3$, -OCH_3, -O-cyclopropyl, -O-CH_2-cyclopropyl, —OCH_2–C≡C–H, —OCH_2–C≡C–CH_3, methyl, cyclopropyl, -CH_2-cyclopropyl, -CH_2OCH_3, —C≡CH, —C≡C–CH_3, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, and -OCH_2CH_2F.

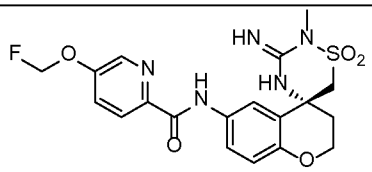
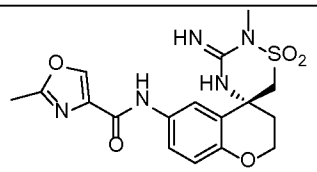
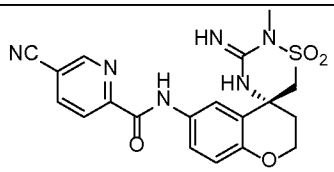
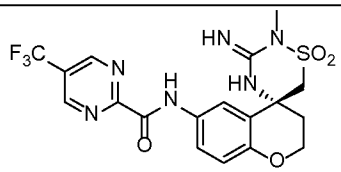
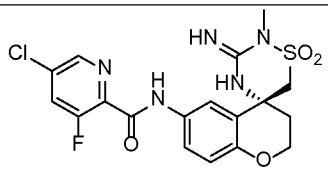
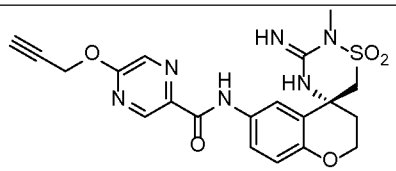
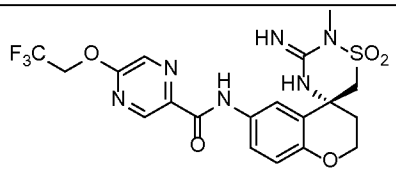
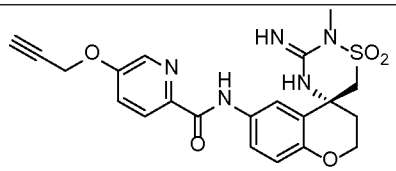
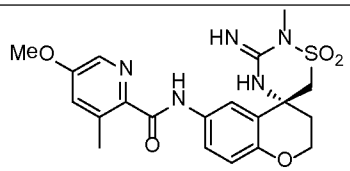
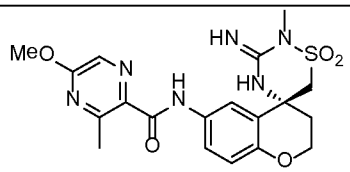
Claim 12. A compound of claim 11, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, wherein:

