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.

The therapeutic potential of inhibiting the deposition of Aβ has motivated many groups to characterize BACE-1 and to identify inhibitors of BACE-1 and of other secretase enzyme inhibitors. Examples from the patent literature are growing and include WO2006009653, WO2007005404, WO2007005366, WO2007038271, WO2007016012, US2005/0282826, US2007072925, WO2007149033, WO2007145568, WO2007145569, WO2007145570,WO2007145571, WO2007114771, US20070299087, WO2005/016876, WO2005/014540, WO2005/058311, WO2006/065277, WO2006/014762, WO2006/014944, WO2006/138195, WO2006/138264, WO2006/138192, WO2006/138217, WO2007/050721, WO2007/053506, WO2007/146225, WO2006/138230, WO2006/138265, WO2006/138266, WO2007/053506, WO2007/146225, WO2008/073365, WO2008/073370, WO2008/103351, US2009/041201, US2009/041202, and WO2010/047372.

SUMMARY ~~OF THE INVENTION~~

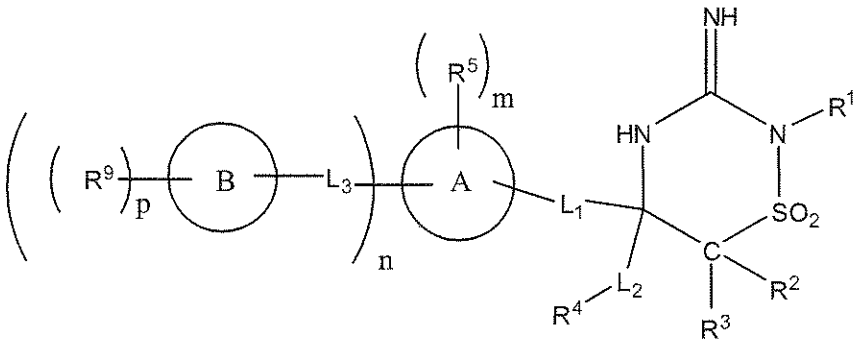
The present ~~invention~~disclosure provides certain iminothiadiazine dioxide compounds which are collectively or individually referred to herein as "compound(s) of the invention" or "compound(s) of the disclosure", as described herein. The novel iminothiadiazine dioxide compounds of the ~~invention~~disclosure have surprisingly been found to exhibit properties which are expected to render them advantageous as BACE inhibitors and/or for the treatment and prevention of the various pathologies described herein.

In each of the various embodiments of the compounds of the ~~invention~~disclosure described herein, each variable including those of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), and the various embodiments thereof, each variable is selected independently of the others unless otherwise indicated.

In each of the various embodiments of the compounds of the ~~invention~~disclosure described herein, including those of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), and the various embodiments thereof and the compounds of the examples, such formulas and examples

are intended to encompass all forms of the compounds such as, for example, any solvates, hydrates, stereoisomers, and tautomers of said compounds and of any pharmaceutically acceptable salts thereof.

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



(I)

and include tautomers, solvates, prodrugs, and esters thereof, and pharmaceutically acceptable salts of said compounds, tautomers, solvates, prodrugs, and esters,

wherein:

-L_1- represents a bond or a divalent moiety selected from the group consisting of -alkyl-, -haloalkyl-, -heteroalkyl-, -alkenyl-, and -alkynyl-;

-L_2- represents a bond or a divalent moiety selected from the group consisting of -alkyl-, -haloalkyl-, -heteroalkyl-, -alkenyl-, and -alkynyl-;

each -L_3- independently represents a bond or a divalent moiety independently selected from the group consisting of -alkyl-, -haloalkyl-, -heteroalkyl-, -alkenyl-, -alkynyl-, -N(R^7)-, –NHC(O)-, -C(O)NH-, -NHS(O)$_2$-, -S(O)$_2$NH-, -O-alkyl-, -alkyl-O-, -N(R^7)-alkyl-, -alkyl-N(R^7)-, -haloalkyl-NH-, and –NH-haloalkyl-;

m, n, and p are each independently selected integers, wherein:

m is 0 or more;

n is 0 or more; and

p is 0 or more,

wherein the maximum value of the sum of m and n is the maximum number of available substitutable hydrogen atoms on ring A, and wherein the maximum value of p is the maximum number of available substitutable hydrogen atoms on ring B;

selected from the group consisting of lower alkyl, lower alkenyl, lower alkynyl, lower heteroalkyl, halo, -CN, $-SF_5$, $-OSF_5$, $-NO_2$, $-N(R^8)_2$, $-OR^7$, $-C(O)N(R^8)_2$, and cycloalkyl;

each R^6 (when present) is independently selected from the group consisting of alkyl, aryl, arylalkyl-, haloalkyl, cycloalkyl, cycloalkylalkyl-, heteroaryl, and heteroarylalkyl-;

each R^7 (when present) is independently selected from the group consisting of H, alkyl, alkenyl, heteroalkyl, haloalkyl, aryl, arylalkyl-, heteroaryl, heteroarylalkyl-, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl, and heterocycloalkylalkyl-;

