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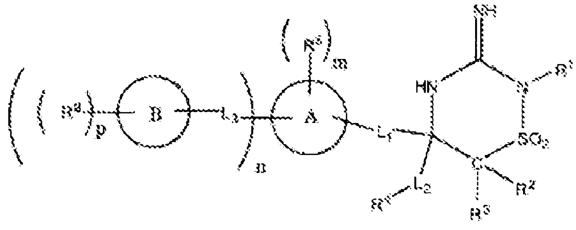
IMINOTHIADIAZINE DIOXIDE COMPOUNDS AS BACE INHIBITORS, COMPOSITIONS, AND THEIR USE

Abstract



(I)

In its many embodiments, the present invention provides certain iminothiadiazine dioxide compounds, including compounds Formula (I): (I) and include stereo isomers thereof, and pharmaceutically acceptable salts of said compounds stereo isomers, wherein each of R^1, R^2, R^3, R^4, R^5, R^9, ring A, ring B, m, n, p, $-L_1-$,L_2-, and L_3- is selected independently and as defined herein. The novel iminothiadiazine dioxide compounds of the invention 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 various pathologies related to B-amyloid (AB) production. 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 in treating pathologies associated with amyloid beta (AB) protein, including Alzheimers disease, are also disclosed.

IMINOTHIADIAZINE DIOXIDE COMPOUNDS AS BACE INHIBITORS, COMPOSITIONS, AND THEIR USE

RELATED APPLICATIONS

This application claims priority to provisional application U.S. Serial No. 61/249,685, filed October 08, 2009, incorporated herein by reference.

FIELD OF THE INVENTION

This invention provides certain iminothiadiazine dioxide compounds and compositions comprising these compounds. The novel iminothiadiazine dioxide compounds of the invention 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 various pathologies related to β-amyloid ("Aβ") production.

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 near the 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®, Forrest 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.

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

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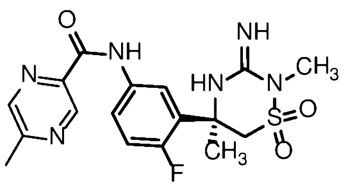
amyloidosis with agents that inhibit Aβ peptide formation. As another example, Loane, et al. report the targeting of amyloid precursor protein secretases as therapeutic targets for traumatic brain injury. (Loane et al., "Amyloid precursor protein secretases as therapeutic targets for traumatic brain 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.

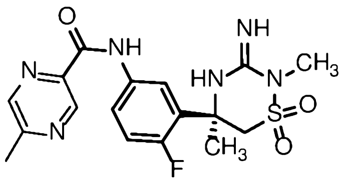
The therapeutic potential of inhibiting the deposition of Aβ has motivated many groups to characterize BACE-1 and to identify inhibitors of BACE-1 and of other secretase enzyme inhibitors. Examples from the patent literature are growing and include WO2006009653, WO2007005404, WO2007005366, WO2007038271, 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

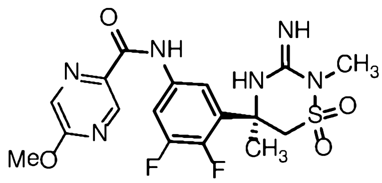
A first aspect of the invention provides for a compound, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound having a structure:



A second aspect of the invention provides for a pharmaceutically acceptable salt of a compound, or a tautomer thereof, said compound having a structure:



A third aspect of the invention provides for a compound, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound having a structure:



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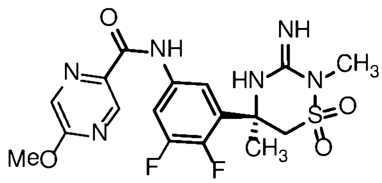
A fourth aspect of the invention provides for a pharmaceutically acceptable salt of a compound, or a tautomer thereof, said compound having a structure:



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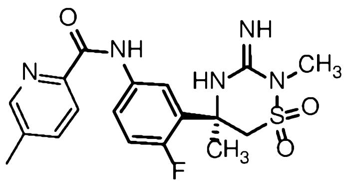
A fifth aspect of the invention provides for a compound, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound having a structure:



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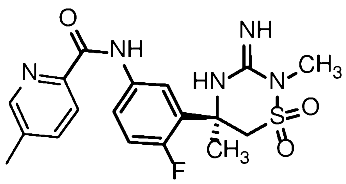
A sixth aspect of the invention provides for a pharmaceutically acceptable salt of a compound, or a tautomer thereof, said compound having a structure:



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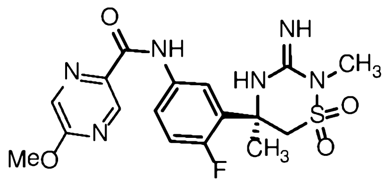
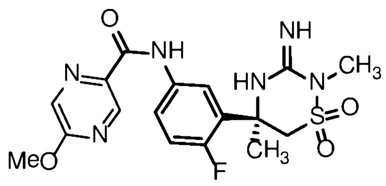
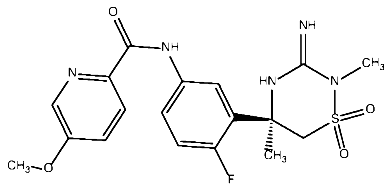
A seventh aspect of the invention provides for a compound, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound having a structure:



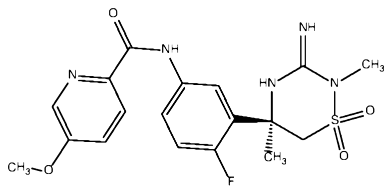
An eighth aspect of the invention provides for a pharmaceutically acceptable salt of a compound, or a tautomer thereof, said compound having a structure:



A ninth aspect of the invention provides for a compound, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound having a structure:



A tenth aspect of the invention provides for a pharmaceutically acceptable salt of a compound, or a tautomer thereof, said compound having a structure:



An eleventh aspect of the invention provides for a pharmaceutically acceptable salt of the compound of the first to tenth aspects of the invention, or a tautomer thereof, wherein said salt is selected from the group consisting of acetate, ascorbate, benzoate, benzenesulfonate, bisulfate, borate, butyrate, citrate, camphorate, camphorsulfonate, fumarate, hydrochloride, hydrobromide, hydroiodide, lactate, maleate, methanesulfonate, naphthalenesulfonate, nitrate, oxalate, phosphate, propionate, salicylate, succinate, sulfate, tartarate, thiocyanate, and tosylate.

A twelfth aspect of the invention provides for a pharmaceutically acceptable salt of the compound of the first to tenth aspects of the invention, or a tautomer thereof, wherein said salt is a hydrochloride salt.

A thirteenth aspect of the invention provides for a pharmaceutically acceptable salt of the compound of the first to tenth aspects of the invention, or a tautomer thereof, wherein said salt is a tosylate salt.

A fourteenth aspect of the invention provides for a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound of the first, third, fifth, seventh or ninth aspects of the invention, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer.

A fifteenth aspect of the invention provides for a use of a compound of the first, third, fifth, seventh or ninth aspects of the invention, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, for the manufacture of a medicament the treatment of an amyloid β pathology.

A sixteenth aspect of the invention provides for a method of treating an amyloid β pathology comprising administering a compound of the first, third, fifth, seventh or ninth aspects of the invention, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, or a pharmaceutical composition of the fourteenth aspect of the invention, to a patient in need thereof in an amount effective to treat said pathology.

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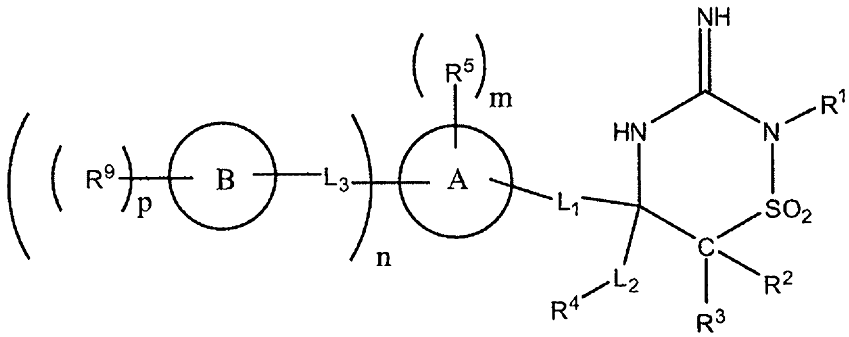
The present invention provides certain iminothiadiazine dioxide compounds which are collectively or individually referred to herein as "compound(s) of the invention", as described herein. The novel iminothiadiazine dioxide compounds of the invention have surprisingly been found to exhibit properties 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 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 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 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-, $-NHS(O)_2-$, $-S(O)_2NH-$, -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;

R^1 is selected from the group consisting of: H, alkyl, haloalkyl, heteroalkyl, heterohaloalkyl, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl, heterocycloalkylalkyl-, aryl, arylalkyl-, heteroaryl, and heteroarylalkyl-,

wherein each of said alkyl, haloalkyl, heteroalkyl, heterohaloalkyl, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl, heterocycloalkylalkyl-, aryl, arylalkyl-, heteroaryl, and heteroarylalkyl- of R^1 is unsubstituted or substituted with one or more independently selected R^{10} groups;

R^2 is selected from the group consisting of H, halo, alkyl, haloalkyl, and heteroalkyl,

wherein each of said alkyl and said haloalkyl of R^2 is unsubstituted or substituted with one or more independently selected R^{10} groups;

R^3 is selected from the group consisting of H, halo, alkyl, haloalkyl, and heteroalkyl,

wherein each of said alkyl and said haloalkyl of R^2 is unsubstituted or substituted with one or more independently selected R^{10} groups;

R^4 is selected from the group consisting of alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl,

wherein each of said alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl of R^4 is unsubstituted or substituted with one or more independently selected R^{10} groups;

ring A is selected from the group consisting of monocyclic aryl, monocyclic heteroaryl, monocyclic cycloalkyl, monocyclic cycloalkenyl, monocyclic heterocycloalkyl, monocyclic heterocycloalkenyl, and a multicyclic group;

each ring B (when present) is independently selected from the group consisting of monocyclic aryl, monocyclic heteroaryl, monocyclic cycloalkyl, monocyclic cycloalkenyl, monocyclic heterocycloalkyl, monocyclic heterocycloalkenyl, and a multicyclic group;

each R^5 (when present) is independently selected from the group consisting of halo, -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, haloalkoxy, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl,

wherein each said alkyl, haloalkyl, haloalkoxy, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^5 (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, $-SF_5$, $-OSF_5$, $-NO_2$, $-N(R^8)_2$, $-OR^7$, $-C(O)N(R^8)_2$, 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 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.

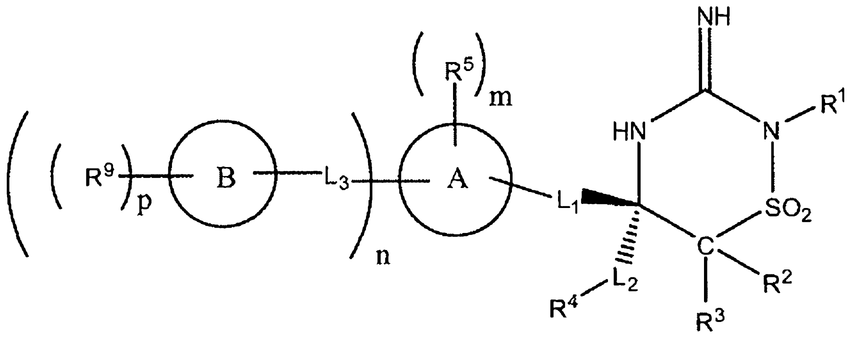
In other embodiments, the invention provides various methods of treating, preventing, ameliorating, and/or delaying the onset of an amyloid β pathology (Aβ pathology) and/or a symptom or symptoms thereof, comprising administering a composition comprising an effective amount of one or more compounds of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

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

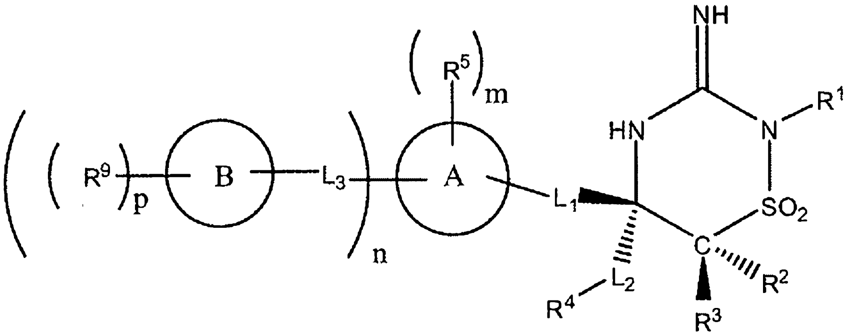
In one embodiment, the compounds of the invention have the structural Formula (IA):



(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).

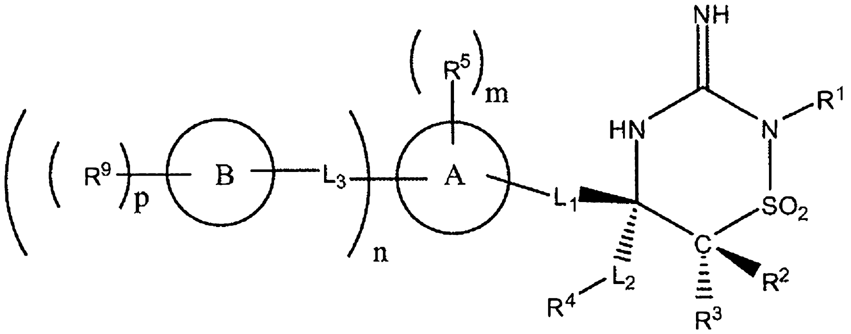
In one embodiment, the compounds of the invention have the structural Formula (IA-1):



(IA-1)

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-2):



(IA-2)

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, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^1 is selected from the group consisting of H, lower alkyl, and cyclopropyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^1 is selected from the group consisting of H and methyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^1 is H.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^1 is methyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^2 is H.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2):

R^1 is selected from the group consisting of H, lower alkyl, and cyclopropyl; and

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R^2 is H.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^3 is H and R^2 is H.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^3 is selected from the group consisting H, alkyl, haloalkyl, and heteroalkyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^3 is selected from the group consisting H, lower alkyl, halo lower alkyl, and lower alkyl ether.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^3 is selected from the group consisting H, alkyl, haloalkyl, and heteroalkyl; and R^2 is H.

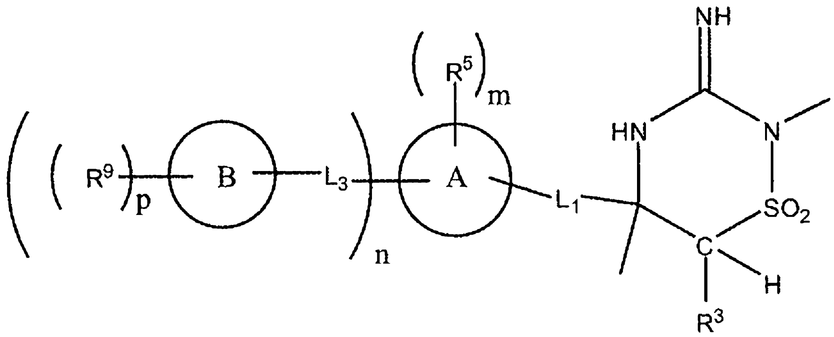
In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^3 is selected from the group consisting H, lower alkyl, halo lower alkyl, and lower alkyl ether; and R^2 is H.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), $-L_2-$ is a bond and R^4 is lower alkyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), $-L_2-$ is a bond and R^4 is methyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), and (IA-2), R^1 is lower alkyl, R^2 is H, $-L_2-$ is a bond, and R^4 is alkyl.

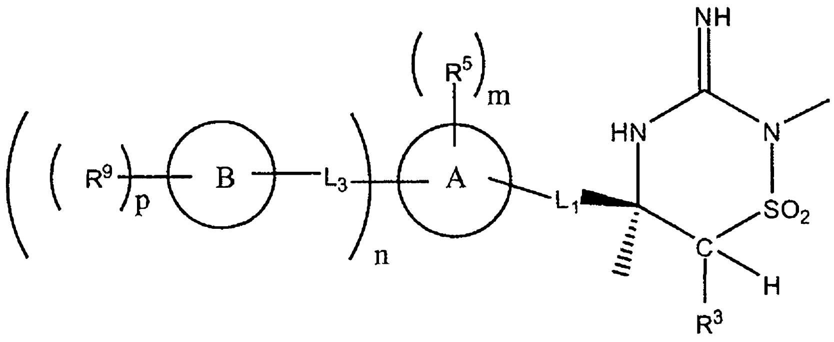
In one embodiment, the compounds of the invention have the structural Formula (II):



(II)

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

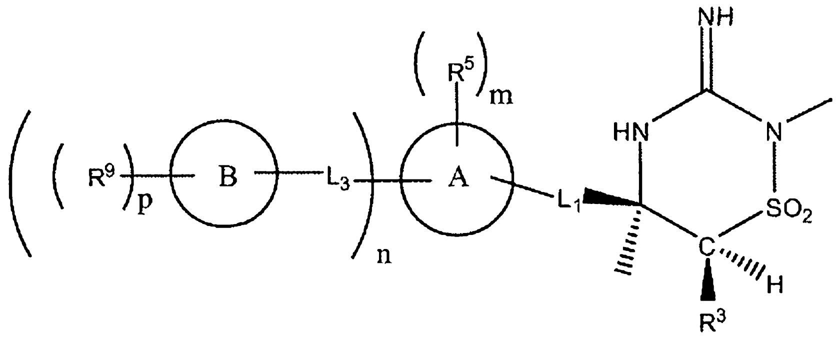
In one embodiment, the compounds of the invention have the structural Formula (IIA):



(IIA)

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

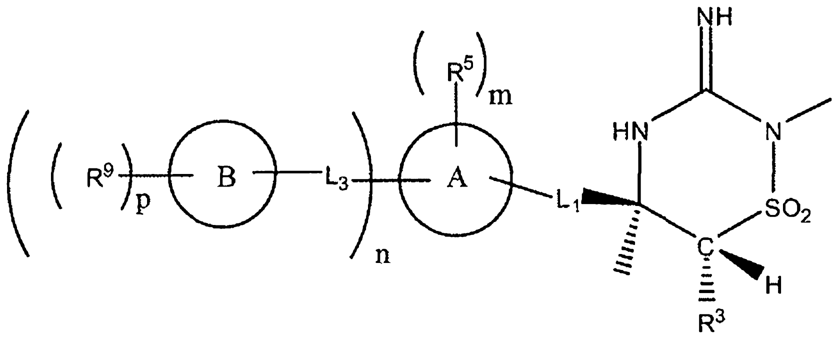
In one embodiment, the compounds of the invention have the structural Formula (IIA-1):



(IIA-1)

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

In one embodiment, the compounds of the invention have the structural Formula (IIA-2):



(IIA-2)

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

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2), R^3 is selected from the group consisting H, alkyl, haloalkyl, and heteroalkyl.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (IIA-2), R^3 is selected from the group consisting H, lower alkyl, halo lower alkyl, and lower alkyl ether.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2), R^3 is H.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2):

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

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2):

-L_1- represents a divalent moiety selected from the group consisting of -alkyl-, -haloalkyl-, -heteroalkyl-, and -alkenyl-.

-L_1- represents a divalent moiety selected from the group consisting of -alkyl-, and -haloalkyl-.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2):

-L_1- represents a bond or a divalent lower alkyl moiety.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2):

-L_1- represents a bond, $-CH_2-$, or $-CH_2CH_2-$.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2):

-L_1- represents a bond.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2):

$-L_1-$ represents a divalent lower alkyl moiety.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2):

$-L_1-$ represents $-CH_2-$.

In one embodiment, in each of Formulas (II), (IIA), (IIA-1), and (II-A2):

$-L_1-$ represents $-CH_2CH_2-$.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 0 and m is 1 or more.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 1 or more, p is 0 or more, and m is 0.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 1, p is 0 or more, and m is 0 or more.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 1, p is 0 or more, and m is 0, 1, 2, or 3.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 1, p is 0 or more, and m is 0, 1, or 2.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 1, p is 0 or more, and m is 0 or 1.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 1, p is 0 or more, and m is 1.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 1, p is 0 or more, and m is 2.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 1, p is 0 or more, and m is 3.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2): $-L_1-$ represents a bond or $-CH_2-$.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

ring A is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, imidazolyl, pyrazolyl, quinazolinyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzothienyl, naphthyl, quinolyl, isoquinolyl, indazolyl, indolyl, and thienopyrazolyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

ring A is selected from the group consisting of phenyl, pyridyl, thienyl, thiazolyl, naphthyl, isoquinolinyl, benzothienyl, benzimidazolyl, indazolyl, indolyl, and thienopyrazolyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

each -L_3- independently represents a bond or a divalent moiety selected from the group consisting of –NHC(O), –C(O)NH-, -NHS$(O)_2$-, -S$(O)_2$NH-, -O-CH_2-, -CH_2-O-, -NHCH_2-, -CH_2NH-, and -CH(CF_3)NH-.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

each -L_3- independently represents a bond or a divalent moiety selected from the group consisting of –NHC(O)- and –C(O)NH-.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 1 and -L_3- is represents a bond or a divalent moiety selected from the group consisting of –NHC(O)- and –C(O)NH-.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 1 and -L_3- represents a bond.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 1 and -L_3- is a divalent moiety selected from the group consisting of -NHC(O)- and -C(O)NH-.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 1 and -L_3- is –C(O)NH-.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 1 and -L_3- is –NHC(O)-.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

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n is 1 or more;

p is 0 or more; and

each ring B is independently selected from the group consisting of phenyl, pyridyl, pyrimidinyl, oxazolyl, isoxazolyl, pyrazinyl, thienyl, pyrazolyl, furanyl, thiazolyl, pyridazinyl, isothiazolyl, isoxazolyl, isothiazolyl, indolyl, pyrrolopyridinyl, and pyrrolopyrimidinyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 1 or more;

p is 0 or more; and

each ring B is independently selected from the group consisting of phenyl, pyridyl, pyrimidinyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, indolyl, pyrrolopyridyl, and pyrrolopyrimidinyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

m is 1 or more and each R^5 group is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-OSF_5$, $-N(R^8)_2$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)N(R^8)_2$, $-NR^8C(O)OR^7$, $-C(O)R^7$, $-C(O)_2R^7$, $-C(O)N(R^8)_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

m is 1 or more and each R^5 group is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, and cycloalkyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

m is 1 or more and each R^5 group is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, and cyclopropyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

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m is 0 or more, n is 1 or more, p is 1 or more, and each R^9 group is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-OSF_5$, $-N(R^8)_2$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)N(R^8)_2$, $-NR^8C(O)OR^7$, $-C(O)R^7$, $-C(O)_2R^7$, $-C(O)N(R^8)_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, aryl, arylalkyl-, cycloalkyl, heteroaryl, heteroarylalkyl-, and heterocycloalkyl.