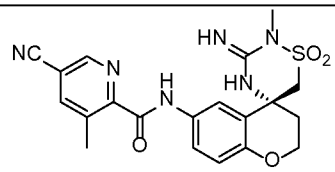
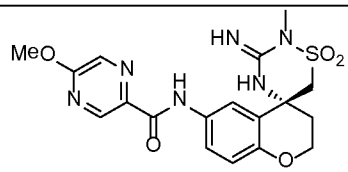
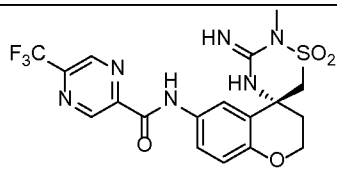
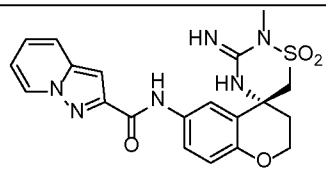
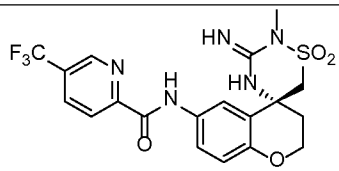
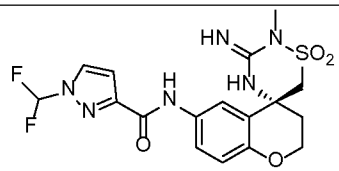
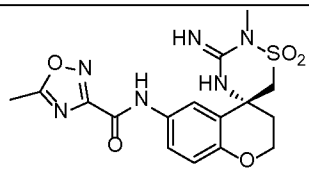
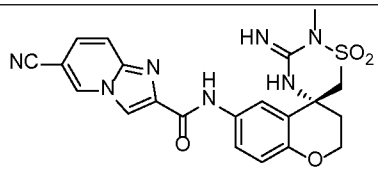
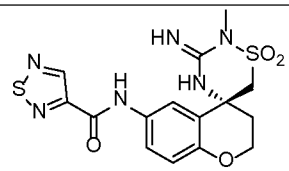
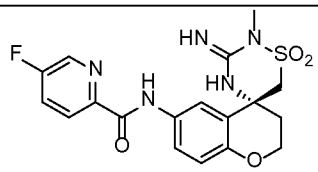
-L_1- is -C(O)NH-.

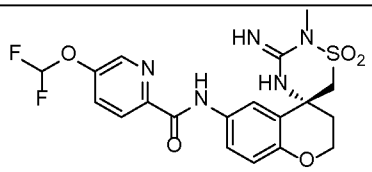
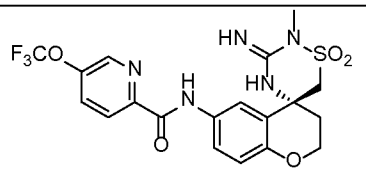
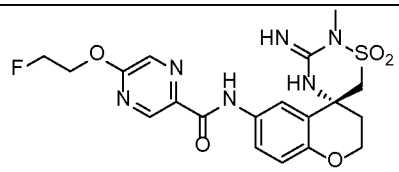
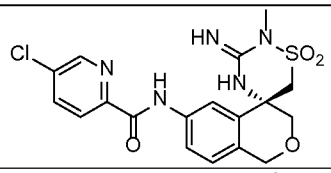
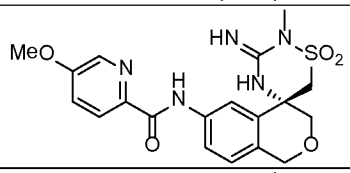
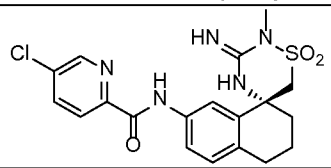
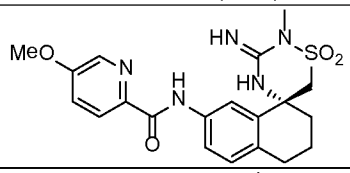
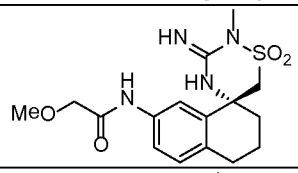
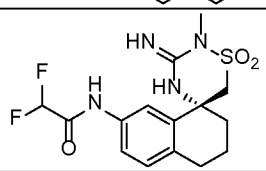
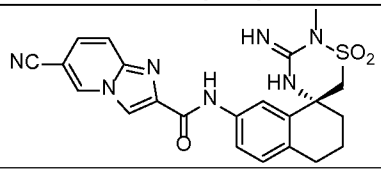
Claim 13. A compound of claim 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound selected from the group consisting of:

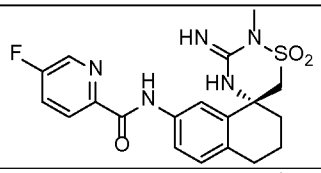
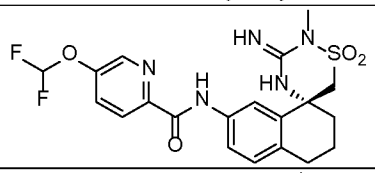
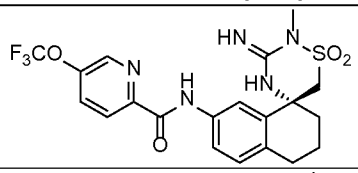
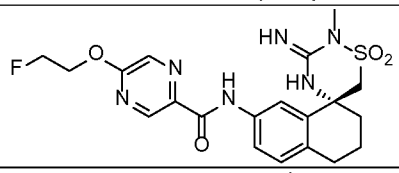
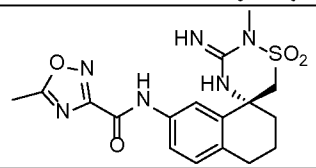
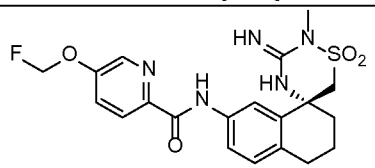
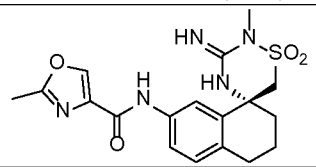
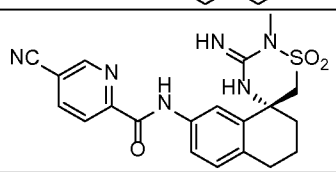
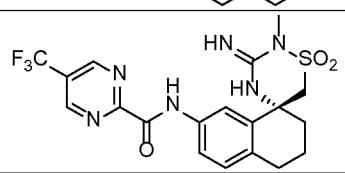
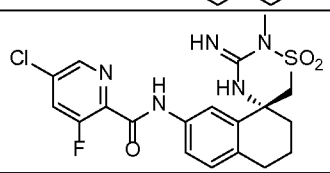
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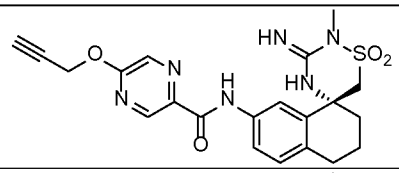
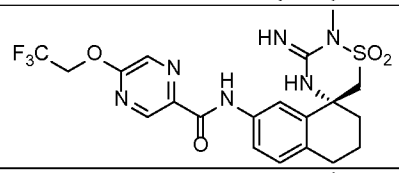
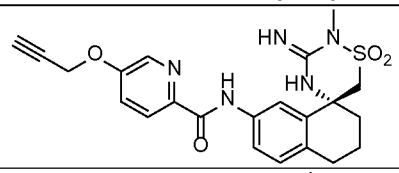
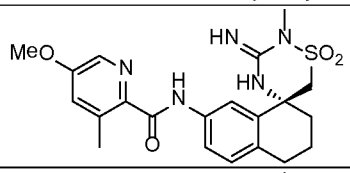
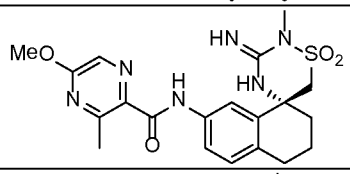
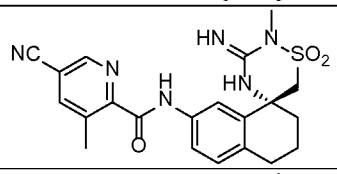
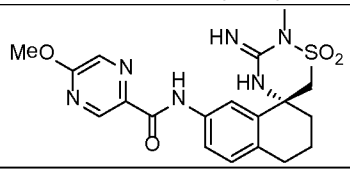
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1d	