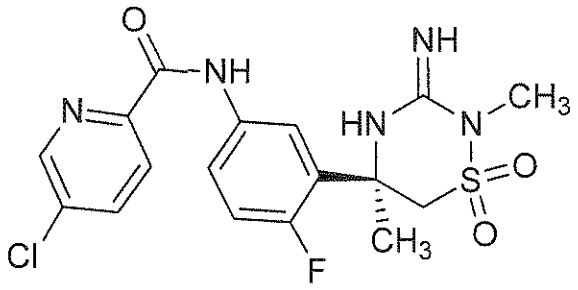
each R^8 (when present) is independently selected from the group consisting of H, alkyl, alkenyl, heteroalkyl, haloalkyl, haloalkenyl, aryl, arylalkyl-, heteroaryl, heteroarylalkyl-, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl, and heterocycloalkylalkyl-;

each R^9 (when present) is independently selected from the group consisting of: halogen, -CN, $-SF_5$, $-OSF_5$, $-NO_2$, $-Si(R^6)_3$, $-P(O)(OR^7)_2$, $-P(O)(OR^7)(R^7)$, $-N(R^8)_2$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)N(R^8)_2$, $-NR^8C(O)OR^7$, $-C(O)R^7$, $-C(O)_2R^7$, $-C(O)N(R^8)_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2N(R^8)_2$, $-OR^7$, $-SR^7$, alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, aryl, arylalkyl-, cycloalkyl, heteroaryl, heteroarylalkyl-, and heterocycloalkyl;

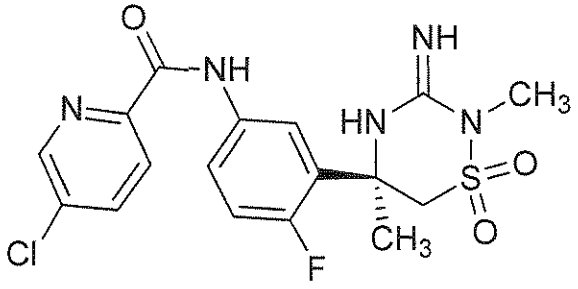
each R^{10} (when present) is independently selected from the group consisting of halo, -CN, $-NO_2$, $-Si(R^6)_3$, $-P(O)(OR^7)_2$, $-P(O)(OR^7)(R^7)$, $-N(R^8)_2$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)N(R^8)_2$, $-NR^8C(O)OR^7$, $-C(O)R^7$, $-C(O)_2R^7$, $-C(O)N(R^8)_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2N(R^8)_2$, $-OR^7$, $-SR^7$, alkyl, haloalkyl, haloalkoxy, heteroalkyl, alkenyl, alkynyl, and cycloalkyl,

wherein each said alkyl, haloalkyl, haloalkoxy, heteroalkyl, alkenyl, alkynyl, and cycloalkyl of R^{10} (when present) is optionally independently unsubstituted or further substituted with one or more independently selected groups selected from the group consisting of lower alkyl, lower alkenyl, lower alkynyl, lower heteroalkyl, halo, -CN, $-NO_2$, $-N(R^8)_2$, $-OR^7$, and $-C(O)N(R^8)_2$.

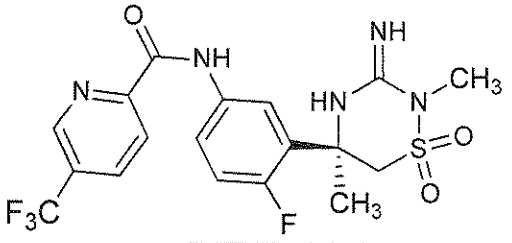
In a first aspect, there is provided a compound, or a tautomer thereof, said compound having a structure:



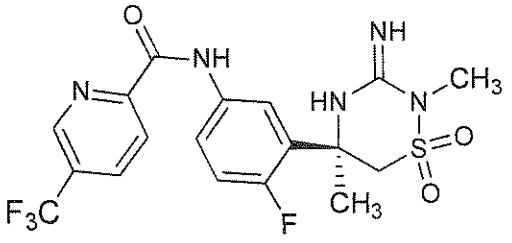
In a second aspect, there is provided a pharmaceutically acceptable salt of a compound or a tautomer thereof, said compound having a structure:



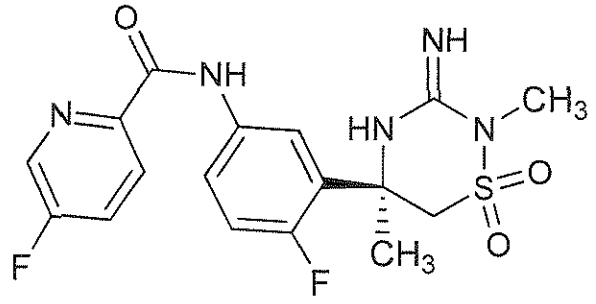
In a third aspect, there is provided a compound, or a tautomer thereof, said compound having a structure:



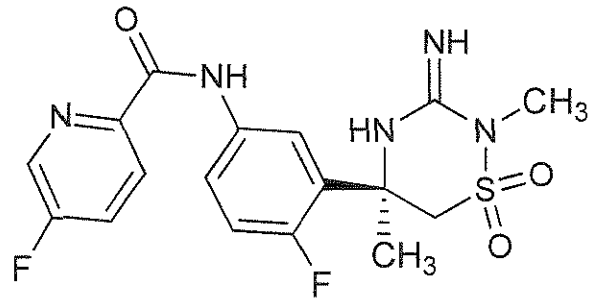
In a fourth aspect, there is provided a pharmaceutically acceptable salt of a compound or a tautomer thereof, said compound having a structure:



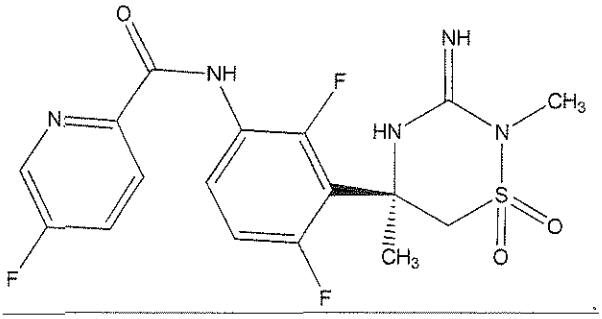
In a fifth aspect, there is provided a compound, or a tautomer thereof, said compound having a structure:



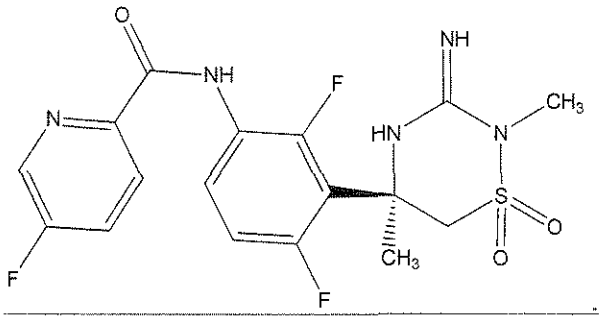
In a sixth aspect, there is provided a pharmaceutically acceptable salt of a compound or a tautomer thereof, said compound having a structure:



In a seventh aspect, there is provided a compound, or a tautomer thereof, said compound having a structure:



In an eighth aspect, there is provided a pharmaceutically acceptable salt of a compound or a tautomer thereof, said compound having a structure:



In a ninth aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the compound as defined herein or a tautomer thereof.

In a tenth aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the pharmaceutically acceptable salt as defined herein.

In an eleventh aspect, there is provided the use of a compound, or a tautomer thereof, as defined herein, or a pharmaceutically acceptable salt of said compound or said tautomer in the manufacture of a medicament for the treatment of an indication selected from the group consisting of Alzheimer's disease, Down's syndrome, Parkinson's disease, stroke, microgliosis, brain inflammation, pre-senile dementia, senile dementia, progressive supranuclear palsy, cortical basal degeneration, olfactory impairment associated with Alzheimer's disease, olfactory impairment associated with Parkinson's disease, olfactory impairment associated with Down's syndrome, 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, and Creutzfeld-Jakob disease.

In other embodiments, the ~~invention~~disclosure provides compositions, including pharmaceutical compositions, comprising one or more compounds of the ~~invention~~disclosure (e.g., one compound of the ~~invention~~disclosure), 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.

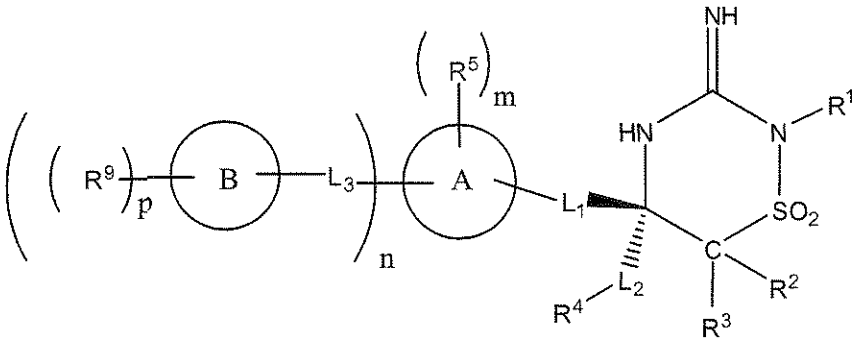
In other embodiments, the ~~invention~~disclosure provides various methods of treating, preventing, ameliorating, and/or delaying the onset of an amyloid β pathology (Aβ pathology) and/or a symptom or symptoms thereof, comprising administering a composition comprising an effective amount of one or more compounds of the ~~invention~~disclosure, 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 suitable for treating the patient being treated.

These and other embodiments of the ~~invention~~disclosure, 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~~disclosure.

DETAILED DESCRIPTION:

In one embodiment, the compounds of the invention have the structural Formula (I) as described above.

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



(IA)

and include tautomers, and prodrugs thereof, and pharmaceutically acceptable salts, and solvates of said compounds, tautomers, and prodrugs, wherein R^1, L_1, L_2, L_3, R^2, R^3, R^4, R^5, R^9, ring A, ring B, m, n, and p are each as defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (IA-1):