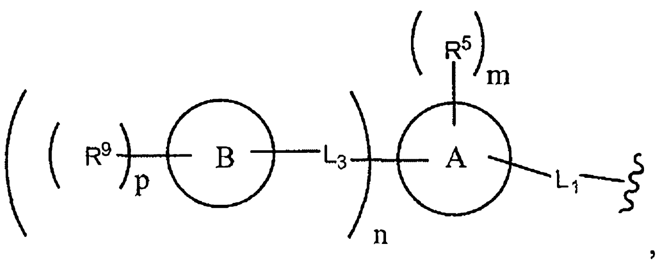
In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

m is 0 or more, n is 1 or more, p is 1 or more, and each R^9 group is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, phenyl, benzyl, and cycloalkyl.

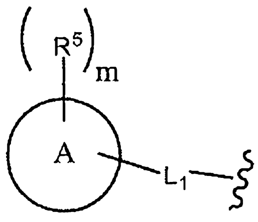
In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

m is 0 or more, n is 1 or more, p is 1 or more, and each R^9 group is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, phenyl, benzyl, and cyclopropyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2), n is 0 and the moiety:



, has the form



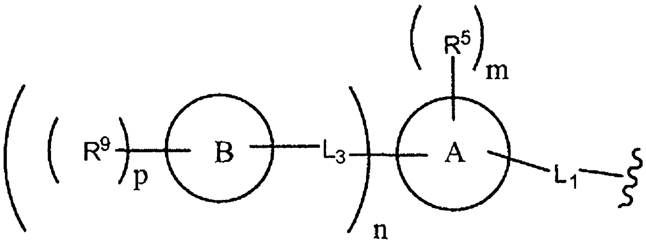
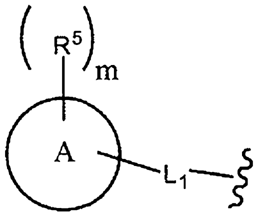
.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 0;

m is 1 or more;

the moiety:

, has the form ;

-L_1- represents a bond, $-CH_2-$, or $-CH_2CH_2-$;

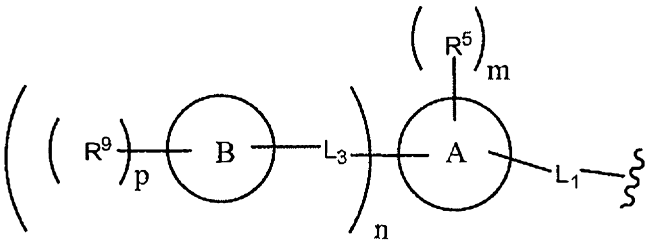
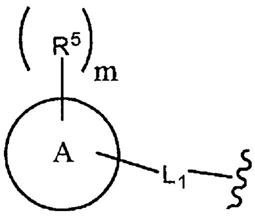
ring A is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, benzothienyl, benzimidazolyl, indazolyl, indolyl, and thienopyrazolyl; and

each R^5 group is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, and cycloalkyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

n is 0;

the moiety:

, has the form ;

-L_1- represents a bond, $-CH_2-$, or $-CH_2CH_2-$;

ring A is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, benzothienyl, benzimidazolyl, indazolyl, indolyl, and thienopyrazolyl;

m is 0 or more; and

each R^5 group (when present) is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, and cyclopropyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

ring A is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, benzothienyl, benzimidazolyl, indazolyl, indolyl, and thienopyrazolyl;

m is 0 or more;

each R^5 group (when present) is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, and cycloalkyl;

n is 1;

$-L_3-$ represents a bond or a divalent moiety selected from the group consisting of –NHC(O)- and –C(O)NH-;

ring B is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, pyrrolopyridyl, and pyrrolopyrimidinyl;

p is 0 or more; and

each R^9 group (when present) is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, phenyl, benzyl, and cycloalkyl.

In one embodiment, in each of Formulas (I), (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2):

$-L_1-$ represents a bond;

ring A is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, imidazolyl, pyrazolyl, quinazolinyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzothienyl, naphthyl, quinolyl, isoquinolyl, indazolyl, indolyl, and thienopyrazolyl.

m is 0 or more;

each R^5 group (when present) is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, and cyclopropyl;

n is 1;

$-L_3-$ represents a bond or a divalent moiety selected from the group consisting of -NHC(O), –C(O)NH-, $-NHS(O)_2-$, $-S(O)_2NH-$, $-O-CH_2-$, $-CH_2-O-$, $-NHCH_2-$, $-CH_2NH-$, and $-CH(CF_3)NH-$;

ring B is selected from the group consisting of phenyl, pyridyl, pyrimidinyl, oxazolyl, isoxazolyl, pyrazinyl, thienyl, pyrazolyl, furanyl, thiazolyl, pyridazinyl, isothiazolyl, isoxazolyl, isothiazolyl, indolyl, pyrrolopyridinyl, and pyrrolopyrimidinyl;

p is 0 or more; and

each R^9 group (when present) is independently selected from the group consisting of halogen, -CN, $-SF_5$, $-OSF_5$, $-N(R^8)_2$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)N(R^8)_2$, $-NR^8C(O)OR^7$, $-C(O)R^7$, $-C(O)_2R^7$, $-C(O)N(R^8)_2$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2N(R^8)_2$, $-OR^7$, $-SR^7$, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, aryl, arylalkyl-, cycloalkyl, heteroaryl, heteroarylalkyl-, and heterocycloalkyl. In one such embodiment, m and p are each independently 0, 1, 2, or 3 up to the maximum number of substitutable hydrogen atoms.

In one such embodiment, each R^5 (when present) is independently selected from the group consisting of halo.

In one such embodiment, each R^9 (when present) is independently selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, halo-substituted heteroalkyl, halo, -O-alkyl, -O-alkyl-OH, -O-deuteroalkyl, -O-heteroalkyl, -O-heteroalkyl-aryl, -O-haloalkyl, heteroaryl, alkyl-substituted heteroaryl, cycloalkyl, -O-alkyl-cycloalkyl, -O-cycloalkyl, OH, heterocycloalkyl, halo-substituted heteroaryl, CN, $-S(F)_5$, -S-alkyl, and $-S(O)_2$alkyl.

In another embodiment, the present invention encompasses deuterates of the compounds of the invention, or tautomers thereof, or a pharmaceutically acceptable salt of said deuterated compound or tautomer of the invention. Specific, non-limiting examples of deuterated compounds of the invention are as described and exemplified herein and include, deuterated compounds of Formulas (I^d), (II^d), and (III^d). Those of ordinary skill in the art will readily appreciate that, in addition to the non-limiting examples shown, other available hydrogen atoms may be deuterated in a similar manner as described hereinbelow. Such deuterated compounds are also to be considered as being among the compounds of the invention. The resulting compound is refered to herein as a "deuterated" compound of the invention or, alternatively, as "deuterate(s)" of compounds of the invention. The compounds of the invention may be deuterated in a manner known to those of ordinary skill in the art, e.g., as described herein.

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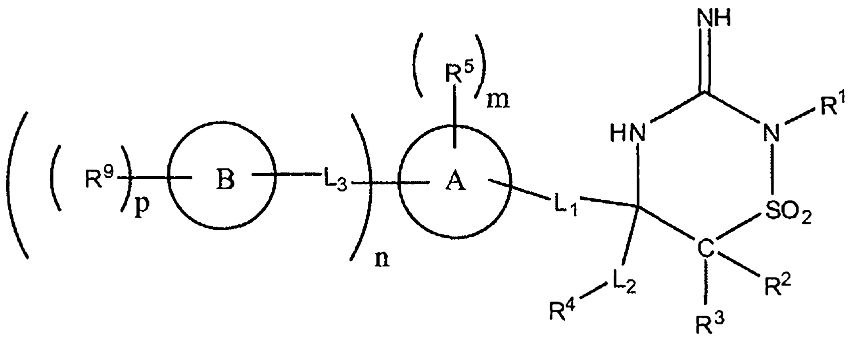
Thus, in one non-limiting embodiment, deuterated compounds of the invention have the structural Formula (I^d):



(I^d)

wherein:

one or more hydrogen atoms present in R^1, R^2, R^3, R^4, R^5 (when present) and/or R^9 (when present), or one or more of any available hydrogen atom(s) present on ring A or ring B (when present) is replaced by deuterium; and

each of the remaining variables is as defined in Formula (I), or as described in any of the embodiments described herein, e.g., those of Formulas (IA), (IA-1), (IA-2), (II), (IIA), (IIA-1), and (IIA-2) and the various embodiments thereof, are also within the scope of the compounds of Formula (I^d).

For example, in one non-limiting embodiment, in Formula (I^d), R^1 is $-CD_3$ and each of R^2, R^3, R^4, R^5, R^9, $-L_1-$, $-L_2-$, $-L_3-$, ring A, ring B, m, n, and p are as defined in Formula (I) or as in any one of (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), or (II-A2), or the various embodiments described herein.

As another example, in another non-limiting embodiment, in Formula (I^d), R^2 is D and each of R^1, R^3, R^4, R^5, R^9, $-L_1-$, $-L_2-$, $-L_3-$, ring A, ring B, m, n, and p are as defined in Formula (I) or as in any one of (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), or (II-A2), or the various embodiments described herein.

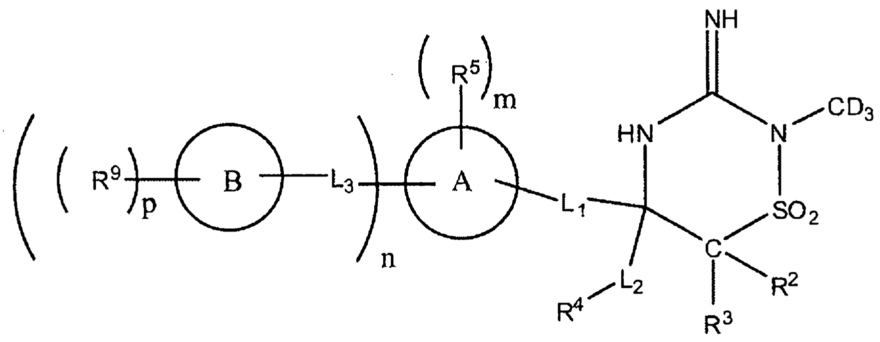
As another example, in another non-limiting embodiment, in Formula (I^d), R^3 is D and each of R^1, R^2, R^4, R^5, R^9, $-L_1-$, $-L_2-$, $-L_3-$, ring A, ring B, m, n, and p are as defined in Formula (I) or as in any one of (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), or (II-A2), or the various embodiments described herein.

As another example, in another non-limiting embodiment, in Formula (I^d), R^4 is partially or fully deuterated lower alkyl and each of R^1, R^2, R^3, R^5, R^9, $-L_1-$, $-L_2-$, $-L_3-$, ring A, ring B, m, n, and p are as defined in Formula (I) or as in any one of (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), or (II-A2), or the various embodiments described herein.

As another example, in another non-limiting embodiment, in Formula (I^d), R^5 is D and each of R^1, R^2, R^3, R^4, R^9, -L_1-, -L_2-, -L_3-, ring A, ring B, m, n, and p are as defined in Formula (I) or as in any one of (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), or (II-A2), or the various embodiments described herein.

As another example, in another non-limiting embodiment, in Formula (I^d), R^9 is D and each of R^1, R^2, R^3, R^4, R^5, -L_1-, -L_2-, -L_3-, ring A, ring B, m, n, and p are as defined in Formula (I) or as in any one of (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), or (II-A2), or the various embodiments described herein.

By way of further illustration, in another non-limiting embodiment, deuterated compounds of the invention have the structural Formula (II^d):



(II^d)

wherein:

the moiety $-CD_3$ represents a deuterated form of the moiety $-CH_3$; and

each of the remaining variables is as defined in Formula (I), or as described in any of the embodiments described herein, e.g., those of formulas (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), and (II-A2), and the various embodiments thereof, are also within the scope of the compounds of Formula (II^d).

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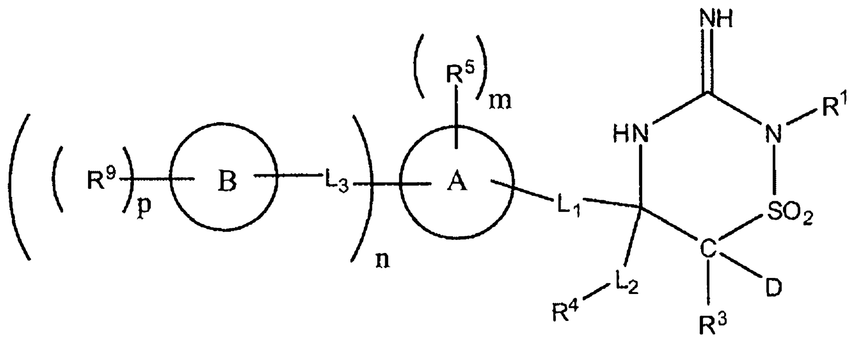
By way of further illustration, in another non-limiting embodiment, deuterated compounds of the invention have the structural Formula (III^d):



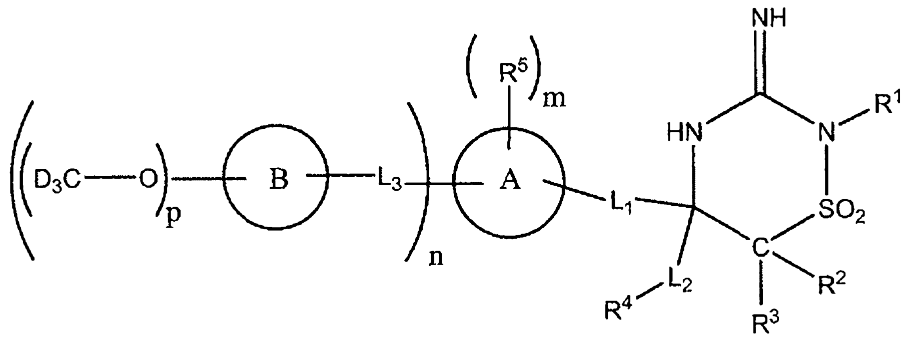
(III^d)

wherein:

the moiety –D represents a deuterated form of hydrogen; and

each of the remaining variables is as defined in Formula (I), or as described in any of the embodiments described herein, e.g., those of formulas (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), and (II-A2), and the various embodiments thereof, are also within the scope of the compounds of Formula (III^d). In one embodiment, in Formula (III^d), R^3 is D.

By way of further illustration, in another non-limiting embodiment, deuterated compounds of the invention have the structural Formula (IV^d):



(IV^d)

wherein:

the moiety –D represents a deuterated form of hydrogen; and

each of the remaining variables is as defined in Formula (I), or as described in any of the embodiments described herein, e.g., those of formulas (IA), (IA-1), (IA-2), (II), (II-A), (II-A1), and (II-A2), and the various embodiments thereof, are also within the scope of the compounds of Formula (IV^d).

In another embodiment, the present invention encompasses a stereoisomer or racemic mixture of a compound of the invention, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer. It shall be appreciated that, while the present invention encompasses all stereoisomers and racemic mixtures of the compounds of the invention, the stereoconfiguration shown in the structural formulas and in the examples are also contemplated as being within the scope of the invention.

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, the compounds of the invention are each of the compounds of the tables below and have a structure shown for the corresponding example in the preparative examples below.

The present invention includes tautomers and stereoisomers of each of the example compounds of the invention, and pharmaceutically acceptable salts and solvates of said compounds, said stereoisomers, and/or said tautomers. Such tautomers and stereosiomers of each of the example compounds, and pharmaceutically and solvates of said compounds, said stereoisomers, and/or said tautomers, each represent additional embodiments of the invention.

In another embodiment, the invention provides a composition comprising at least one compound of the invention, or a tautomer or stereoisomer thereof, or salt or solvate of said compound, said stereoisomer, or said tautomer, and a suitable carrier or diluent.

In another embodiment, the invention provides a pharmaceutical composition comprising at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, and a pharmaceutically acceptable carrier or diluent.

In another embodiment, the invention provides a pharmaceutical composition comprising at least one solvate of a compound of the invention, or a tautomer or isomer thereof, or pharmaceutically acceptable salt or solvate of said compound or said tautomer, and a pharmaceutically acceptable carrier or diluent.

In another embodiment, the invention provides a pharmaceutical composition comprising at least one pharmaceutically acceptable salt of a compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, and a pharmaceutically acceptable carrier or diluent.

In another embodiment, the invention provides a pharmaceutical composition comprising at least one tautomer of a compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, and a pharmaceutically acceptable carrier or diluent.

In another embodiment, the invention provides a pharmaceutical composition comprising at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, together with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier or diluent.

Non-limiting examples of additional therapeutic agents for use in combination with the compounds of the invention include drugs selected from the group consisting of: (a) drugs useful for the treatment of Alzheimer's disease and/or drugs useful for treating one or more symptoms of Alzheimer's disease, (b) drugs useful for inhibiting the synthesis Aβ, and (c) drugs useful for treating neurodegenerative diseases.

Additional non-limiting examples of additional therapeutic agents for use in combination with the compounds of the invention include drugs 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, Parkinson's disease, and/or Down'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, traumatic brain injury ("TBI"), 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 said pathology or pathologies.

In embodiments of the invention comprising at least one additional therapeutic agent, additional non-limiting examples of additional therapeutic agents for use 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®), 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

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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).

In another embodiment, the invention provides a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of the invention, and effective amount of one or more cholinesterase inhibitors (e.g., acetyl- and/or butyrylchlolinesterase inhibitors), and a pharmaceutically acceptable carrier.

In another embodiment, the invention provides a pharmaceutical composition comprising an effective amount of one or more (e.g., one) compounds of the invention, and effective amount of one or more muscarinic agonists or antagonists (e.g., m_1 agonists or m_2 antagonists), and a pharmaceutically acceptable carrier.

In one embodiment, the invention provides combinations comprising an effective (i.e., therapeutically effective) amount of one or more compounds of the invention, in combination with an effective (i.e., therapeutically effective) amount of one or more compounds selected from the group consisting of cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 H -inden-1-one hydrochloride, i.e, donepezil hydrochloride, available as the Aricept ® brand of donepezil hydrochloride), N-methyl-D-aspartate receptor inhibitors (such as, for example, Namenda® (memantine HCl)); anti-amyloid antibodies (such as bapineuzumab, Wyeth/Elan), gamma secretase inhibitors, gamma secretase modulators, and beta secretase inhibitors other than the compounds of the invention.

In one embodiment, the invention provides combinations comprising an effective (i.e., therapeutically effective) amount of one or more compounds of the invention, in combination with an effective (i.e., therapeutically effective) amount of one or more compounds selected from the group consisting of cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 H -inden-1-one hydrochloride, i.e, donepezil hydrochloride, available as the Aricept ® brand of donepezil hydrochloride), N-methyl-D-aspartate receptor inhibitors (such as, for example, Namenda® (memantine HCl)).

In one embodiment, the invention provides combinations comprising an effective (i.e., therapeutically effective) amount of one or more compounds of the invention, in combination with an effective (i.e., therapeutically effective) amount of one or more gamma secretase inhibitors.

In one embodiment, the invention provides combinations comprising an effective (i.e., therapeutically effective) amount of one or more compounds of the invention, in combination with an effective (i.e., therapeutically effective) amount of one or more gamma secretase modulators.

In one embodiment, the invention provides combinations comprising an effective (i.e., therapeutically effective) amount of one or more compounds of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in combination with an effective (i.e., therapeutically effective) amount of one or more gamma secretase inhibitors and in further combination with one or more gamma secretase modulators.

In another embodiment, the invention provides a compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in pure form, in isolated form, and/or in isolated and pure form.

Prodrugs of the compounds of the invention, or tautomers or stereoisomers thereof, or pharmaceutically acceptable salts or solvates of said compounds, said stereoisomers, and/or said tautomers, are also contemplated as being included within the scope of the invention, and are described more fully below.

Deuterates of the compounds of the invention, or tautomers or stereoisomers of said deuterates, or pharmaceutically acceptable salts or solvates of said deuterates, said stereoisomers, and/or said tautomers, are also contemplated as being included within the scope of the invention, and are described more fully above.

In another embodiment, the invention provides a method of preparing a pharmaceutical composition comprising the step of admixing at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, and a pharmaceutically acceptable carrier or diluent.

In another embodiment, the invention 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 or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in an amount effective to inhibit β-secretase.

In another embodiment, the invention provides a method of inhibiting β-secretase in a patient in need thereof comprising administering at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in a therapeutically effective amount to inhibit β-secretase in said patient.

In another embodiment, the invention provides a method of inhibiting BACE-1 comprising exposing a population of cells expressing BACE-1 to at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound or said tautomer, in an amount effective to inhibit BACE-1 in said cells. 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*.

In another embodiment, the invention provides a method of inhibiting BACE-2 comprising exposing a population of cells expressing BACE-2 to at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound or said tautomer, in an amount effective to inhibit BACE-2 in said cells. 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*.