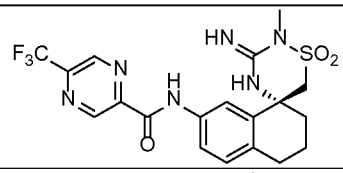
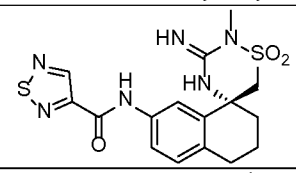
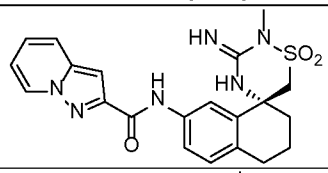
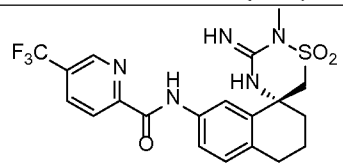
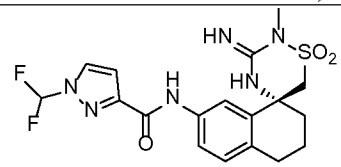
2a	
2b	
2c	
2d	
2e	
2f	
2g	
2h	
2i	
2j	

2k	
2l	
2m	
2n	
2o	
2p	
2q	
2r	
2s	
2t	

2u	
2v	
2w	
3a	
3b	
4a	
4b	
4c	
4d	
5a	

5b	
5c	
5d	
5e	
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5g	
5h	
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5l	
5m	
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5q	
5r	

5s	
5t	
5u	
5v	 , and
5w	 .

Claim14. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, and a pharmaceutically acceptable carrier or diluent.

Claim15. A method of treating a disease or pathology, wherein said disease or pathology is Alzheimer's disease, olfactory impairment associated with Alzheimer's disease, Down's syndrome, olfactory impairment associated with Down's syndrome, Parkinson's disease, olfactory impairment associated with Parkinson's disease, stroke, microgliosis brain inflammation, pre-senile dementia, senile dementia, progressive supranuclear palsy, cortical basal degeneration, β-amyloid angiopathy, cerebral amyloid angiopathy, hereditary cerebral

hemorrhage, mild cognitive impairment, glaucoma, amyloidosis, type II diabetes, diabetes-associated amyloidogenesis, scrapie, bovine spongiform encephalitis, traumatic brain injury, or Creutzfeld-Jakob disease, said method comprising administering a compound according to any one of claims 1 to 13, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, to a patient in need thereof in an amount effective to treat said disease or pathology.

Claim16. The method of claim 15, wherein disease or pathology is Alzheimer's disease.

Claim17. A compound according to any one of claims 1 to 13, or a tautomer thereof, or pharmaceutically acceptable salt of said compound or said tautomer, for use as a medicament.

Claim18. Use of a compound according to any one of claims 1 to 13, or a tautomer thereof, or pharmaceutically acceptable salt of said compound or said tautomer, for the manufacture of a medicament for the treatment of a disease or pathology, wherein said disease or pathology is Alzheimer's disease, olfactory impairment associated with Alzheimer's disease, Down's syndrome, olfactory impairment associated with Down's syndrome, Parkinson's disease, olfactory impairment associated with Parkinson's disease, stroke, microgliosis brain inflammation, pre-senile dementia, senile dementia, progressive supranuclear palsy, cortical basal degeneration, β-amyloid angiopathy, cerebral amyloid angiopathy, hereditary cerebral hemorrhage, mild cognitive impairment, glaucoma, amyloidosis, type II diabetes, diabetes-associated amyloidogenesis, scrapie, bovine spongiform encephalitis, traumatic brain injury, or Creutzfeld-Jakob disease.

Claim19. Use according to claim 18, wherein said disease or pathology is Alzheimer's disease.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 23057	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US13/75400	International filing date *(day/month/year)* 16 December 2013 (16.12.2013)	(Earliest) Priority Date *(day/month/year)* 21 December 2012 (21.12.2012)
Applicant Merck Sharp & Dohme Corp.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

CS-SPIRO IMINOTHIADIAZINE DIOXIDES AS BACE INHIBITORS

5. With regard to the **abstract**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

International application No.
PCT/US13/75400

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

In its many embodiments, the present invention provides certain C5-spiro iminothiadiazine dioxide compounds, including compounds Formula (I): (structurally represented) or tautomers thereof, and pharmaceutically acceptable salts of said compounds, wherein R1, R2, R3, X, Y, s, ring A, RA, m, -L1-, and RL are as defined herein. The novel compounds of the invention are useful as BACE inhibitors and/or for the treatment and prevention of various pathologies related thereto. Pharmaceutical compositions comprising one or more such compounds (alone and in combination with one or more other active agents), and methods for their preparation and use, including for the possible treatment of Alzheimer's disease, are also disclosed.