In another embodiment, the invention provides a method of inhibiting BACE-1 in a patient in need thereof comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in a therapeutically effective amount to inhibit BACE-1 in said patient.

In another embodiment, the invention provides a method of inhibiting BACE-2 in a patient in need thereof comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in a therapeutically effective amount to inhibit BACE-2 in said patient.

In another embodiment, the invention provides a method of inhibiting the formation of Aβ from APP in a patient in need thereof, comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in an amount effective to inhibit said Aβ formation.

In another embodiment, the invention provides a method of inhibiting the formation of Aβ plaque in a patient in need thereof, comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in an amount effective to inhibit said Aβ plaque formation.

In another embodiment, the invention provides a method of inhibiting the formation of Aβ fibrils in a patient in need thereof, comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in an amount effective to inhibit said Aβ fibril formation.

In another embodiment, the invention provides a method of inhibiting the formation of Aβ oligomers in a patient in need thereof, comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in an amount effective to inhibit said Aβ fibril formation.

In another embodiment, the invention provides a method of inhibiting the formation of Aβ fibrils and Aβ oligomers in a patient in need thereof, comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in an amount effective to inhibit said Aβ fibril formation.

In another embodiment, the invention provides a method of inhibiting the formation of senile plaques and/or neurofibrillary tangles in a patient in need thereof, comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in an amount effective to inhibit said Aβ fibril formation.

In another embodiment, the invention provides a method of treating, preventing, and/or delaying the onset of an amyloid β pathology ("Aβ pathology") and/or one or more symptoms of said pathology comprising administering at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, to a patient in need thereof in an amount effective to treat said pathology.

In another embodiment, the invention provides 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 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, Parkinson's disease, and/or Down'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, diabetes-associated amyloidogenesis, hemodialysis complications (from β_2 microglobulins and complications arising therefrom in hemodialysis patients), scrapie, bovine spongiform encephalitis, traumatic brain injury ("TBI") and Creutzfeld-Jakob disease, comprising administering to said patient at least one compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in an amount effective to inhibit said pathology or pathologies.

In one embodiment, the invention provides a method of treating one or more neurodegenerative diseases, comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional therapeutic agents useful in treating one or more neurodegenerative diseases, to a patient in need of such treatment.

In one embodiment, the invention provides a method of inhibiting the deposition of amyloid protein (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional therapeutic agents useful in treating one or more neurodegenerative diseases, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating Alzheimer's disease, comprising administering an effective (i.e., therapeutically effective) amount of one or more compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional therapeutic agents useful in treating Alzheimer's disease, to a patient in need of such treatment.

In one embodiment, the invention provides 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 or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with an effective (e.g., therapetucially effective) amount of one or more additional active agents useful in treating Down's syndrome, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating mild cognitive impairment, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional active agents useful in treating mild cognitive impairement, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating glaucoma, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional active agents useful in treating glaucoma, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating cerebral amyloid angiopathy, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional active agents useful in treatingcerebral amyloid angiopathy, to a patient in need of such treatment. to a patient in need of treatment.

In one embodiment, the invention provides a method of treating stroke, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer) , alone or optionally in combination with one or more additional active agents useful in treating stroke, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating dementia, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional active agents useful in treating dementia, to a patient in need of such treatment. to a patient in need of treatment.

In one embodiment, the invention provides a method of treating microgliosis, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional active agents useful in treating microgliosis, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating brain inflammation, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional active agents useful in treating brain inflammation, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating traumatic brain injury, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with one or more additional active agents useful in treating traumatic brain injury, to a patient in need of such treatment.

In one embodiment, the invention provides a method of treating olfactory function loss, comprising administering an effective amount of one or more (e.g., one) compounds of the invention (or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer), alone or optionally in combination with

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one or more additional active agents useful in treating olfactory function loss, to a patient in need of such treatment.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more cholinesterase inhibitors (such as, for example, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 H - inden-1-one hydrochloride, i.e, donepezil hydrochloride, available as the Aricept® brand of donepezil hydrochloride).

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from the group consisting of Aβ antibody inhibitors, gamma secretase inhibitors, gamma secretase modulators, and beta secretase inhibitors other than a compound of the invention.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is Exelon (rivastigmine).

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from Cognex (tacrine).

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from Tau kinase inhibitor (e.g., GSK3beta inhibitor, cdk5 inhibitor, ERK inhibitor).

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from an anti-Aβ vaccine.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from an APP ligand.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more agents that upregulate insulin degrading enzyme and/or neprilysin.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more cholesterol lowering agents. Non-limiting examples of said cholesterol lowerin agents include: statins such as Atorvastatin, Fluvastatin, Lovastatin, Mevastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin, and cholesterol absorption inhibitors such as Ezetimibe and phytonutrients.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more fibrates. Non-limiting examples of said fibtrates include clofibrate, Clofibride, Etofibrate, and Aluminium Clofibrate.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more LXR agonists.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more LRP mimics.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more 5-HT6 receptor antagonists.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more nicotinic receptor agonists.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more H3 receptor antagonists.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more histone deacetylase inhibitors.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more hsp90 inhibitors.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more m1 muscarinic receptor agonists.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more 5-HT6 receptor antagonists, mGluR1, and mGluR5 positive allosteric modulators or agonists.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more mGluR2/3 antagonists.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more anti-inflammatory agents that can reduce neuroinflammation.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more prostaglandin EP2 receptor antagonists.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more PAI-1 inhibitors.

In one embodiment, in each of the above recited methods of treatment, said one or more additional therapeutic agent is selected from one or more agents that can induce Aß efflux. One non-limiting example of an agent that can induce Aß influx is gelsolin.

In one embodiment, the invention provides 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 or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer) in a pharmaceutically acceptable carrier, and, optionally, another container (i.e., a second container) comprises an effective amount of another pharmaceutically active ingredient (as described below), 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 (e.g., amyloid beta protein) in, on or around neurological tissue (e.g., the brain), or (c) treat neurodegenerative diseases, or (d) inhibit BACE.

In its various embodiments, the invention provides any one of the 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 below.

In its various embodiments, the invention provides any one of the pharmaceutical compositions 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 below.

Other embodiments of this invention are directed to any one of the embodiments above or below that are directed to compounds of the invention, or the use of compounds of the invention (e.g. the embodiments directed to methods of treatment, pharmaceutical compositions and kits).

In another embodiment, the invention provides for the use of a compound of the invention, or a tautomer or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, or said tautomer, in the manufacture of a medicament for use in the treatment, the delay of onset, and/or the prevention of one or more Aβ pathologies and/or in the treatment, the delay of onset, and/or the prevention of one or more symptoms of one or more Aβ pathologies.

DEFINITIONS

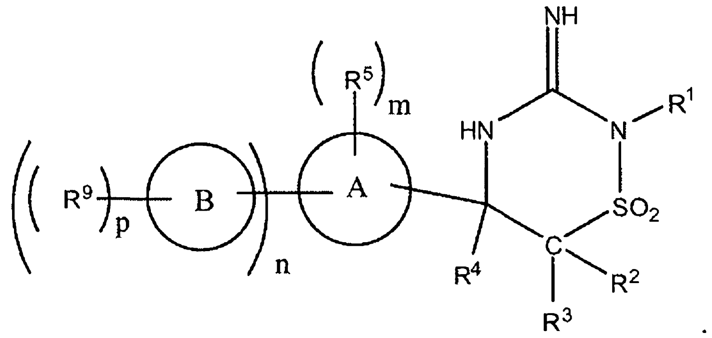
The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names and chemical structures 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" portion of "hydroxyalkyl", "haloalkyl", arylalkyl-, alkylaryl-, "alkoxy" etc.

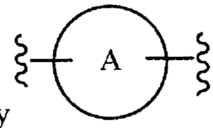
It shall be understood that, in the various embodiments of the invention described herein, any variable not specifically defined in the context of the embodiment is as defined in Formula (I). Any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

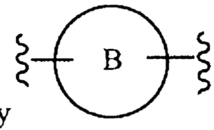
As described herein, the "example compounds of the invention" (or "example compounds" or "examples") include, collectively and individually, each of the compounds set forth with example numbers in the preparative examples.

As described herein, variables such as R^1, R^2, R^3, and R^4 may be unsubstituted or substituted with one or more R^5 groups. It shall be understood that the upper limit of the number of substituents (referred to in the phrase "one or more substituents") is the number of available hydrogen atoms on the relevant moiety (R^1, R^2, R^3, or R^4) that are available for replacement by a substituent which will result in a chemically stable moiety.

As described herein, one or more of the variables $-L_1-$, $-L_2-$, and $-L_3-$ of the general formulae optionally independently represent a bond. It shall be understood that where such a variable represents a bond, the moieties which are shown connected by that variable are directly attached by covalent bond. Thus, by way of non-limiting illustration, a compound of Formula (I) wherein $-L_1-$, $-L_2-$ and $-L_3-$ each represent a bond can be shown as:



The moiety  , which may be optionally substituted as described herein, represents a ring referred to herein as "ring A."

The moiety  , which may be optionally substituted as described herein, represents a ring referred to herein as "ring B."

"At least one" means one or more than one, for example, 1, 2, or 3, or in another example, 1 or 2, or in another example 1.

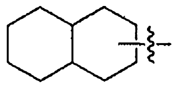
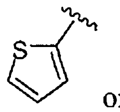
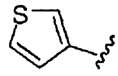
In the various Formulas of the compounds of the invention, e.g., in Formula (I), m, n, and p are each independently selected integers, wherein:

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. Except for salt forms, the "maximum number of available substitutable hydrogen atoms" refers to the maximum number that will result in a neutral molecule.

By way of non-limiting illustration, when ring A is a  group, the maximum value of the sum of m and n 17. When ring A is a  or  group, the maximum value of the sum of m and n is 3.

In the compounds of the invention, e.g., in Formula (I), each of ring A and ring B (when present) is selected from the group consisting of a monocyclic aryl, a monocyclic heteroaryl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocycloalkyl, a monocyclic heterocycloalkenyl, and a multicyclic group, each of which groups may be unsubstituted or optionally further substituted as shown in Formula (I).

As used herein, the term "monocyclic aryl" refers to phenyl.

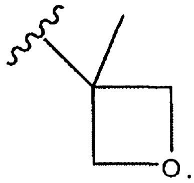
As used herein, the term "monocyclic heteroaryl" refers to a 4- to 7-membered monocyclic heteroaryl group comprising from 1 to 4 ring heteroatoms, said ring heteroatoms being independently selected from the group consisting of N, O, and S, and oxides thereof. The point of attachment to the parent moiety is to any available ring carbon or ring heteroatom. Non-limiting examples of monocyclic heteroaryl moities include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, pyridone, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl), pyrazinyl, pyridazinyl, imidazolyl, and triazinyl (e.g., 1,2,4-triazinyl), and oxides thereof.

As used herein, the term "monocyclic cycloalkyl" refers to a 3- to 7-membered monocyclic cycloalkyl group. Non-limiting examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

As used herein, the term "monocyclic cycloalkenyl" refers to a non-aromatic 3- to 7-membered cycloalkyl group which contains one or more carbon-carbon double bonds. Non-limiting examples include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl.

As used herein, the term "monocyclic heterocycloalkyl" refers to a 4- to 7-membered monocyclic heterocycloalkyl group 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, pyrrolidinyl, 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.

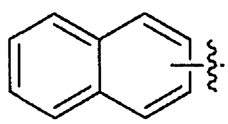
Non-limiting examples of lower alkyl-substituted oxetanyl include the moiety:



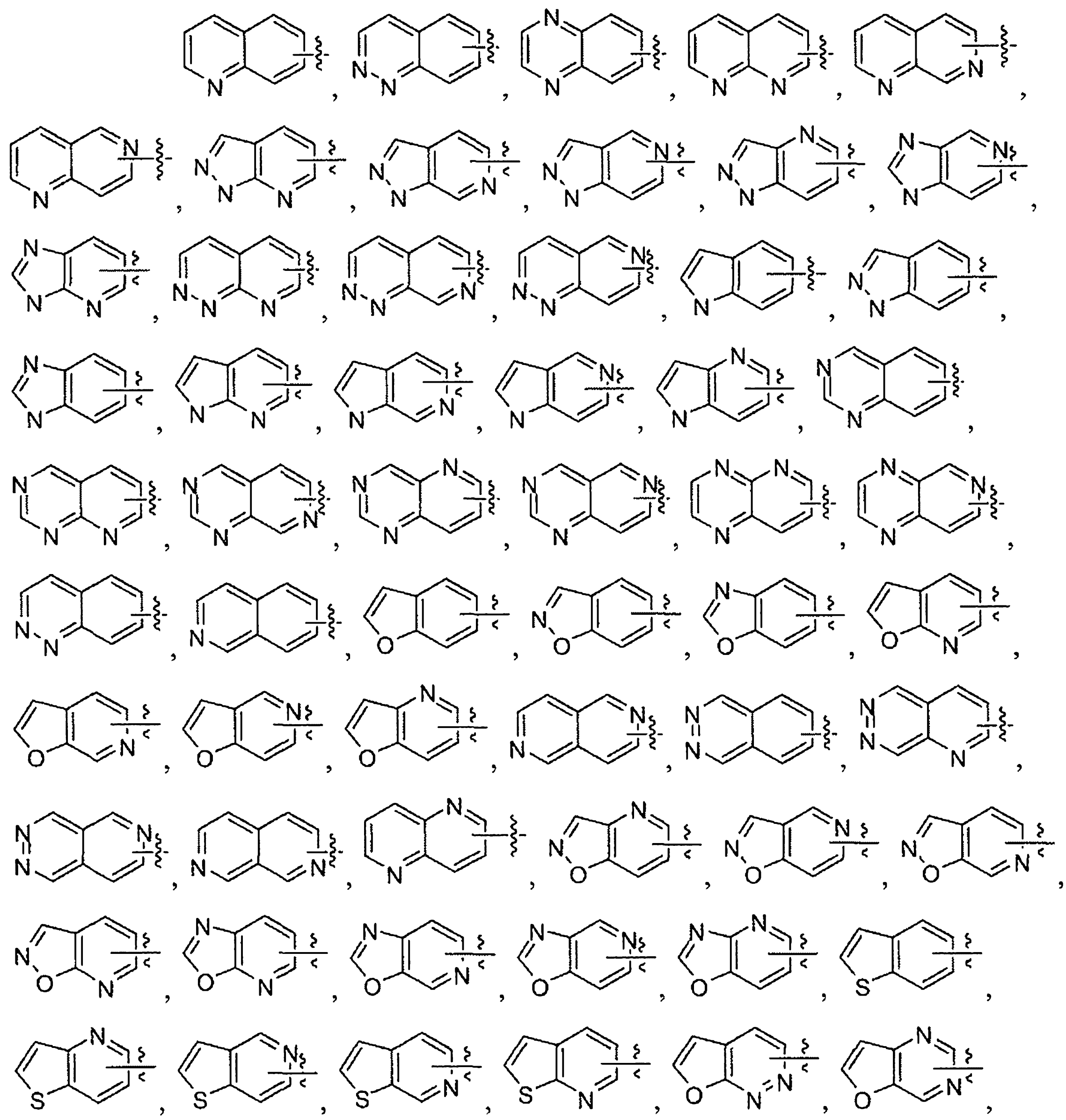
As used herein, the term "monocyclic heterocycloalkenyl" refers to a 4- to 7-membered monocyclic heterocycloalkenyl group comprising from 1 to 4 ring heteroatoms, said ring heteroatoms being independently selected from the group consisting of N, N-oxide, O, S, S-oxide, S(O), and $S(O)_2$. The point of attachment to the parent moiety is to any available ring carbon or ring heteroatom. Non-limiting examples of monocyclic heterocycloalkenyl 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.

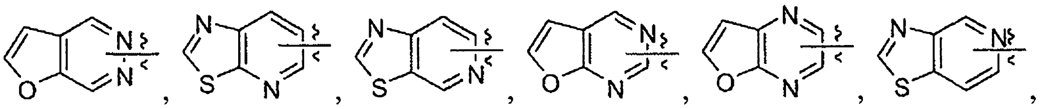
As used herein, the term "multicyclic group" refers to a fused ring system comprising two (bicyclic), three (tricyclic), or more fused rings, wherein each ring of the fused ring system is independently selected from the group consisting of phenyl, monocyclic heteroaryl, monocyclic cycloalkyl, monocyclic cycloalkenyl, monocyclic heterocycloalkyl, and monocyclic heterocycloalkenyl. The point of attachment to the parent moiety is to any available ring carbon or (if present) ring heteroatom on any of the fused rings.

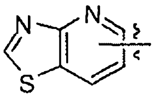
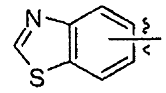
It shall be understood that each of the following multicyclic groups pictured may be unsubstituted or substituted, as described herein. Only the point of attachment to the parent moiety is shown by the wavy line.

The term multicyclic groups includes bicyclic aromatic groups. Non-limiting examples of multicyclic groups which are bicyclic aromatic groups include:  .

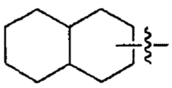
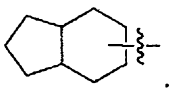
The term multicyclic groups includes bicyclic heteroaromatic groups comprising from 1 to 3 or more ring heteroatoms, each said ring heteroatom being independently selected from the group consisting of N, O, and S, S(O), $S(O)_2$, and oxides of N, O, and S, and oxides thereof. Non-limiting examples of multicyclic groups which are bicyclic heteroaromatic groups comprising from 1 to 3 ring heteroatoms, each said ring heteroatom being independently selected from N, O, and S include the following, and oxides thereof:



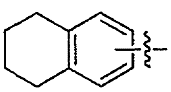
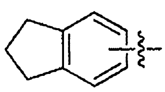
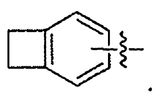


, and .

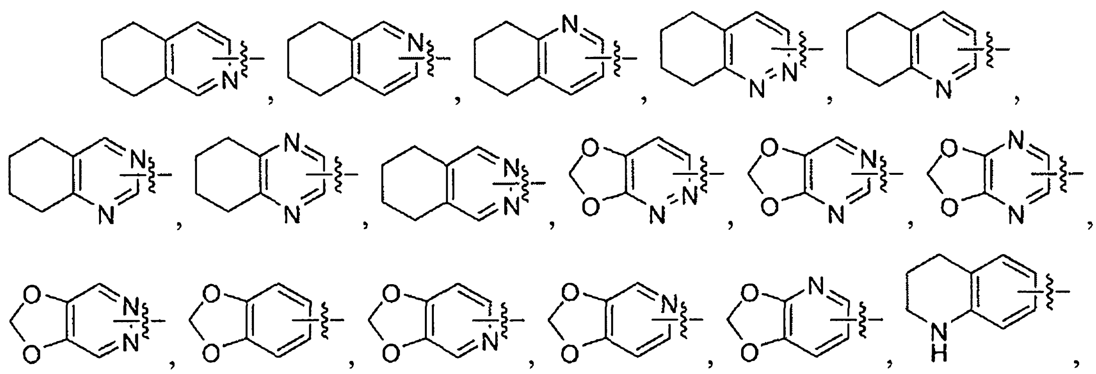
The term multicyclic groups includes saturated bicyclic cycloalkyl groups. Non-limiting examples of multicyclic groups which are saturated bicyclic cycloalkyl groups include the following:

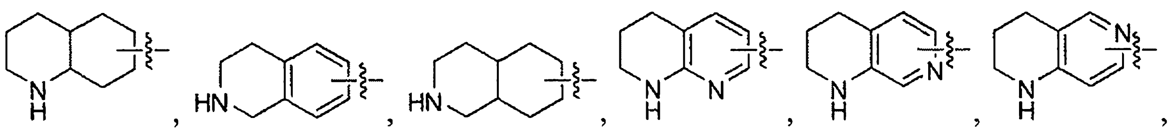
 and .

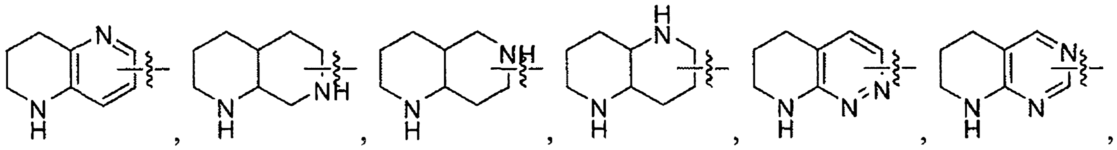
The term multicyclic group includes partially unsaturated bicyclic cycloalkyl groups. Non-limiting examples of multicyclic groups which comprise partially unsaturated bicyclic cycloalkyl groups include the following:

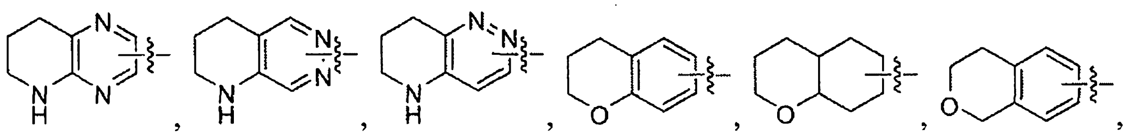
, , and .

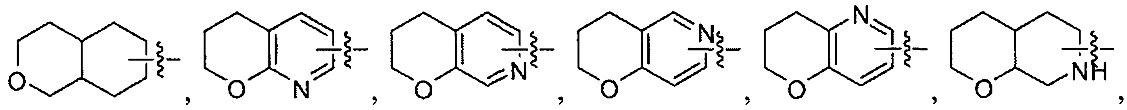
The term multicyclic groups includes partially or fully saturated bicyclic groups comprising from 1 to 3 ring heteroatoms, each said ring heteroatom is independently selected from the group consisting of N, O, and S, S(O), $S(O)_2$, and oxides of N and S. Such rings may also optionally contain one or more oxo groups, as defined herein. Non-limiting examples of multicyclic groups which are partially or fully saturated bicyclic groups comprising from 1 to 3 ring heteroatoms, each said ring heteroatom being independently selected from N, O, and S include the following, and oxides thereof:

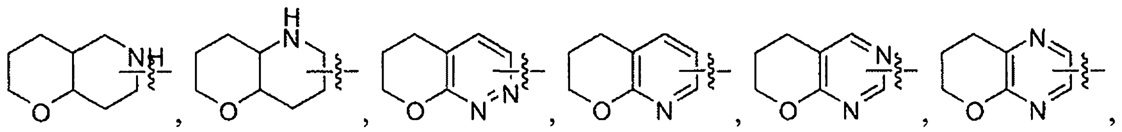


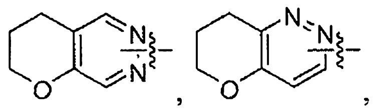


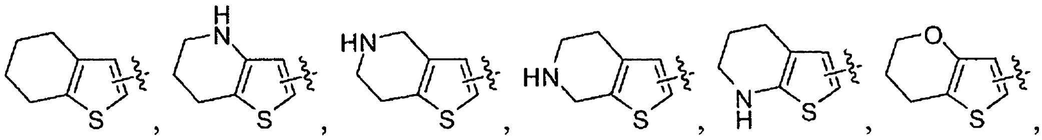


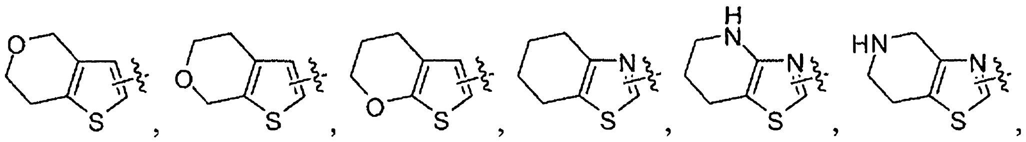


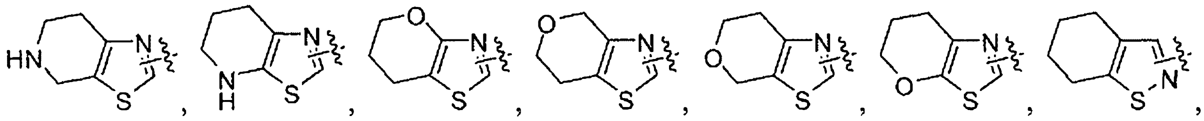


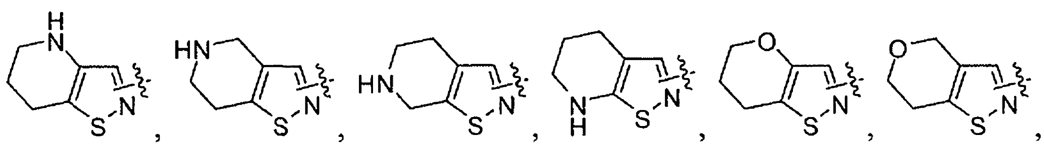


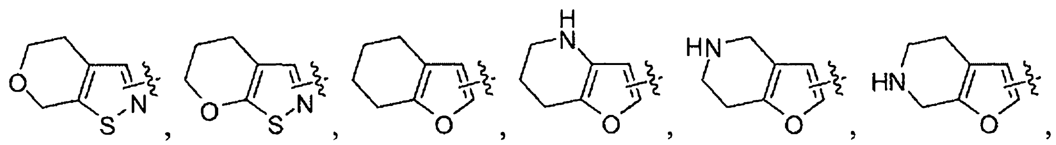


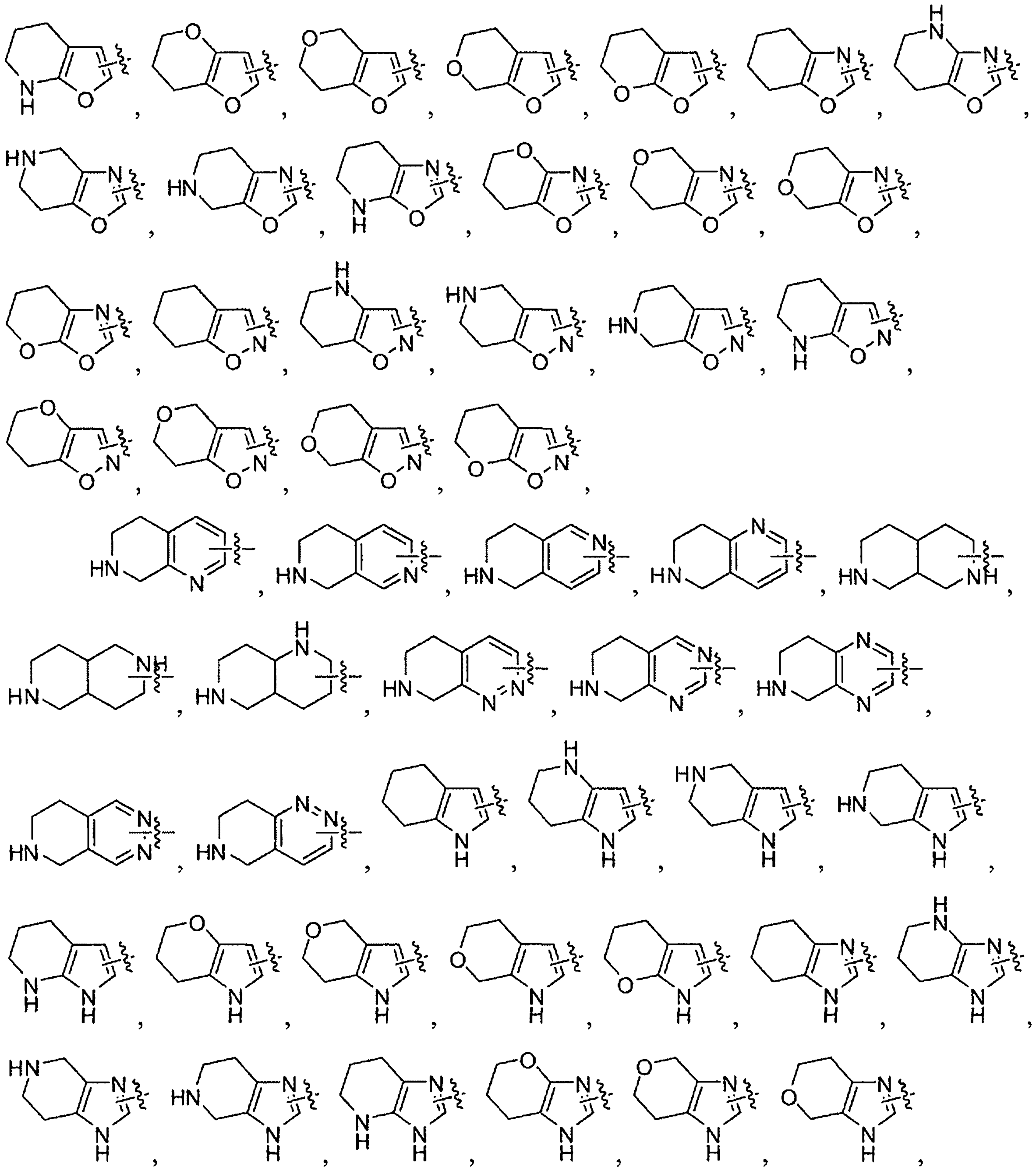


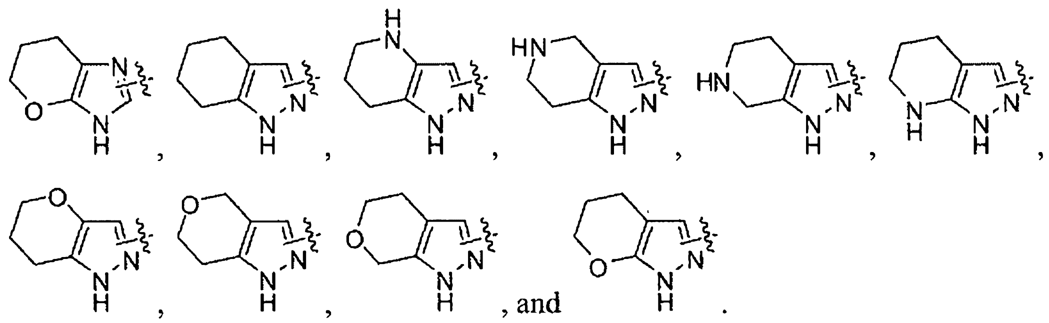




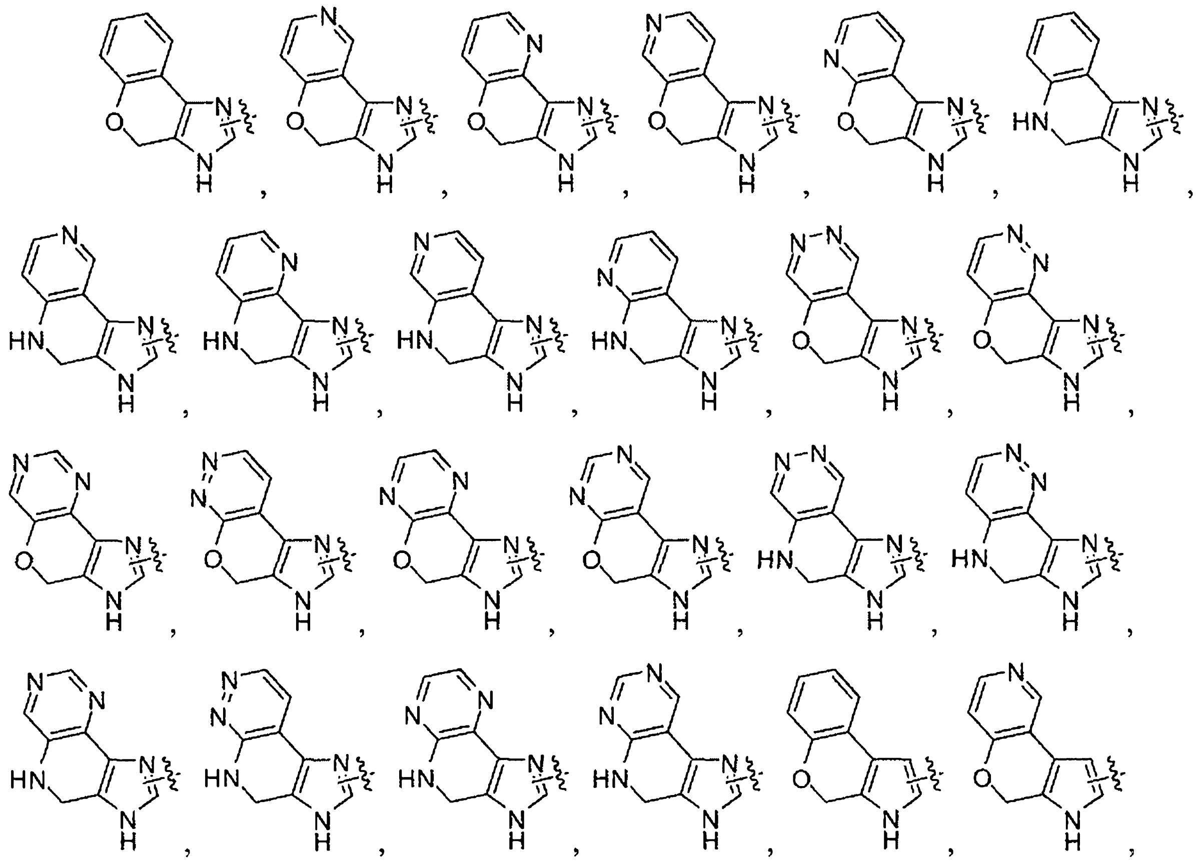








The term multicyclic groups includes aromatic tricyclic groups, cycloalkyl tricyclic groups, as well as heteroaromatic and partially and fully saturated tricyclic groups. For tricyclic groups comprising ring heteroatoms, said tricyclic groups comprise one or more (e.g., from 1 to 5) ring heteroatoms, wherein each said ring heteroatom is independently selected from N, O, and S, S(O), $S(O)_2$, and oxides of N, O, and S: Non-limiting examples of tricyclic multicyclic groups include the following, and, where possible, oxides thereof:



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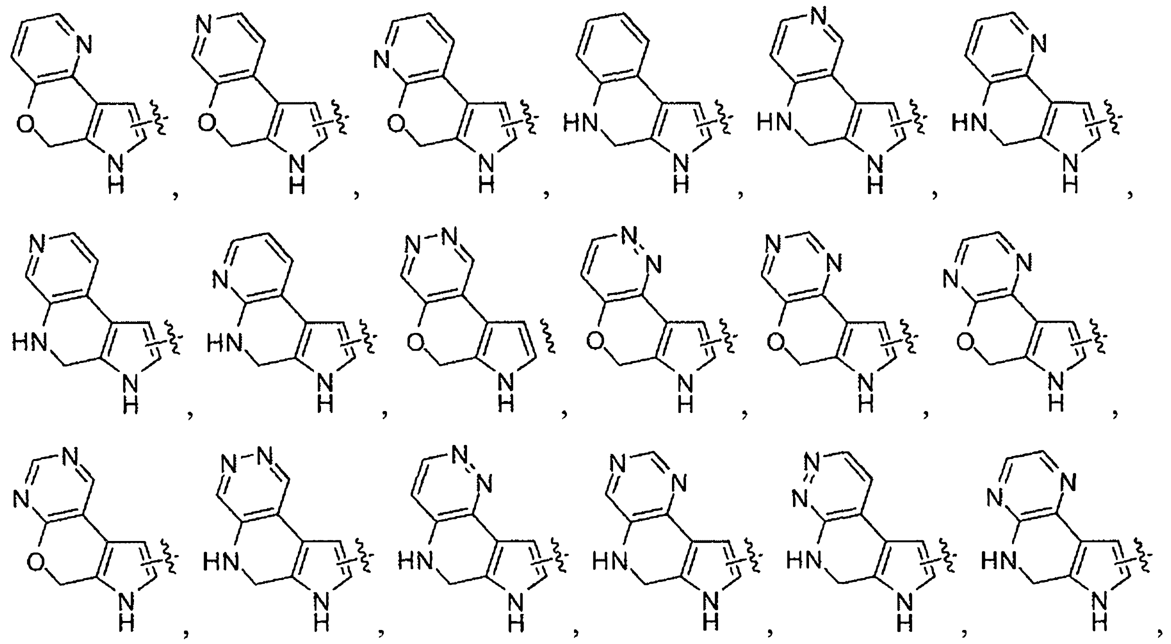
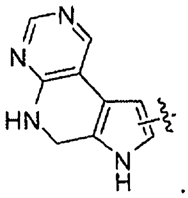


and  .

"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” means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. "Alkyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being as described herein or independently selected from the group consisting of halo, alkyl, haloalkyl, spirocycloalkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), $-N(alkyl)_2$, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl 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, having one or more carbon atoms, for example one, two or three carbon atoms, replaced with one or more heteroatoms, which may be the same or different, where the point of attachment to the remainder of the molecule is through a carbon atom of the heteroalkyl radical. Suitable such heteroatoms include O, S, S(O), $S(O)_2$, and -NH-, -N(alkyl)-. Non-limiting examples include ethers, thioethers, amines, hydroxymethyl, 3-hydroxypropyl, 1,2-dihydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2-dimethylaminoethyl, and the like.

"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 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain.

"Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. "Alkenyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, alkoxy and –S(alkyl). 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 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 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. "Alkynyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"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.

"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 "ring system substituents" which may be the same or different, and are 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 (alternatively referred to as thiophenyl), pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, 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.

"Cycloalkyl" 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. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl 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 monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like. Further non-limiting examples of cycloalkyl include the following:

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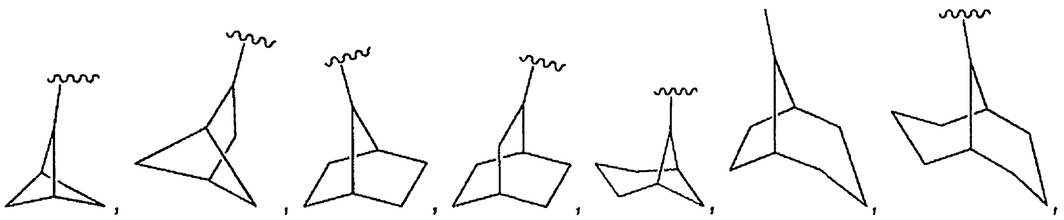

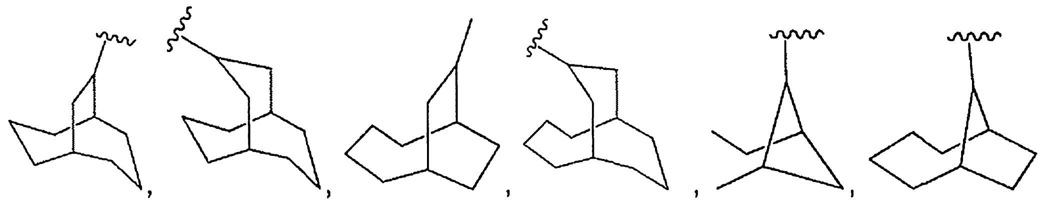

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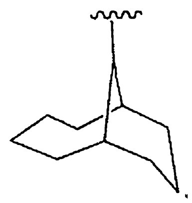
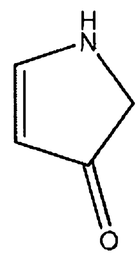


"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, 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 "ring system substituents" which may be the same or different, and are as defined 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. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like. "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," as described below.

"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 ring system substituents, wherein "ring system substituent" is as defined above. 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., heterocyclenyl includes rings having a carbonyl group in the ring). Example of such moiety is pyrrolidenone (or pyrrolone):



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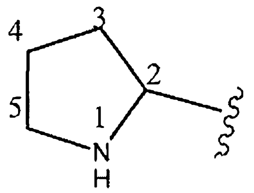
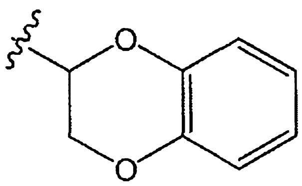
It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



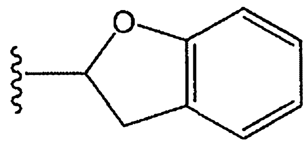
there is no -OH attached directly to carbons marked 2 and 5.

"Arylcycloalkyl" (or "arylfused cycloalkyl") means a group derived from a fused aryl and cycloalkyl as defined herein. Preferred arylcycloalkyls are those wherein aryl is phenyl (which may be referred to as "benzofused") and cycloalkyl consists of about 5 to about 6 ring atoms. The arylcycloalkyl can be optionally substituted as described herein. Non-limiting examples of suitable arylcycloalkyls include indanyl (a benzofused cycloalkyl) and 1,2,3,4-tetrahydronaphthyl and the like. The bond to the parent moiety is through a non-aromatic carbon atom.

"Arylheterocycloalkyl" (or "arylfused heterocycloalkyl") means a group derived from a fused aryl and heterocycloalkyl as defined herein. Preferred arylheterocycloalkyls are those wherein aryl is phenyl (which may be referred to as "benzofused") and heterocycloalkyl consists of about 5 to about 6 ring atoms. The arylheterocycloalkyl can be optionally substituted, and/or contain the oxide or oxo, as described herein. Non-limiting examples of suitable arylfused heterocycloalkyls include:



and



The bond to the parent moiety is through a non-aromatic carbon atom.

It is also understood that the terms "arylfused aryl", "arylfused cycloalkyl", "arylfused cycloalkenyl", "arylfused heterocycloalkyl", arylfused heterocycloalkenyl", "arylfused heteroaryl", "cycloalkylfused aryl", "cycloalkylfused cycloalkyl", "cycloalkylfused cycloalkenyl", "cycloalkylfused heterocycloalkyl", "cycloalkylfused heterocycloalkenyl", "cycloalkylfused heteroaryl, "cycloalkenylfused aryl", "cycloalkenylfused cycloalkyl", "cycloalkenylfused cycloalkenyl", "cycloalkenylfused heterocycloalkyl", "cycloalkenylfused heterocycloalkenyl", "cycloalkenylfused heteroaryl", "heterocycloalkylfused aryl", "heterocycloalkylfused cycloalkyl", "heterocycloalkylfused cycloalkenyl", "heterocycloalkylfused heterocycloalkyl", "heterocycloalkylfused heterocycloalkenyl", "heterocycloalkylfused heteroaryl", "heterocycloalkenylfused aryl", "heterocycloalkenylfused cycloalkyl", "heterocycloalkenylfused cycloalkenyl", "heterocycloalkenylfused heterocycloalkyl", "heterocycloalkenylfused heterocycloalkenyl", "heterocycloalkenylfused heteroaryl", "heteroarylfused aryl", "heteroarylfused cycloalkyl", "heteroarylfused cycloalkenyl", "heteroarylfused heterocycloalkyl", "heteroarylfused heterocycloalkenyl", and "heteroarylfused heteroaryl" are similarly represented by the combination of the groups aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, and heteroaryl, as previously described. Any such groups may be unsubstituted or substituted with one or more ring system substituents at any available position as described herein.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. 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-" 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. Preferred groups contain a lower alkyl group. Such alkyl groups may be straight or branched, unsubstituted and/or substituted as described herein.

Similarly, "arylfused arylalkyl-", arylfused cycloalkylalkyl-, etc., means an arylfused aryl group, arylfused cycloalkyl group, etc. linked to a parent moiety through an alkyl group. Preferred groups contain a lower alkyl group. Such alkyl groups may be straight or branched, 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.

“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, 2-pyridinylmethyl, quinolinylmethyl, and quinolin-3-ylmethyl, and the like. 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.

“Cyanoalkyl” means a NC-alkyl- group in which alkyl is as previously defined. Preferred cyanoalkyls contain lower alkyl. Non-limiting examples of suitable cyanoalkyl groups include cyanomethyl and 2-cyanoethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Heteroaroyl" means an heteroaryl-C(O)- group in which the heteroaryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include pyridoyl.