INTERNATIONAL SEARCH REPORT PCT/US2013/075400 22.04.2014

International application No.
PCT/US13/75400

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/519, 31/497 (2014.01)
USPC - 514/255; 544/314
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) Classification(s): A61K 31/519, 31/497, 31/513; C07D 413/02 (2014.01)
USPC Classification(s): 514/255; 544/314, 405; 546/272; 548/311

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 practicable, search terms used)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); ProQuest; Scifinder; Google/Google Scholar; KEYWORDS: merck, sharp, dohme, cumming, bace, inhibitors, alzheimer's, disease, c5-spiro, iminothiadiazine, dioxide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/0111370 A1 (ZHU, Z et al.) 25 May 2006; formula I; paragraphs [0014]-[0020], [0025], [0057], [0059], [0110], [0114] and [0126]	1-12, 14/1-12, 15/1-12, 16/15/1-12, 17/1-12, 18/1-12, 19/18/1-12
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A		13, 14/13, 15/13, 16/15/13, 17/13, 18/13, 19/18/13
A	WO 2012/138734 A1 (CUMMING, JN et al.) 11 October 2012; formulas I and I'; page 6, lines 1-10	1-13, 14/1-13, 15/1-13, 16/15/1-13, 17/1-13, 18/1-13, 19/18/1-13
A	WO 2012/139425 A1 (WU, WL et al.) 18 October 2012; formula I; formulas I and I'; page 7, lines 15-20; page 8, lines 1-5	1-13, 14/1-13, 15/1-13, 16/15/1-13, 17/1-13, 18/1-13, 19/18/1-13
A	US 2011/0110957 A1 (STAMFORD, AW et al.) 12 May 2011; entire document	1-13, 14/1-13, 15/1-13, 16/15/1-13, 17/1-13, 18/1-13, 19/18/1-13
A	US 2012/0148603 A1 (STAMFORD, AW et al.) 14 June 2012; entire document	1-13, 14/1-13, 15/1-13, 16/15/1-13, 17/1-13, 18/1-13, 19/18/1-13
A	US 2012/0183563 A1 (SCOTT, JD et al.) 19 July 2012; entire document	1-13, 14/1-13, 15/1-13, 16/15/1-13, 17/1-13, 18/1-13, 19/18/1-13

☒ 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
11 March 2014 (11.03.2014)

Date of mailing of the international search report
22 APR 2014

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:
Shane Thomas
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

International application No.
PCT/US13/75400

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2012/0189642 A1 (SCOTT, JD et al.) 26 July 2012; entire document	1-13, 14/1-13, 15/1-13, 16/15/1-13, 17/1-13, 18/1-13, 19/18/1-13
A	US 2012/0195881 A1 (ISERLOH, U et al.) 02 August 2012; entire document	1-13, 14/1-13, 15/1-13, 16/15/1-13, 17/1-13, 18/1-13, 19/18/1-13
A	WO 2012/138590 A1 (STAMFORD, AW et al.) 11 October 2012; entire document	1-13, 14/1-13, 15/1-13, 16/15/1-13, 17/1-13, 18/1-13, 19/18/1-13
A	US 2004/0043979 A1 (PICARD, JA) 04 March 2004; entire document	1-13, 14/1-13, 15/1-13, 16/15/1-13, 17/1-13, 18/1-13, 19/18/1-13
A	US 2009/0131342 A1 (ELLIS, JL et al.) 21 May 2009; entire document	1-13, 14/1-13, 15/1-13, 16/15/1-13, 17/1-13, 18/1-13, 19/18/1-13