"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.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" (or "arylalkyloxy") means an aralkyl-O- group (an arylaklyl-O- group) in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Arylalkenyl" means a group derived from an aryl and alkenyl as defined herein. Preferred arylalkenyls are those wherein aryl is phenyl and the alkenyl consists of about 3 to about 6 atoms. The arylalkenyl can be optionally substituted by one or more substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

"Arylalkynyl" means a group derived from a aryl and alkenyl as defined herein. Preferred arylalkynyls are those wherein aryl is phenyl and the alkynyl consists of about 3 to about 6 atoms. The arylalkynyl can be optionally substituted by one or more substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-$S(O_2)$- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-$S(O_2)$- group. The bond to the parent moiety is through the sulfonyl.

“Spirocycloalkyl” means a cycloalkyl group attached to a parent moiety by replacement of two available hydrogen atoms at a single carbon atom. Non-limiting examples of spirocycloalkyl wherein the parent moiety is a cycloalkyl include spiro [2.5] octane, spiro [2.4] heptane, etc. The moiety may optionally be substituted as described herein. Non-limiting spirocycloalkyl groups include spirocyclopropyl, spriorcyclobutyl, spirocycloheptyl, and spirocyclohexyl.

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.

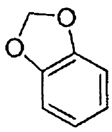
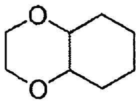
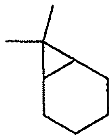
The term “optionally substituted” means optional substitution with the specified groups, radicals or moieties.

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.

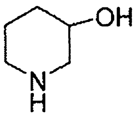
When a variable appears more than once in a group, e.g., R^8 in $-N(R^8)_2$, or a variable appears more than once in a structure presented herein, the variables can be the same or different.

With reference to the number of moieties (e.g., substituents, groups or rings) in a compound, unless otherwise defined, the phrases "one or more" and "at least one" mean that there can be as many moieties as chemically permitted, and the determination of the maximum number of such moieties is well within the knowledge of those skilled in the art. With respect to the compositions and methods comprising the use of "at least one compound of the invention, e.g., of Formula (II)," one to three compounds of the invention, e.g., of Formula (II) can be administered at the same time, preferably one.

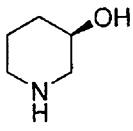
Compounds of the invention may contain one or more rings having one or more ring system substituents. "Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being as described herein or independently selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- and -$SO_2NY_1Y_2$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moieties are rings such as heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl rings. Additional non-limiting examples include methylene dioxy, ethylenedioxy, -$C(CH_3)_2$- and the like which form moieties such as, for example:

  and .

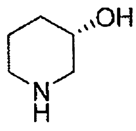
The line — as a bond generally indicates a mixture of, or either of, the possible isomers, e.g., containing (R)- and (S)- stereochemistry. For example:



indicates a mixture of, or either of,



and/or



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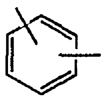
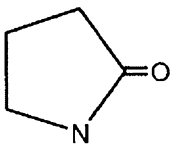
The wavy line ∿∿∿, as used herein, indicates a point of attachment to the rest of the compound.

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.,



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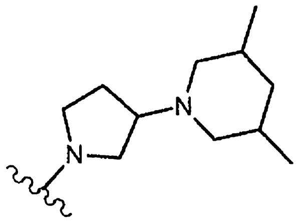
In this specification, where there are multiple oxygen and/or sulfur atoms in a ring system, there cannot be any adjacent oxygen and/or sulfur present in said ring system.

It is noted that the carbon atoms for compounds of the invention may be replaced with 1 to 3 silicon atoms so long as all valency requirements are satisfied.

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:



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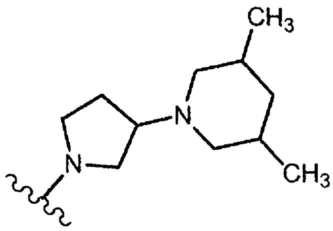

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In the compounds of Formula (I)

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 or stereoisomer thereof, or pharmaceutically acceptable salt or solvate of said compound, said stereoisomer, 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.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. 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.

For example, if a compound of the invention or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, $(C_1\text{–}C_8)$alkyl, $(C_2\text{-}C_{12})$alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-$(C_1\text{-}C_2)$alkylamino$(C_2\text{-}C_3)$alkyl (such as β-dimethylaminoethyl), carbamoyl-$(C_1\text{-}C_2)$alkyl, N,N-di $(C_1\text{-}C_2)$alkylcarbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino$(C_2\text{-}C_3)$alkyl, and the like.

Similarly, if a compound of the invention contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, $(C_1\text{-}C_6)$alkanoyloxymethyl, 1-($(C_1\text{-}C_6)$alkanoyloxy)ethyl, 1-methyl-1-($(C_1\text{-}C_6)$alkanoyloxy)ethyl, $(C_1\text{-}C_6)$alkoxycarbonyloxymethyl, N-$(C_1\text{-}C_6)$alkoxycarbonylaminomethyl, succinoyl, $(C_1\text{-}C_6)$alkanoyl, α-amino$(C_1\text{-}C_4)$alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, -P(O)(O$(C_1\text{-}C_6)$alkyl$)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of the invention incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently $(C_1\text{-}C_{10})$alkyl, $(C_3\text{-}C_7)$ cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, $(C_1\text{-}C_6)$alkyl or benzyl, —C(OY^2)Y^3 wherein Y^2 is $(C_1\text{-}C_4)$ alkyl and Y^3 is $(C_1\text{-}C_6)$alkyl, carboxy $(C_1\text{-}C_6)$alkyl, amino$(C_1\text{-}C_4)$alkyl or mono-N—or di-N,N-$(C_1\text{-}C_6)$alkylaminoalkyl, —C(Y^4)Y^5 wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N,N-$(C_1\text{-}C_6)$alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

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. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

"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.

The compounds of the invention can form salts which are also within the scope of this invention. 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 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 useful. Salts of the compounds of the invention may be formed, 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 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.

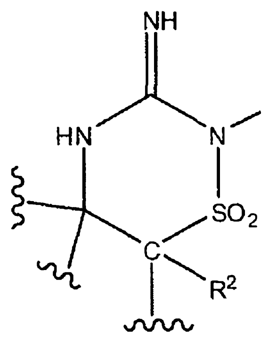
Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids 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 equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds 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.

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.

It is also possible that the compounds of the invention may exist in different tautomeric forms, and all such forms 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. Thus, for example, the compounds of the invention conforming to the formula:



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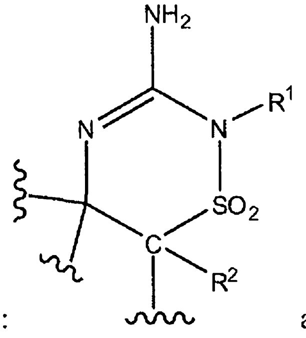
and their tautomers:  are both contemplated as being within the scope of the compounds of the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (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 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.

The present invention also embraces isotopically-labelled compounds of the present invention which 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, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

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

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.

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.

As discussed above, the amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated.

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, in an aspect, this invention includes 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.

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. Certain assays are exemplified elsewhere in this document.

For preparing pharmaceutical compositions from the compounds described by this 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. As an example may be mentioned 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.

The compounds of the invention may also be deliverable transdermally. 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.

The compounds of this invention may also be delivered subcutaneously.

In one embodiment, the compound is administered orally.

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 is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

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.

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

Thin layer chromatography: TLC

High performance liquid chromatography: HPLC

ethyl acetate: AcOEt or EtOAc

methanol: MeOH

ether or diethyl ether: Et_2O

tetrahydrofuran: THF

Acetonitrile: MeCN or ACN

1,2-dimethoxyethane: DME

Trifluoroacetic acid: TFA

Dimethylacetamide: DMA

Dimethylformamide: DMF

Dimethylsulfoxide: DMSO

triethylamine: Et_3N or TEA

tert-Butoxycarbonyl: t-Boc or Boc

2-(Trimethylsilyl)ethoxycarbonyl: Teoc

liquid chromatography mass spectrometry: LCMS

milliliters: mL

millimoles: mmol

micromoles : μmol

microliters: μl

grams: g

milligrams: mg

N-iodosuccinimide: NIS

room temperature (ambient, about 25°C): rt (or RT)

Retention time: t_R

N-bromosuccinimide: NBS

Methyl magnesium bromide: MeMgBr

iron(III) acetylacetonate: $Fe(acac)_3$

Diphenylphosphoryl azide: DPPA

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride: EDCI

Diisopropylethylamine: DIEA or iPr_2NEt

Diisopropylamine: iPr_2NH

2-(Trimethylsilyl)ethanol: TMSethanol

3-Chloroperoxybenzoic acid: mCPBA

n-Butyllithium: nBuLi

lithium diisopropylamide: LDA

[1,1'Bis(diphenylphosphino)ferrocene]dichloropalladium(II): $PdCl_2dppf$

Palladium(II) acetate: $Pd(OAc)_2$

Methanesulfonyl chloride: $MeSO_2Cl$

Benzyl: Bn

4-methoxy benzyl: PMB

Phenyl: Ph

Ethanol: EtOH

Liter: L

Minutes: min

Reverse phase: RP

Hexanes: Hex

Methylene Chloride: DCM

Acetic acid: HOAc or AcOH

Saturated: Sat (or sat)

Bis(2-oxo-3-oxazolidinyl) phosphinic chloride: BOPCl

4-(dimethylamino)pyridine: DMAP

Molar: M

2-((trimethylsilyl)ethoxy)methyl: SEM

Diisopropyl azodicarboxylate: DIAD

Triethylborane: Et_3B

Tris(dibenzylideneacetone)dipalladium(0): Pd_2dba_3

Pyridine: Pyr

(2-Biphenyl)di-*tert*-butylphosphine: John-Phos

2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl: X-Phos

2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate: HATU

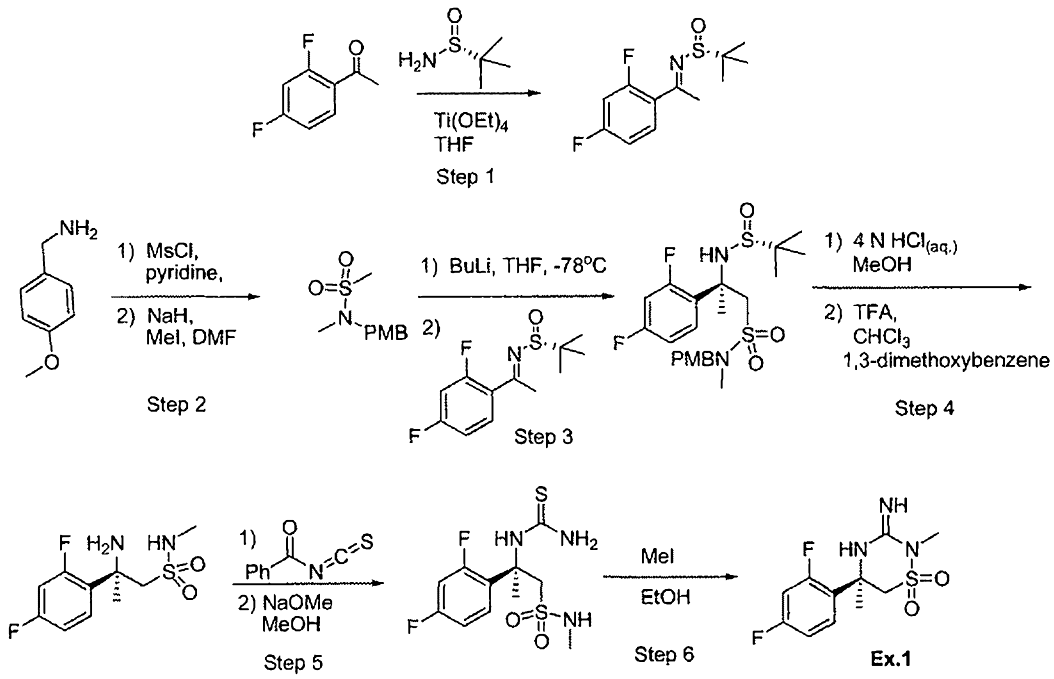
Concentrated: conc.

Tetrabutyl ammonium fluoride: TBAF

2-Dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl: RuPhos

Tetrakis(triphenylphosphine)palladium: $Pd(PPh_3)_4$

Scheme 1a



Step 1: To a solution of 2,4-difloroacetophenone (15.0 g, 96 mmol) in THF (100 mL) was added (R)-2-methyl-2-propanesulfinamide (12.8 g, 106 mmol) and $Ti(OEt)_4$, (32.0 g, 120 mmol). The resultant solution was heated to reflux overnight. After that time, the solution was cooled to RT and poured onto ice. To this mixture was added CH_2Cl_2 and the resultant mixture was stirred at RT for 10 min. The mixture was then filtered through Celite. The filter cake was washed with CH_2Cl_2. The layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 45:55 hexanes:EtOAc) to afford the ketimine (12.3 g).

Step 2: To a stirred solution of 4-methoxybenzyl amine (198.9 g, 1.45 mol) in anhydrous pyridine (400 mL) at 0°C was added dropwise via an addition funnel methanesulfonyl chloride (116 mL, 1.45 mol) over 45 min. After the addition was complete, the cooling bath was removed and the resultant solution was stirred at RT overnight. The reaction was concentrated *in vacuo* (water bath 60-65°C) to remove most of the pyridine. The residue was taken up in CH_2Cl_2 (1 L). The organic solution was washed with 1 N $HCl_{(aq.)}$ (2 x 1 L), sat. $NaHCO_3$ (aq) (2 x 1 L) and brine (1 x 500 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to afford a crude solid. This solid was dissolved in 95% EtOH (430 mL) using a steam bath to warm the solution. The solution was allowed to cool, causing the product to precipitate from solution. The product was removed by filtration and the solid was washed with cold EtOH (3 x 150 mL). A second crop was obtained after allowing the mother liquor to stir at RT overnight. The overall yield of the product was 246.5 g (79% yield).

This product was dissolved in anhydrous DMF (3.0 L), cooled to 0°C and placed under an atmosphere of N_2. To this solution was added in small portions sodium hydride (60% in mineral oil, 60.2 g, 1.51 mol, 1.3 eq.). After the addition was complete, the mixture was stirred for an additional 10 min. To this mixture was added dropwise via an addition funnel methyl iodide (250 g, 1.76 mol, 1.5 eq.). After the addition was complete, the cooling bath was removed and the mixture was allowed to stir at RT overnight. The mixture was then concentrated *in vacuo* (p = 10 torr, bath temp = 55-60°C) to remove ca. 2.5 L of DMF. Some solids precipitated from the solution. The remaining mixture was partitioned between 5 L ice water, 5 L Et_2O and 500 mL of EtOAc. The organic layer was separated. The aqueous layer was extracted with Et_2O (2 x 1 L). The combined organic layers were washed with brine (2 x 1 L), dried over Na_2SO_4, filtered and concentrated. The solid was stirred with hexanes using a wire stir blade to powderize the solid. The solid was removed by filtration and washed with hexanes (2 x 250 mL). The solid was dissolved in hexanes/EtOAc (1:1, 450 mL) using a steam bath to warm the mixture. An off white precipitate formed on cooling and was filtered off (182 g). The remaining mother liquor was purified via flash chromatography (SiO_2: 1:1 hexanes:EtOAc) to afford additional product (51.8 g) for an overall yield of 233.8g (89% yield).

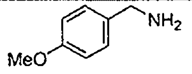
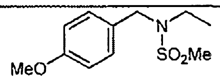
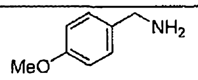
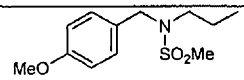
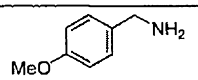
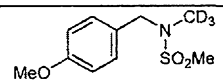
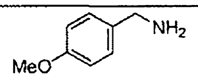
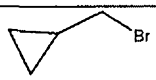
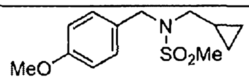
Step 3: To a solution of the sulfonamide from step 2 (4.18 g, 18.2 mmol) in anhydrous THF (50 mL) at -78°C under an atmosphere of N_2 was added dropwise a solution of *n*-BuLi (1.6 M in hexanes, 11.4 mL, 18.2 mmol). The resultant solution was stirred at -78°C for 30 min. After that time, a solution of the ketimine from step 1 (3.15 g, 12.1 mmol) in THF (50 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 hours. Water was added and the mixture was allowed to warm to RT. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 40:60 hexanes:EtOAc) to afford the sulfinamide (3.95 g, 67% yield).

Step 4: To a solution of the sulfinamide from step 3 (3.80 g, 7.6 mmol) in CH_2Cl_2/MeOH (3:1 80 mL) was added a solution of 4 M HCl $_{(dioxane)}$ (11.4 mL, 45.4 mmol). The resultant solution was stirred at RT for 1.5 hours. The solution was concentrated. The residue was re-concentrated from toluene (1x). The residue was then taken up in $CHCl_3$ and TFA (26 mL, 1:1). To this solution was added 1,3-dimethoxybenzene (6.5 mL, 50 mmol). The resultant solution was stirred at RT overnight. The resultant solution was concentrated. The resultant oil was partitioned between Et_2O and 1 M HCl $_{(aq.)}$. The aqueous layer was extracted with Et_2O (2x). The aqueous layer was then adjusted to pH 10 with the addition of sat. Na_2CO_3 $_{(aq.)}$. The aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were extracted from the basic aqueous layer, combined, dried over Na_2SO_4, filtered and concentrated to afford the amine (1.88 g, 85%).

Step 5: To a solution of the amine from step 4 (1.80 g, 6.8 mmol) in CH_2Cl_2 (30 mL) was added benzoyl isothiocyanate (1.01 mL, 7.49 mmol). The resultant solution was stirred at RT overnight. The solution was then concentrated. The residue was redissolved in MeOH (20 mL). To this solution was added a solution of NaOMe in MeOH (25%, 3.9 mL). The resultant solution was stirred at RT for 45 min. The solution was concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 and water. The pH of the aqueous layer was adjusted to ca 11 with the addition of $NaHCO_3$ (aq.). The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford the thiourea (1.90 g, 86%).

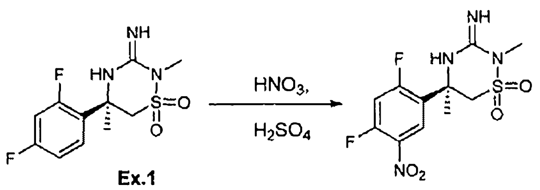
Step 6: To the thiourea from step 5 (1.90 g, 5.88 mmol) in EtOH (40 mL) was added methyl iodide (0.42 mL, 6.7 mmol). The resultant solution was heated to reflux for 3 hours. The solution was cooled to RT and concentrated *in vacuo*. The residue was partitioned between EtOAc and Na_2CO_3 $_{(aq.)}$. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 92:8 CH_2Cl_2:MeOH) to afford **Ex. 1** (1.12 g, 66% yield). LCMS (conditions D): t_R = 1.73 min, *m/e* = 290.2 (M+H).

Table I: The following sulfonamides were prepared using a procedure similar to that described in Scheme 1a step 2.

Entry	Amine	Alkyl halide	sulfonamide
1			
2			
3*		CD_3I	
4*			

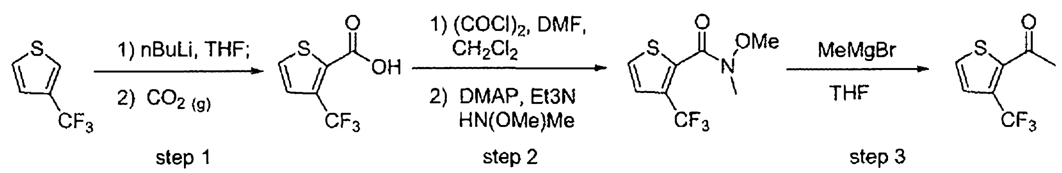
* Cesium carbonate was used as the base instead of NaH for entries 3 and 4.

Scheme 1b:



Step 1: To a mixture of **Ex. 1** (8.00 g, 28.0 mmol) and concentrated sulfuric acid (16 mL) was added fuming nitric acid (2.24 mL) at 0 °C. The reaction mixture was stirred from 0 °C to room temperature over 2 h. After this time, the reaction mixture was basified with sodium carbonate to pH 10 and extracted with ethyl acetate (2 × 200 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the nitro compound (8.81 g, 94%).

Scheme 2:



Step 1: To a solution of 3-trifluoromethyl thiophene (3.75g, 24.6 mmol) in anhydrous THF (60 mL) at -78°C was added a solution of n-BuLi (2.5 M in hexanes, 13 mL, 32.5 mmol). The

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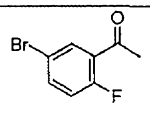
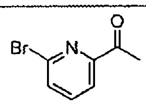
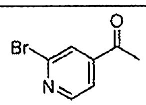
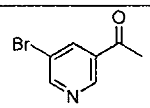
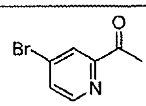
resultant solution was stirred at -78°C for 10 min. To the solution was bubbled $CO_{2\,(g)}$ for 20 min at -78°C. The solution was allowed to warm to RT and stirred for an additional 40 min at RT while bubbling of $CO_{2\,(g)}$ through the solution was continued. After that time,1 M HCl $_{(aq.)}$ was added to the solution. The aqueous layer was then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: 85:15:1 CH_2Cl_2:MeOH:AcOH) to afford the carboxylic acid (4.33 g, 90%).

Step 2: To a solution of a portion of the acid from step 1 (465 mg, 2.37 mmol) in CH_2Cl_2 (12 mL) and DMF (0.20 mL) at 0°C was added dropwise a solution of oxalyl chloride (2 M in CH_2Cl_2, 3.5 mL, 3 eq.). The resultant solution was stirred at 0°C for 15 min followed by an additional 1 hour at RT. The solution was concentrated. To the residue was added N,O-dimethylhydroxylamine hydrochloride (470 mg, 2 eq.) followed by CH_2Cl_2 (18 mL). The resultant mixture was cooled to 0°C. To this mixture was added Et_3N (1.4 mL) and DMAP (10 mg). The solution was stirred at 0°C for 1 hour. To the solution was added 1 M $HCl_{(aq.)}$ (60 mL) and CH_2Cl_2 (60 mL). The layers were separated. The organic layer was washed with brine, dried and concentrated. The crude residue was purified via flash chromatography (SiO_2: gradient elution 100:0 to 60:40 heptane:EtOAc) to afford the amide (426 mg, 75%).

Step 3: To a solution of the amide from step 2 (4.10 g, 17.1 mmol) in THF (70 mL) at 0°C was slowly added a solution of methyl magnesium bromide (3 M in Et_2O, 7 mL). The resultant solution was stirred at 0°C for 3 hours. After that time, 1 M HCl $_{(aq.)}$ was added. The mixture was then extracted with Et_2O. The organic layer was dried, filtered and concentrated. The residue was purified via flash chromatography (SiO_2: gradient elution 100:0 to 60:40 pentane:EtOAc) to afford the ketone (3.22 g, 97%) as a colorless oil.

Table Ib: The following ketones were prepared using similar procedures to that described in Scheme 2, Steps 2 and 3 using the appropriate carboxylic acids.

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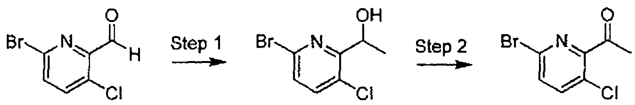
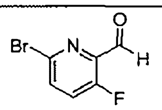
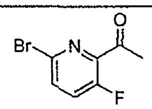
Scheme 2b:



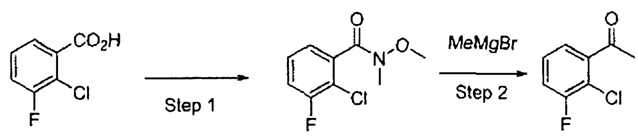
Step 1: To a solution of 6-bromo-3-chloropicolinaldehyde (10.0 g, 45.45 mmol) in 200 mL THF stirring at -78°C under N_2 was slowly added methylmagnesium bromide (3.0 M in diethyl ether, 16.63 mL, 50 mmol). The reaction was stirred at this temperature for 3 hours, and then saturated ammonium chloride was added. The mixture was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-10% EtOAc/hexanes over 20 minutes) to provide 1-(6-bromo-3-chloropyridin-2-yl)ethanol (8.4 g, 78%).

Step 2: The material prepared above (8.4 g, 35.5 mmol) was stirred overnight at room temperature in 100 mL DCM along with pyridinium chlorochromate (15 g, 71 mmol) and approximately 5 g celite. The reaction was filtered through celite and washed with DCM. The filtrate was concentrated to dryness *in vacuo* and the residue was purified by silica gel chromatography (0-10% EtOAc/hexanes over 22 minutes) to provide 1-(6-bromo-3-chloropyridin-2-yl)ethanone (6.85 g, 82%).

Table Ic: The following ketone was made using methods similar to those described in Scheme 2b:

Entry	Aldehyde	Ketone
1		

Scheme 2c:

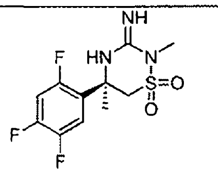
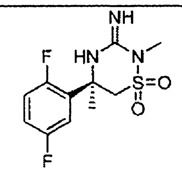
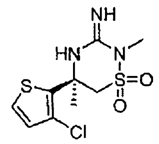
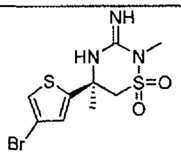
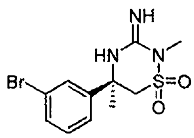
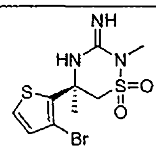
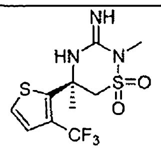
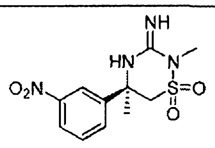
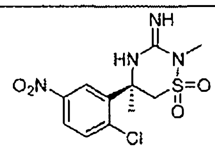
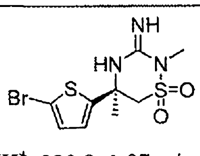
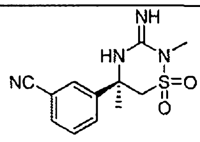
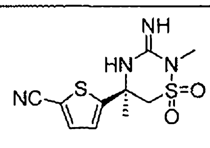
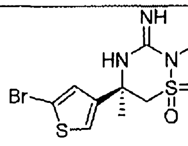
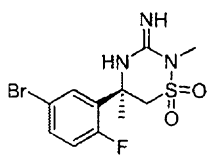
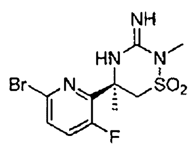


Step 1: To a solution of 2-chloro-3-fluorobenzoic acid (30 g, 172 mmol) in 300 mL of DCM was added carbonyldiimidazole (CDI) (32.0 g, 198 mmol) in portions. After addition and then stirring at RT for 1 h, N,O-dimethylhydroxylamine HCl salt (18.5 g, 189 mmol) was added into the mixture followed by Et_3N (20 mL). The mixture was stirred at RT overnight. After the reaction was quenched with water, the aqueous layer was extracted with DCM (2x). The

organic layers were washed with 2N HCl (aq), water, sat. $NaHCO_3$ (aq) and brine. The solution was dried ($MgSO_4$) and concentrated. The product 2-chloro-3-fluoro-N-methoxy-N-methylbenzamide (32.0 g) was obtained by silica gel chromatography (elution with 0-30% EtOAc/Hex).

Step 2: The above material was treated according to Scheme 2, Step 3 to provide the ketone product (89% yield).

Table II: The following examples were prepared using similar procedures to that described in Scheme 1a using the appropriate starting materials.

Examples (LCMS data listed with each compound: observed MH^+, HPLC retention time and LCMS method)					
2	 MH^+: 308.2, 1.64 min, D	**3**	 MH^+: 290.0, 1.99 min, B	**4**	 MH^+: 294.2, 1.43 min, A
5	 MH^+: 340.2, 2.64 min, A	**6**	 MH^+: 331.9, 1.95 min, B	**7**	 MH^+: 340.2, 2.19 min, A
8		**9**		**10**	
11	 MH^+: 339.8, 1.87 min, A	**12**	 MH^+: 278.9, 1.73 min, B	**13**	 MH^+: 285.0, 1.54 min, B
14	 MH^+: 340.2, 2.44 min, A	**14a**		**14b**	

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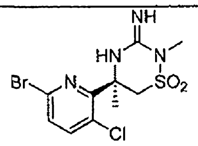
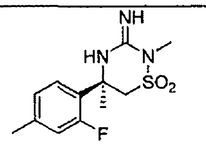
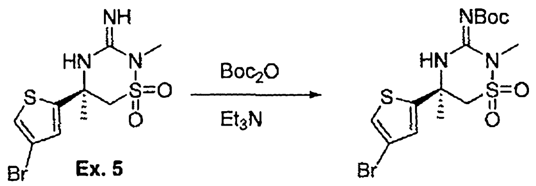
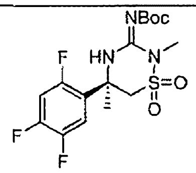
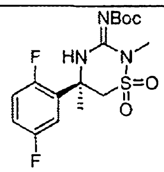
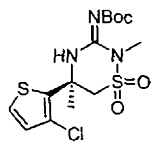
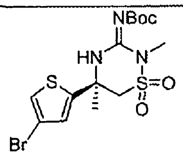
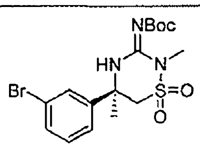
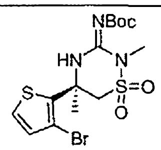
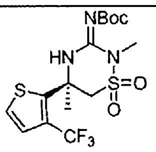
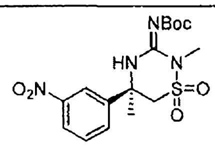
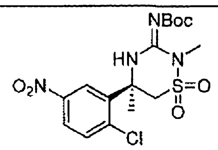
			MH^+: 350.0, 1.72 min, D		
14c		**14d**			

Scheme 3:



To a solution of **Ex. 5** (1.60 g, 5.53 mmol) in CH_2Cl_2 was added Boc_2O (1.24 g, 5.68 mmol) and Et_3N (0.82 mL, 5.91 mmol). The resultant solution was stirred at RT overnight. The solution was washed with 1/2 saturated $NaHCO_3$ $_{(aq.)}$. The aqueous layer was back extracted with CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 70:30 hexanes:EtOAc) to afford the *tert*-butyl carbamate (1.74 g, 84% yield).

Table IIb: The following carbamates were prepared using similar procedures to that described in Scheme 3 using the appropriate starting materials.

Entries					
1		**2**		**3**	
4		**5**		**6**	
7		**8**		**9**	

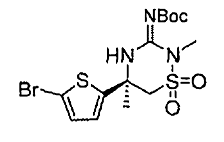
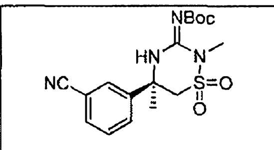
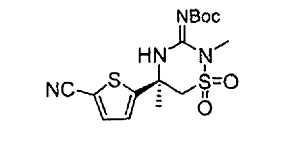
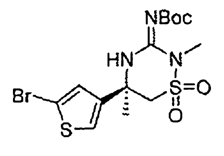
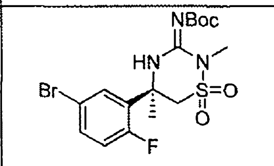
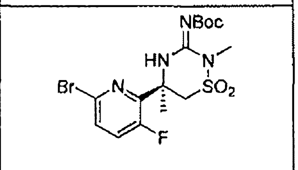
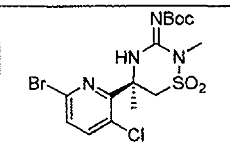
10		**11**		**12**	
13		**14**		**15**	
16					

Table IIc: The following example was prepared using a procedure similar to that described in Scheme 1b, using the following modified temperature profile: nitric acid addition at -40 degrees C, then warming to 0 degrees C.

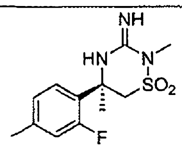
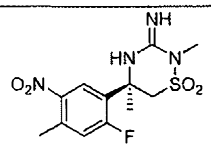
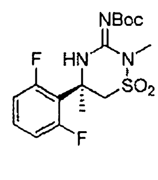
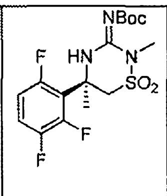
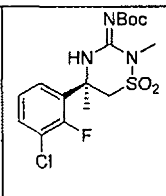
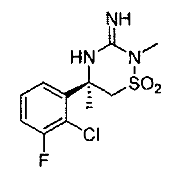
Example	Starting material	Product
14e	 Example 14d	

Table IId: The following thiadiazine dioxides were made according to methods similar to those in Schemes 1a and 3, with the noted exceptions:

Entries							
1[a,b]		2[a,b]		3[c]		**Ex. 14f**[d,e]	

a: (S)-2-Methyl-2-propanesulfinamide was used in Step 1 Scheme 1a instead of (R)-2-methyl-2-propanesulfinamide.

b: Re-crystallization from 95% MeOH / 5% water was used to remove a diastereomeric product after silica gel purification in Step 3 Scheme 1a.

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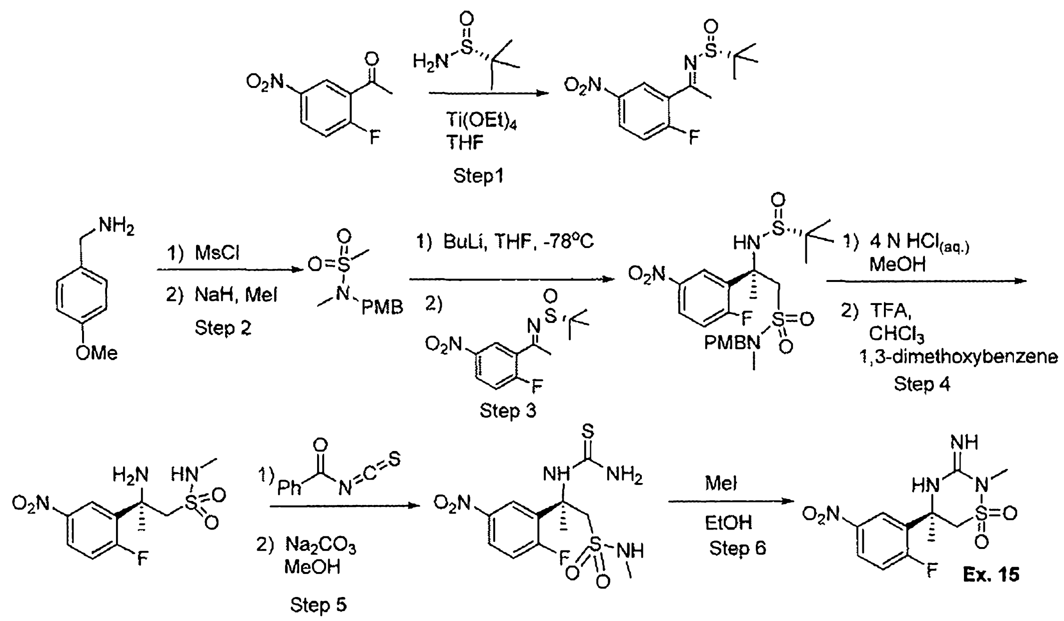
c: SFC chromatography (TharSFC80, Chiralpak OD-H, 50 x 250 mm, 5 μm, 150 bar with 30% iPrOH, 250 g/min, 40 °C) used to remove a diastereomeric product after silica gel purification in Step 3 Scheme 1a.

d: SFC chromatography (TharSFC80, Chiralpak OJ-H, 50 x 250 mm, 5 μm, 150 bar with 25% iPrOH, 250 g/min, 40 °C) used to remove a diastereomeric product after silica gel purification in Step 3 Scheme 1a.

e: The product of Scheme 1a Step 4 was treated according to Scheme 3b to afford Example 14f directly, instead of employing Scheme 1a, Steps 5 and 6.

Scheme 3a:



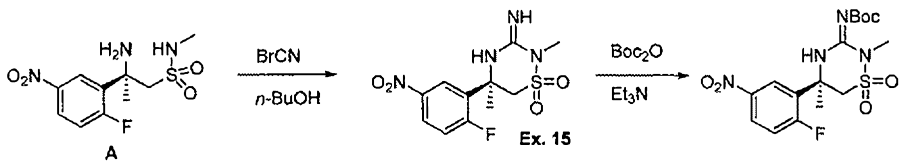
Steps 1-4: These steps were performed using similar procedures to those described in steps 1-4 of Scheme 1a.

Step 5: To a solution of the amine from step 4 (10.5 g, 36 mmol) in CH_2Cl_2 (200 mL) was added benzoylisothiocyanate (4.3 mL, 1.1 eq.). The resulting solution was stirred at RT for 2.5 days. Additional benzoylisothiocyanate (0.86 mL, 0.2 eq.) was added and the solution was stirred at RT for an additional 2 hours. The solution was then concentrated *in vacuo*.

A portion of this material (6.5 g, ~14 mmol) was dissolved in MeOH (200 mL). To this solution was added $Na_2CO_{3\,(s)}$ (1.52 g, 14 mmol). The resultant mixture was stirred at RT for 45 min. After that time, a slight excess of HOAc was added to the solution. The mixture was then concentrated. The residue was partitioned between CH_2Cl_2 and ½ sat. $NaHCO_{3\,(aq.)}$. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The thiourea (~ 4.9 g) was carried onto the next reaction without further purification.

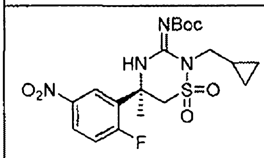
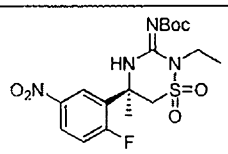
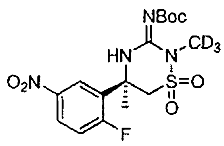
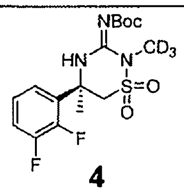
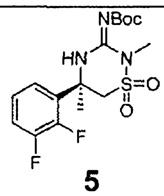
Step 6: Example 15 was prepared using a method similar to that described in Scheme 1a step 6.

Scheme 3b:

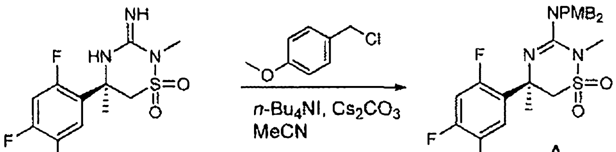


To a slurry of amine **A** (Scheme 3a step 4) (13.7 grams) in n-butanol (150 mL) was added a solution of cyanogen bromide (5M in MeCN). The resultant mixture was heated to reflux for 4 hours. The mixture was concentrated to 1/3 of the original volume. To the mixture was added Et_2O (200 mL). The resultant solid was removed via filtration and the solid was washed with Et_2O (2x). The solid was partitioned between EtOAc and sat. Na_2CO_3 (aq.). The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford 10.6 grams of **Ex. 15**. This material was converted to the t-butyl carbamate using a procedure similar to that described in Scheme 3.

Table IIe: The following thiadiazine dioxides were prepared using procedures similar to those described in Schemes 3a (entry 1), 3b (entries 2-5) and 3 using the sulfonamides shown in Table I and Scheme 1a.

Entries				
 **1**	 **2**	 **3**	 **4**	 **5**

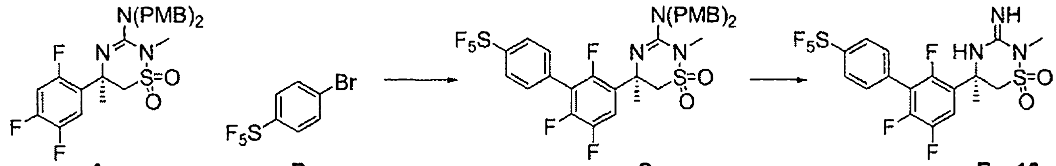
Scheme 4:



Ex. 2 A

To a solution of **Ex. 2** (3.8 g, 12.2 mmol) in MeCN (40 mL) was added 4-methoxybenzyl chloride (4.6 g, 29 mmol), Cs_2CO_3 (9.9 g, 31 mmol) and n-Bu_4NI (450 mg, 1.2 mmol). The resultant mixture was heated to reflux for 16 hours. After that time, additional 4-methoxybenzyl chloride (1.9 g, 12 mmol) and Cs_2CO_3 (4.4 g, 12 mmol) were added and the mixture was heated to reflux for an additional 4 hours. The mixture was then concentrated *in vacuo* at RT. The residue was partitioned between water and CH_2Cl_2. 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 via flash chromatography (SiO_2: gradient elution 100:0 to 80:20 hexanes:EtOAc) to afford the bis-PMB compound **A** (4.9 g, 73%).

Scheme 5:



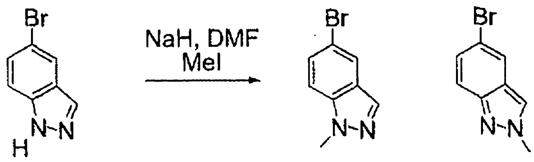
A B C Ex. 16

A 20 mL microwave vessel was flame-dried and cooled under vaccum, then backfilled with N_2, followed by two cycles of vacuum/N_2 backfill. NaHMDS (1 M in THF, 2.2 mL, 2.2 mmol) was added to a solution of thiadiazine dioxide **A** ((Scheme 4) 547 mg, 1.0 mmol) in dioxane (5 mL) at RT, and stirred for 30 min. A freshly prepared solution of $ZnCl_2$ (1.2 M in THF, 2.0 mL, 2.4 mmol) was added, and stirring continued for 30 min at RT. $Pd(OAc)_2$ (45 mg, 0.2 mmol), X-Phos (190 mg, 0.4 mmol) and arylbromide **B** (509 mg 1.80 mmol) were added and the reaction mixture was degassed (4 x vacuum/N_2), capped and placed into a preheated 100°C oil bath for 3h. The crude reaction was cooled to RT, diluted with EtOAc/water, filtered through a pad of celite, and the aqueous layer extracted with EtOAc (2x). The combined organic layers were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude residue that was subjected to silica gel chromatography

(0→30 % EtOAc/hexanes) followed by RP-HPLC conditions (monitoring at 220 nm) to give intermediate **C** (73 mg, 97 umol).

A solution of intermediate **C** (73 mg, 97 umol) in CH_3CN (4 mL) was heated to 75° C, and a solution of K_2HPO_4 (26 mg, 147 umol), KH_2PO_4 (20 mg, 147 umol) and $K_2S_2O_8$ (158 mg, 588 umol) in water (2 mL) was added via pipette. After 60 min at 75° C, the reaction mixture was cooled to RT and concentrated under vacuum. The residue was subjected to RP-HPLC conditions to give **Ex. 16** (TFA salt, 26 mg). LCMS data: (method D): t_R = 2.17 min, *m/e* = 510.0 (M+H).

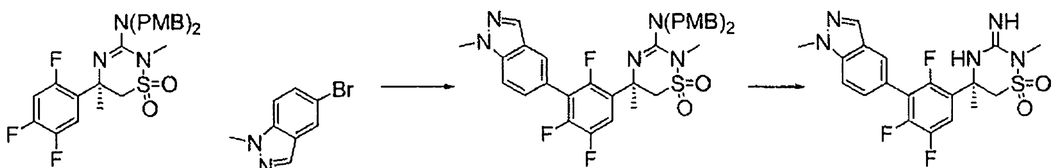
Scheme 6a:



D E R = Me F

Sodium hydride (60% in oil, 1.5 g, 37.5 mmol) was added to a solution of 5-bromoindazole **D** (6 g, 30.6 mmol) in DMF (60 mL) at RT. After stirring for 30 min, methyl iodide (2.83 mL, 45.9 mmol) was added and the reaction stirred for another 2 h at RT. The reaction was quenched with sat. $NaHCO_3$ (aq), extracted with EtOAc (1x), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a mixture of *N*-1 and *N*-2 methylated 5-bromoindazoles **E** and **F**, which were separated by silica-gel chromatography using 0→30 % EtOAc/hexanes.

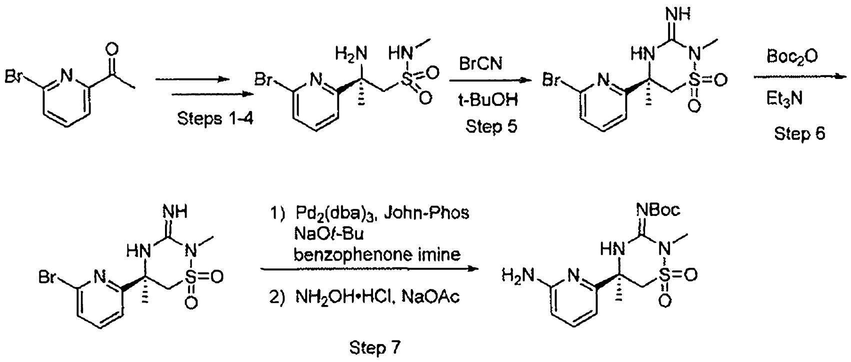
Scheme 6b:



A E G Ex. 17

Example 17 was prepared as described for **Example 16** in Scheme 5, substituting arylbromide **E** for **B**. LCMS data: (method C): t_R = 3.12 min, *m/e* = 438.2 (M+H).

Scheme 7a:



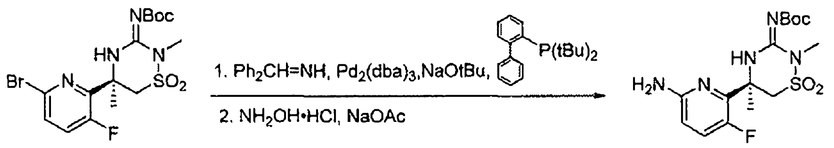
Steps 1-4: These steps were performed using similar procedures to those described in steps 1-4 of Scheme 1a.

Step 5: This step was performed using a procedure similar to that described in Scheme 3b except *t*-BuOH was used as the solvent instead of n-BuOH.

Step 6: The *t*-butyl carbamate was installed using a procedure similar to that described in Scheme 3.

Step 7: A mixture of the bromide (3.00 g, 6.92 mmol), benzophenone imine (1.39 mL, 8.30 mmol), $Pd_2(dba)_3$ (0.634 g, 0.692 mmol), John-Phos (0.413 g, 1.38 mmol), sodium *tert*-butoxide (2.13 g, 22.1 mmol), and toluene (51 mL) was degassed (vacuum/N_2). The mixture was then stirred at 65 °C under nitrogen for 3 h. After this time, the reaction mixture was cooled to room temperature and filtered through a pad of Celite and rinsed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure. The residue was then dissolved in methanol (76 mL) and the resulting solution was charged with hydroxyl amine hydrochloride (2.16 g, 31.1 mmol) and sodium acetate (2.55 g, 31.1 mmol). The reaction mixture was stirred at room temperature for 40 min. After this time, the reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate (200 mL) and washed with saturated aqueous sodium bicarbonate (100 mL), water (100 mL), and brine (100 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0–100% ethyl acetate/heptane) to afford the amino pyridine (0.880 g, 34%) .

Scheme 7b:



To a flame-dried flask was added a pyridyl bromide (Table IIb, Entry 15, 1.5 g, 3.3 mmol), $Pd_2(dba)_3$ (305 mg, 0.3 mmol), (2-biphenyl)di-*tert*-butylphosphine (200 mg, 0.7 mmol), sodium *tert*-butoxide (1.02 g, 0.011 mmol), benzophenone imine (670ul, 4 mmol), and toluene (21 mL). The mixture was evacuated under vacuum and back-filled with N_2 (3X). The mixture was stirred at 60 °C for 1 h. After filtration through celite, the filtrate was concentrated. The crude residue was dissolved in 36 mL of methanol, and hydroxyl amine hydrochloride (458 mg, 6.6 mmol) and sodium acetate (541 mg, 6.6 mmol) were added. The reaction was stirred for 35 min and then quenched with saturated aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate, and the combined organic portions were dried over magnesium sulfate and concentrated. The crude residue was purified by a flash silica column (50% ethyl acetate/hexane) to get an aminopyridine product (730 mg, 68%).

Table IIIa: The following amino-pyridines were prepared using similar procedures to those described in Scheme 7a using the appropriate ketones from Table Ib.

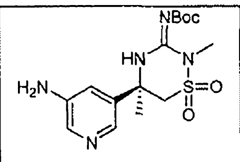
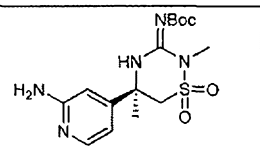
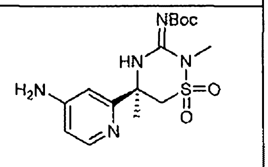
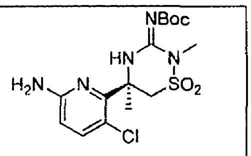
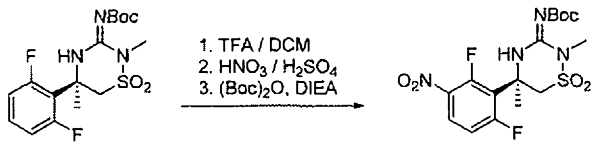
Entries					
1		**2**		**3**	

Table IIIb: The following compound was prepared from the bromide (Table IIb entry 16) using methods similar to those described in Scheme 7b:



Scheme 7c:



To a solution of a halophenyl thiadiazine (Table IId, entry 1: 2.31 g, 5.9 mmol) in 5 mL of DCM was added 1 mL of TFA. The mixture was stirred for 4 h and then concentrated. At 0 °C, to a solution of this crude residue in 4 mL of sulfuric acid was carefully added a mixture of 0.5 mL of fuming nitric acid and 1.2 mL of sulfuric acid. The mixture was stirred at 0 °C for 2 h and then poured into 150 mL of ice. The mixture was neutralized by carefully adding saturated sodium bicarbonate solution and solid sodium hydroxide. The resulting mixture was extracted with ethyl acetate, and the combined organic layers were dried over magnesium sulfate and concentrated. This crude residue was dissolved in 20 mL of DCM, and $(Boc)_2O$ (1.29g, 5.9 mmol), and DIEA (2.56 mL, 14.75 mmol) were added. The reaction was stirred overnight, and then quenched with 1N HCl. The mixture was extracted with DCM, the organic portions were combined, dried over magnesium sulfate, and concentrated. The crude residue was purified by a flash silica column (25% ethyl acetate/hexane) to give a nitrophenyl thiadiazine product (1.93 g, 76% yield).

Table IIIc: The following compounds were made using methods similar to those described in Scheme 7c starting from the appropriate starting materials shown in Table IIb:

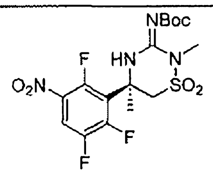
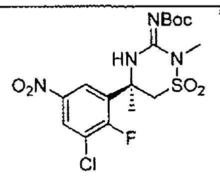
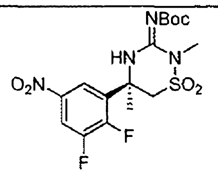
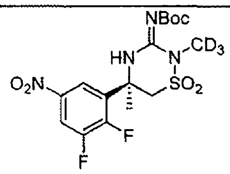
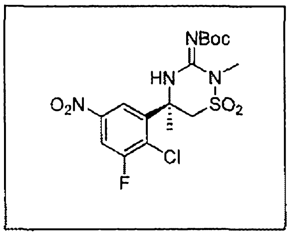
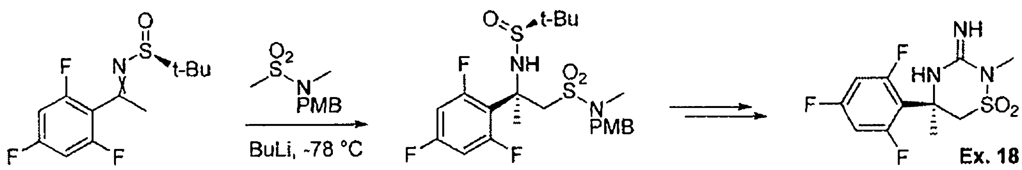
Entries			
			
1	**2**	**3**	**4**

Table IIId: The following compound was made from Ex. 14f using methods similar to those described in Scheme 7c, omitting the initial treatment with TFA:



Scheme 8:



To a solution of N-(4-methoxybenzyl)-N-methylmethanesulfonamide (26.8 g, 117 mmol) in THF (200 mL) at -78 °C was added n-butyllithium (2.5 M in hexanes, 47 mL, 118 mmol) over 10 minutes. After the addition was complete, the mixture was allowed to stir at -78 °C for 1h.

To this mixture was then added a solution of (S)-2-methyl-N-(1-(2,4,6-trifluorophenyl)ethylidene)propane-2-sulfinamide (21.6 g, 77.9 mmol, prepared from 2,4,6-trifloroacetophenone and (S)-2-methyl-2-propanesulfinamide according to Scheme 1a, Step 1) in THF (150 mL) at -78 °C. The resulting mixture was allowed to stir at -78 °C for 4h. At that time, the reaction was quenched by rapid dilution with water (~ 400 mL). The mixture was then warmed to RT, further diluted with EtOAc and brine. The phases were separated, and the aqueous layer was extracted with EtOAc (4X). The organic portions were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. This crude residue was subjected to column chromatography (600g silica, 100 mL/min, 0% to 60% EtOAc/hexanes) to give (R)-2-((S)-1,1-dimethylethylsulfinamido)-N-(4-methoxybenzyl)-N-methyl-2-(2,4,6-trifluorophenyl)propane-1-sulfonamide as a 4:1 mixture with its diastereomer (14.5 g total mass, 37%).

This material was further subjected to SFC chromatography (TharSFC80, Chiralpak OJ-H, 21 x 250 mm, 5 μm, 200 bar with 5% MeOH, 55 g/min, 35 °C) to give (R)-2-((S)-1,1-dimethylethylsulfinamido)-N-(4-methoxybenzyl)-N-methyl-2-(2,4,6-trifluorophenyl)propane-1-sulfonamide).

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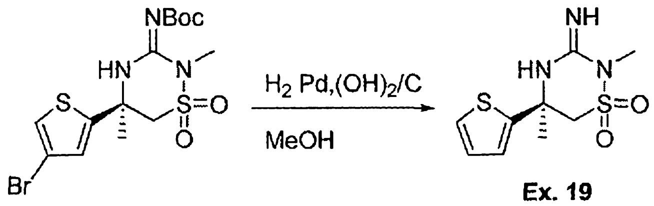
The above material was treated according to Scheme 1a, Steps 4–6 to afford Example 18, dihydro-2,5(R)-dimethyl-5-(2,4,6-trifluorophenyl)-2H-1,2,4-thiadiazin-3(4H)-imine-1,1-dioxide. LCMS (conditions A): t_R = 1.45 min, *m/e* = 308.2 (M+H).

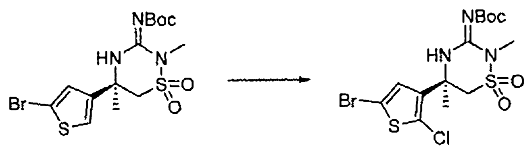
Scheme 9:



Ex. 19

To a degassed solution the *tert*-butyl carbamate (Scheme 3) (348 mg, 0.794 mmol) in MeOH (10 mL) was added 20% $Pd(OH)_2/C$ (50% water) (52 mg, 0.074 mmol). The flask was purged with H_2 and allowed to stir at RT under a balloon of H_2 for 2.75 hours. The mixture was purged with N_2, filtered through Celite and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 95:5 CH_2Cl_2:MeOH) to afford **Ex. 19** (69 mg). LCMS (conditions A): t_R = 2.00 min, *m/e* = 260.1 (M+H).

Scheme 9a:



To the bromide (Table IIb, entry 13) (0.8 g, 1.8 mmol) in DMF (6 mL) was added *N*-chlorosuccinimide (0.7 g, 5.5 mmol). The reaction was warmed to 60°C and stirred for 5 h. Ethyl acetate was added and the mixture was washed with saturated $NaHCO_3$ (aq), water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-30% EtOAc/hex over 30 minutes) to provide a white foam that was further purified by reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:formic acid) to afford the chlorothiophene (0.63 g, 1.3 mmol).

Scheme 10:

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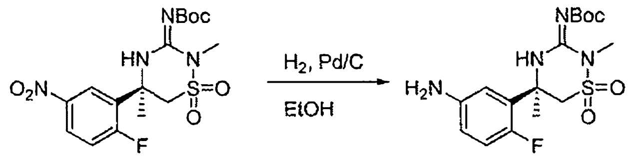
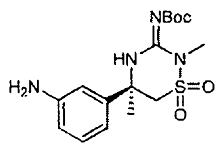
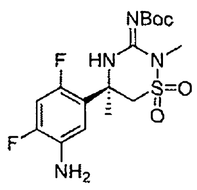
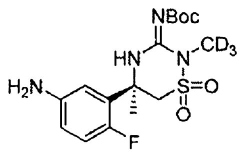
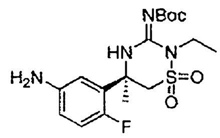
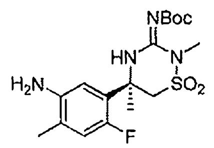
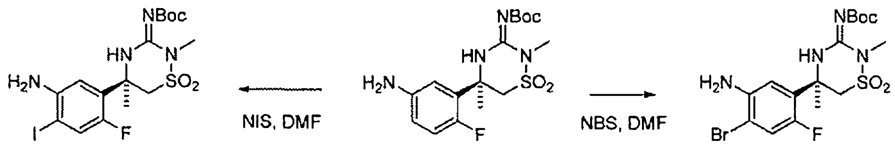


A solution of the nitro compound (Scheme 3b) (2.50 g, 6.0 mmol) in EtOH (150 mL) was degassed by bubbling N_2 through the solution for 3 min. To this solution was added Pd/C (10% w/w, 50% H_2O, 698 mg.). The mixture was placed under an atmosphere of N_2. The atmosphere was evacuated and back-filled with H_2 (3x). The resulting mixture was stirred at RT under a H_2 balloon for 2 h. The mixture was purged by bubbling N_2 through it, filtered through Celite and concentrated. The product was purified by filtering through a small plug of silica gel column eluting with EtOAc to afford the aniline (2.2g, 97%) .

Table IV: The following anilines were prepared from the corresponding nitro compounds using a procedure similar to that described in Scheme 10.

Entries				
 **1**	 **2**	 **3**	 **4**	 **5**

Scheme 10a:

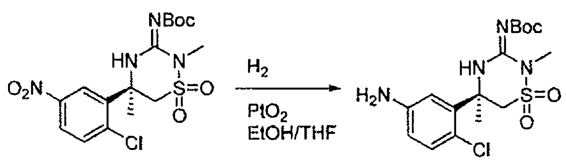


A B

Iodoaniline A preparation: NIS (2.52 g, 11.2 mmol) was added at 0°C to a solution of the aniline (3.6 g, 9.31 mmol, Scheme 10) in DMF (40 mL). After 60 minutes at 0°C and 60 min at RT, the reaction was quenched with saturated aq. $NaHCO_3$ (aq), extracted with EtOAc (3 x), and the combined organic layers dried over Na_2SO_4. After removal of the volatiles under reduced pressure, the residue was subjected to silica gel chromatography (gradient elution 100:0 to 70:30 hexanes:EtOAc) to give the iodoaniline (3.2 g, 67%).

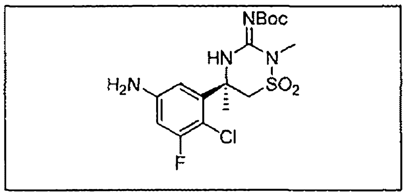
Bromoaniline **B** preparation: NBS (1.05 g, 6.21 mmol) was added at RT to a solution of the aniline (2.0 g, 5.17 mmol, Scheme 10) in DMF (21 mL). After 30 minutes, the reaction was quenched with 10% aq. Na_2SO_3 (aq), diluted with EtOAc, and the organic layer was washed with saturated aq. $NaHCO_3$ (2 x), brine (1x) and dried over Na_2SO_4. After removal of the volatiles under reduced pressure, the residue (2.57 g) was subjected to silica gel chromatography (gradient elution 100:0 to 50:50 hexanes:EtOAc) to give the bromoaniline (2.065 g, 86%).

Scheme 11a:



A solution of the nitro compound (Entry 9, Table IIb) (515 mg, 1.19 mmol) in 1:1 EtOH:THF (24 mL) in a pressure vessel was degassed by bubbling N_2 through it for 5 min. To this solution was added PtO_2 (27 mg, 0.12 mmol). The vessel was sealed. The vessel was then evacuated and backfilled with N_2 (3x). The vessel was then evacuated and purged with H_2 (3x). The vessel was pressurized to 60 psi with H_2 and shaken at RT overnight. After that time, the vessel was purged with N_2. The mixture was then filtered through Celite. The solvent was removed *in vacuo* to afford the aniline (500 mg, 100%).

Table IVa: The following compound was prepared from the corresponding nitro compound (Table IIId) according the methods described in Scheme 11a:



Scheme 11b:

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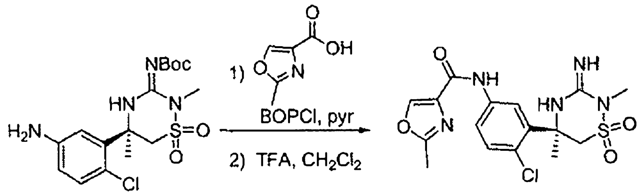
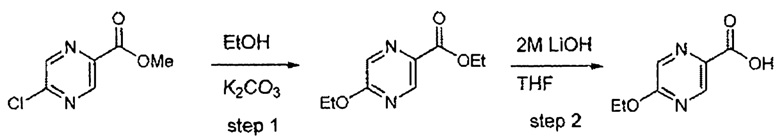


Ex. 20

Step 1: To a flask containing the aniline (Scheme 11a) (100 mg, 0.25 mmol) and 2-methyl-1,3-oxazole-4-carboxylic acid (47 mg, 0.37 mmol) was added BOPCl (145 mg, 0.57 mmol). The flask was sealed and purged with N_2. To the flask was added pyridine (1.0 mL). The resultant solution was stirred at RT for 1 hour. After that time, the solution was partitioned between EtOAc and water. The mixture was filtered through Celite to remove the solids. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 65:35 hexanes:EtOAc) to afford the amide (81 mg, 64%).

Step 2: To a solution of the amide from step 1 (81 mg, 0.16 mmol) in CH_2Cl_2 (1.5 mL) was added TFA (1.5 mL). The resultant solution was stirred at RT for 2 hours. The solution was concentrated *in vacuo* to afford **Ex. 20** (83 mg) as the trifluoroacetate salt. LCMS data: (method D): t_R = 1.75 min, *m/e* = 412.0 (M+H).

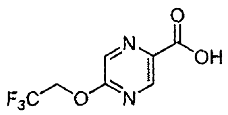
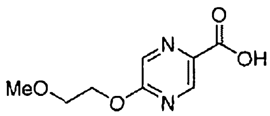
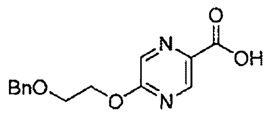
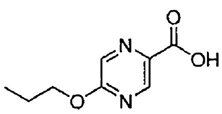
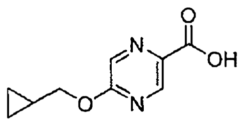
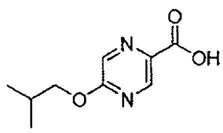
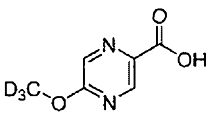
Scheme 11c:



Step 1: To a slurry of methyl 5-chloropyrazine-2-carboxylate (250 mg, 1.45 mmol) in EtOH (5 mL) was added potassium carbonate (300 mg, 2.18 mmol). The resultant solution was stirred at RT for 2 hours. The mixture was concentrated. The residue was partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford ethyl 5-ethoxypyrazine-2-carboxylate (110 mg, 39%) as a yellow solid.

Step 2: To a solution of the material from step 1 (110 mg, 0.60 mmol) in THF (3 mL) was added a solution of LiOH (2M in water, 0.90 mL, 1.8 mmol). The solution was stirred at RT for 1 h. The solution was adjusted to pH 1 using 1M HCl (aq.). The aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford the acid (75 mg, 74%).

Table IVb: The following pyrazine carboxylic acids were prepared using a procedure similar to that described in Scheme 11c using the appropriate alcohol in step 1. Modifications for specific examples are listed below the table.

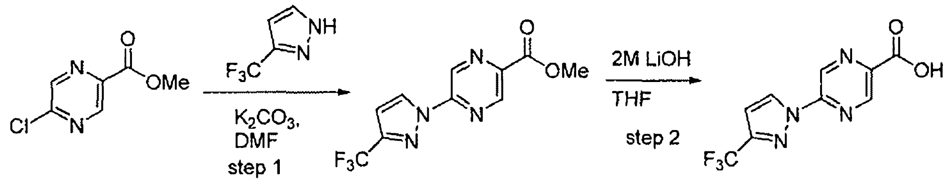
Entries					
1		2[a]		3[b]	
4[a]		5[b]		6[c]	
7					

[a] Step 1 modification: the ether was purified via flash chromatography (SiO_2 gradient elution 100:0 to 70:30 hexanes:EtOAc).

[b] Step 1 modification: the ether was purified via flash chromatography (C_{18} gradient elution 90:10:0.1 to 0:100:0.1 water:MeCN:formic acid).

[c] Step 2 modification: the pyrazine acid was purified via flash chromatography (C_{18} gradient elution 90:10:0.1 to 0:100:0.1 water:MeCN:formic acid).

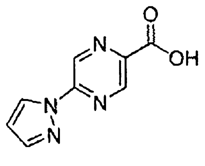
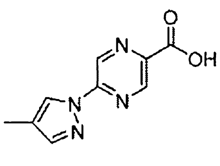
Scheme 11d:



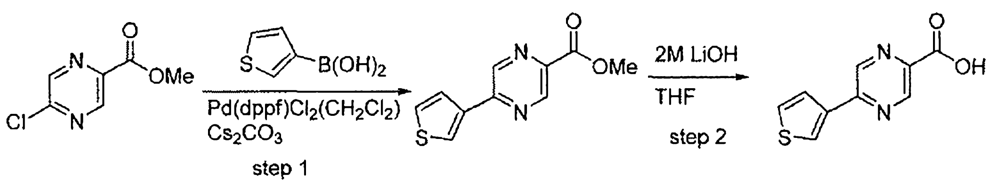
Step 1: To a solution of methyl 5-chloropyrazine-2-carboxylate (500 mg, 2.90 mmol) and 3-(trifluoromethyl)-1H-pyrazole (591 mg, 4.35 mmol) in DMF (7 mL) was added potassium carbonate (591 mg, 4.35 mmol). The resultant solution was stirred at RT overnight. The mixture was partitioned between water and EtOAc and separated. The organic layer was dried over Na_2SO_4, filtered and concentrated to afford the biaryl ester (560 mg, 71%).

Step 2: The acid was formed using a procedure similar to that described in Scheme 11c step 2.

Table IVc: The following pyrazine carboxylic acids were prepared using a procedure similar to that described in Scheme 11d using the appropriate pyrazole.

Entries	
 **1**	 **2**

Scheme 11e:

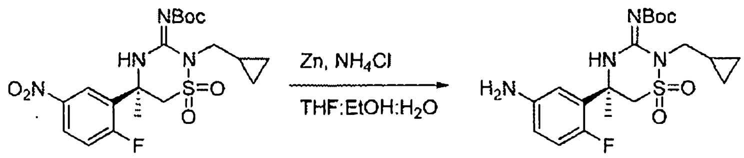


Step 1: A degassed mixture of 5-chloropyrazine-2-carboxylate (500 mg, 2.90 mmol), Cs_2CO_3 (1.1 g, 3.5 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (237 mg, 0.29 mmol) and thiophen-3-ylboronic acid (445 mg, 3.5 mmol) in dioxane (10 mL) was heated to reflux for 2 hours. The mixture was concentrated. The residue was partitioned between water and CH_2Cl_2 and filtered through

Celite. The aqueous layer of the filtrate was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified via flash chromatography (SiO_2 gradient elution 100:0 to 10:90 hexanes:EtOAc) to afford the biaryl ester (560 mg, 88%).

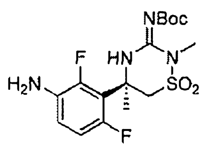
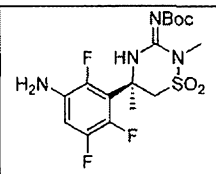
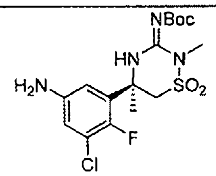
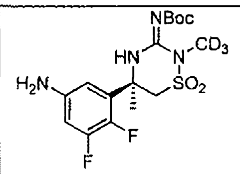
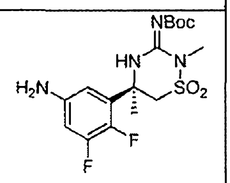
Step 2: The acid was formed using a procedure similar to that described in Scheme 11c step 2.

Scheme 11f:

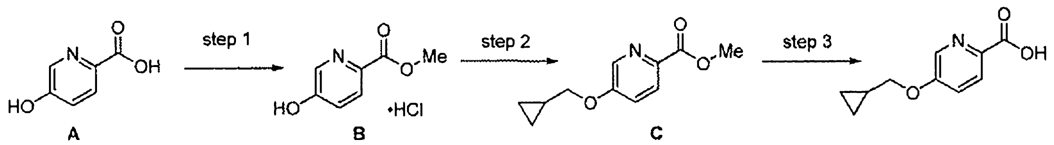


A solution of the nitro compound (Table IIe, entry 1, 1.70 grams, 3.7 mmol) in THF:EtOH:H_2O (30 mL, 3:1:0.3) was degassed by bubbling N_2 through the solution for 3 min. To the solution was added Zn (2.4 g, 37 mmol) and NH_4Cl (996 mg, 18 mmol). The resultant mixture was heated to reflux under an atmosphere of N_2 for 3 hours. The mixture was filtered through celite and concentrated. The residue was purified via reverse phase flash chromatography (C_{18}, gradient elution 90:10:0.1 to 0:100:0.1 H_2O:MeCN:formic acid). The resultant formate salt was partitioned between EtOAc and sat $NaHCO_3$ (aq.). The aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford the aniline (847 mg, 54%).

Table IVd: The following compounds were prepared according the methods described in Scheme 11f except they were purified via SiO_2 flash chromatography:

Entries				
 1	 2	 3	 4	 5

Scheme 11g:

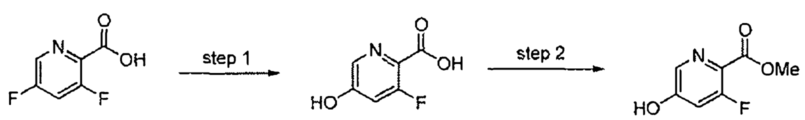


Step 1: To 5-hydroxypyridine-2-carboxylic acid (4.40 g, 32 mmol) suspended in methanol (77 mL) was added thionyl chloride (6.9 mL, 95 mmol) dropwise. The reaction was warmed to reflux and stirred for 22 h. After cooling to room temperature, the mixture was concentrated *in vacuo* to provide the methyl ester (5.71 g, 95%).

Step 2: To the methyl ester (0.40 g, 2.1 mmol) formed in step 1 in DMF (3 mL) was added potassium carbonate (0.88 g, 6.3 mmol) and cyclopropylmethyl bromide (0.41 mL, 4.2 mmol). The reaction was warmed to 65 °C and stirred for 18 h. The reaction was cooled to room temperature and then concentrated *in vacuo*. The residue was triturated with EtOAc and filtered washing with EtOAc. The filtrate was concentrated *in vacuo* to provide a crude product that was purified by silica gel chromatography (0-50% EtOAc/hex over 30 minutes) to provide the cyclopropylmethyl ether (0.27 g, 61%).

Step 3: To the product of step 2 (0.27 g, 1.3 mmol) in THF (2 mL) was added 2N $LiOH_{(aq.)}$ (1.9 mL, 3.9 mmol). The reaction was stirred at room temperature for 2 h. The pH was adjusted to pH 4 using saturated aqueous citric acid. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the carboxylic acid (0.23 g, 94%).

Scheme 11h:

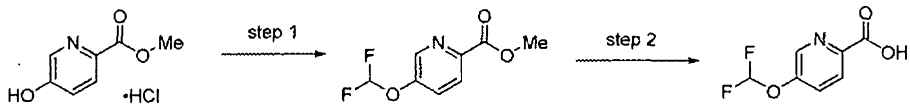


Step 1: To 3,5-difluoropyridine-2-carboxylic acid (3.0 g, 19 mmol) in THF (30 mL) in a glass tube reaction vessel was added 2N $LiOH_{(aq)}$. The reaction mixture was capped and warmed to 100 °C. The reaction was stirred for 18 h and then cooled to room temperature. TFA (5 mL) was added and the reaction was concentrated *in vacuo*. The residue was purified by reverse phase chromatography [C18 (360g) 0.1% formic acid/water for 20 minutes followed by 0-

100% 0.1% formic acid/acetonitrile//0.1% formic acid/water] to provide the hydroxy pyridine (2.1 g) as a ~1:1 mixture of starting material and product. The mixture was carried on directly.

Step 2: To the hydroxy pyridine prepared in the previous step (2.1 g) in methanol (20 mL) was added thionyl chloride (2.2 mL, 31 mmol). The reaction was warmed to 70 °C and stirred for 18 h. The reaction was cooled to room temperature and concentrated *in vacuo*. The residue was purified by reverse phase chromatography [C18 (205 g), 0-100% over 20 minutes 0.1% formic acid/acetonitrile//0.1% formic acid/water] to provide the methyl ester (1.0 g, 31% over 2 steps).

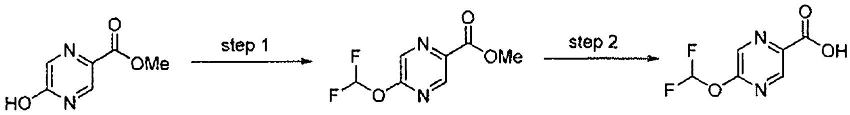
Scheme 11i:



Step 1: To the methyl 5-hydroxypicolinate hydrochloride prepared in step 1 of Scheme 11g (0.21 g, 1.1 mmol) in a glass tube reactor in acetonitrile (4 mL) was added water (4 mL), potassium carbonate (5.5 g, 40 mmol) and 2-chloro-2,2-difluoroacetophenone (1.0 g, 5.5 mmol). The reaction vessel was capped and warmed to 80 °C. The reaction was stirred at 80 °C for 3h and cooled to room temperature. The mixture was filtered washing with ether. The filtrate was washed with ether. The ether washes were combined and washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a tan oil. The oil was purified by silica gel chromatography (0-40% EtOAc/hex over 30 minutes) to provide the ether (0.13 g, 60%).

Step 2: Using the procedure described in step 3 of Scheme 11g, the product of step 1 was converted to the carboxylic acid.

Scheme 11j:

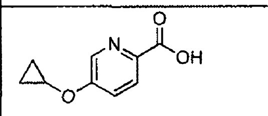
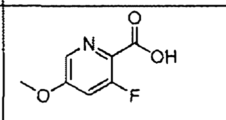
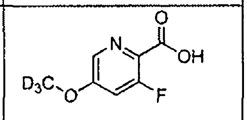
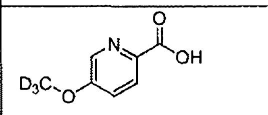
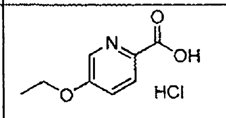
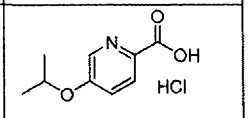
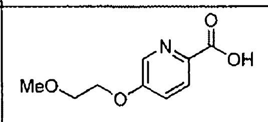
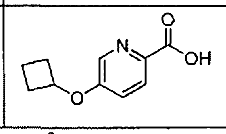
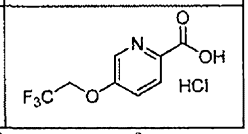


Step 1: To 5-hydroxypyrazine-2-carboxylic acid methyl ester (2.0 g, 13 mmol) in a glass tube reaction vessel in DMF (26 mL) was added potassium carbonate (5.3 g, 39 mmol) and sodium 2-chloro-2,2-difluroacetate (4.0 g, 26 mmol). The reaction vessel was capped and warmed to 100 °C. The reaction was stirred for 30 minutes and cooled to room temperature. The

reaction was filtered washing with EtOAc. The filtrate was concentrated *in vacuo*. The residue was taken up into EtOAc and washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-40% EtOAc/hex) to give methy-5-(difluoromethoxy)pyrazine-2-carboxylate (0.09 g, 0.46 mmol) (0.40 g, 20%).

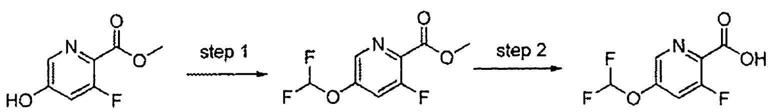
Step 2: To the product of step 1 (0.09 g, 0.46 mmol) was added 3N $HCl_{(aq)}$. The reaction was heated in a sealed microwave reactor vial to 100 °C for 2 h. The reaction was concentrated in vacuo to provide the carboxylic acid (0.88 g, 100%).

Table IVf: The following pyridine carboxylic acids were prepared from either intermediate **B**, Scheme 11g or the hydroxypyridine from Scheme 11h using conditions similar to those described in Scheme 11g steps 2 and 3. Modifications of the experimental conditions are noted below the table.

Entry		Entry		Entry	
1[a]		2[b]		3[b]	
4[b]		5[c, g]		6[c, g]	
7[f]		8[d]		9[e]	

Alkylation conditions: a: Cs_2CO_3, NaI, 150°C, 7 h; b: rt; c: 45°C; d: 100°C; e:130°C, microwave, 1 h; f: 70°C.
Hydrolysis conditions: g: See Scheme 11j, step 2.

Scheme 11k:

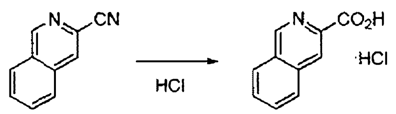


Step 1: To the hydroxypyridine prepared in Scheme 11h (0.19 g, 1.1 mmol) in acetonitrile (4 mL) and water (4 mL) was added potassium carbonate (5.5 g, 40 mmol) and 2-chloro-2,2-difluoroacetophenone. The glass reaction tube was sealed and warmed to 80 °C. After 3.5 h,

the reaction was cooled to room temperature and filtered washing with EtOAc. The filtrate was extracted with ether. The combined ether layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-30% EtOAc/hex over 30 minutes) to provide product (0.15 g, 60%).

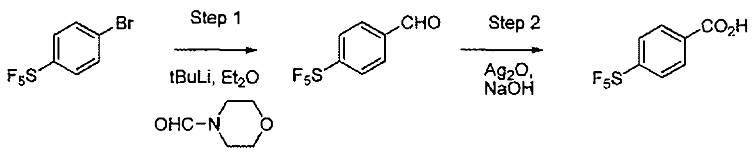
Step 2: The product of step 1 was converted to the carboxylic acid using the conditions found in step 3 of Scheme 11g.

Scheme 11l:



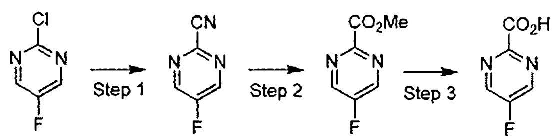
3-Cyanoisoquinoline (1.047 g, 6.79 mmol) was suspended in 6 M HCl (aq) (50 mL) and refluxed at 95°C for 18 h. The reaction was cooled to RT, and the volatiles removed under vacuum to provide the carboxylic acid (2.07 g) that was used as is.

Scheme 11m:



4-Pentafluorosulfur benzoic acid was obtained in two steps from 4-bromophenyl sulfurpentafluoride according to the literature procedure by Zarantonello et al., *J. Fluor. Chem.* **2007**, *128*, 1449-1453.

Scheme 11n:



Step 1: To 2-chloro-5-fluoropyrimidine (2 g, 15 mmol) in a 250-mL round bottom flask was added DMA (8 mL), tris(dibenzylideneacetone)dipalladium (0.544 g, 0.6 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.67 g, 1.2 mmol), zinc cyanide (1.15 g, 9.8 mmol), and zinc dust (0.237 g, 3.62 mmol). The flask was capped, flushed with nitrogen, and stirred for 2.5 h at 100°C. The reaction was cooled to room temperature, filtered through celite, and

washed with DCM. The filtrate was poured into water and extracted with DCM. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-10% EtOAc/hexanes over 20 minutes) to provide the nitrile compound (0.58 g, 31%).

Step 2: To the nitrile compound prepared in Step 1 (0.51 g, 4.14 mmol) stirring in 5 mL MeOH was added 5 mL conc. HCl. The reaction was fitted with a reflux condenser and heated at 80°C for 2 hours, then cooled to room temperature. Saturated aqueous sodium bicarbonate was added and stirred for 1 hour at room temperature. The mixture was acidified to pH 4 using 1 N HCl (aq) and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the methyl ester (0.256 g, 40%).

Step 3: To the methyl ester compound prepared in Step 2 (0.256 g, 1.64 mmol) in 6 mL 1:1:1 THF: H_2O: MeOH was added LiOH hydrate (0.272 g, 4.04 mmol), and the mixture stirred at room temperature for 1 hour. The reaction was acidified to pH 4 using 1 N HCl (aq) and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the carboxylic acid (0.136 g, 58%).

Table IVg: The following acids were made using methods similar to those described in Scheme 11n using the appropriate aryl chloride (entries 1-3) or bromide (entries 4 and 5):

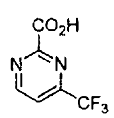
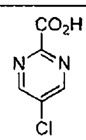
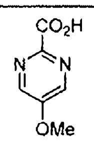
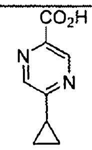
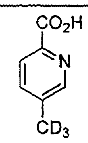
Entries									
1		**2**		**3**		**4**		**5**	

Table IVh: The following acid was made using methods similar to those described in Scheme 11n, Step 3:

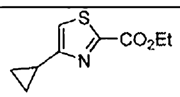
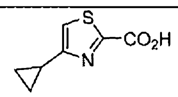
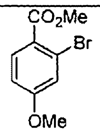
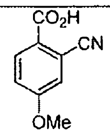
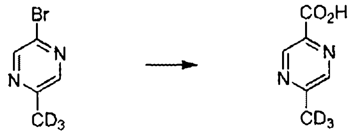
Entry	Starting material	Acid
1		

Table IVi: The following acid was made according to methods similar to those described in Scheme 11n, using Step 1 and then Step 3, omitting Step 2:

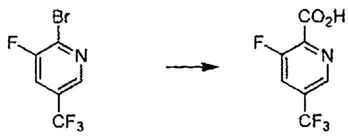
Entry	Starting material	Acid
1		

Scheme 11o:

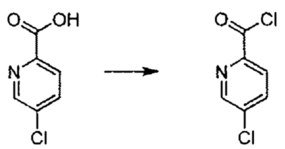


To 2-bromo-5-(methyl-D$_3$)-pyrazine (400 mg, 2.27 mmol) stirring in 8 mL anhydrous THF at -78 °C under N_2 atmosphere was slowly added *n*-BuLi (2.5 M in hexanes, 1.14 mL, 2.85 mmol). The reaction was stirred for 30 minutes at this temperature, upon which carbon dioxide was bubbled through the solution for 15 minutes via cannulating needle. The cold bath was removed and the reaction allowed to come to room temperature slowly over 1 hour. Water was then added and the reaction was extracted with ethyl acetate. The organics were combined, dried ($MgSO_4$), and concentrated *in vacuo* to provide an oil (120 mg, 38%) that was used without further purification.

3-Fluoro-5-(trifluoromethyl)picolinic acid was prepared from 2-bromo-3-fluoro-5-(trifluoromethyl)pyridine using a procedure similar to that described above in Scheme 11o.

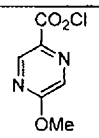
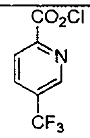


Scheme 11p:

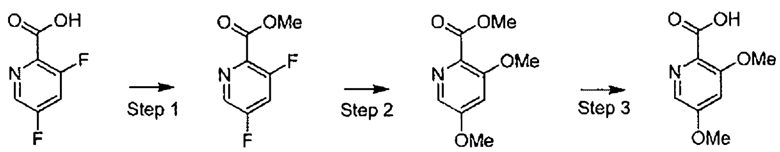


To 5-chloropicolinic acid (0.3 g, 1.9 mmol) stirring at room temperature in 6 mL THF and 1 drop of DMF was slowly added dropwise oxalyl chloride (0.48 mL, 5.7 mmol). Vigourous outgassing was observed. The reaction was stirred at room temperature for 1.5 hours, then concentrated to dryness *in vacuo* and the product used without further purification.

Table IVj: The following acid chlorides were made using methods similar to those described in Scheme 11p from the appropriate carboxylic acid.

Entries	
 **1**	 **2**

Scheme 11q:

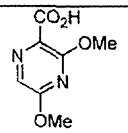
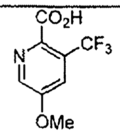


Step 1: To 3,5-difluoropyridine-2-carboxylic acid (2 g, 12.6 mmol) stirring in 20 mL 4:1 toluene:MeOH at room temperature was slowly added dropwise trimethylsilyldiazomethane (2.0 M in hexanes, 15.1 mmol, 7.5 mL). The reaction was allowed to stir for 30 minutes, and then was concentrated to dryness *in vacuo* and used without further purification.

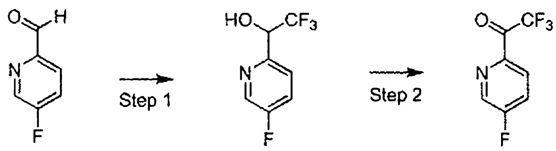
Step 2: To the methyl ester prepared in step 1 (1.09 g, 6.3 mmol) stirring at room temperature in 20 mL MeOH in a 350-mL sealed vessel was added 25 weight % sodium methoxide in methanol (3.4 g sodium methoxide, 13.6 g solution, 63 mmol). The reaction was flushed with nitrogen, sealed, and stirred 16 hours in a 100°C oil bath. The next day the reaction was cooled to room temperature and acidified to pH 4 using 1 N HCl. The solution was extracted with 1:1 EtOAc:THF (250 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-60% EtOAc/hexanes over 20 minutes) to provide the desired *bis*-methoxy compound (0.53 g, 43%).

Step 3: The methyl ester was converted to the carboxylic acid using methods similar to those described in Scheme 11n, Step 3.

Table IVk: The following acids were made using methods similar to those described in Scheme 11q using the appropriate aryl chloride:

Entries	
 **1**	 **2**

Scheme 11r:



Step 1: To 2-fluoro-5-formylpyridine (1.57 g, 12.55 mmol) stirring in anhydrous THF (20 mL) at 0°C under a nitrogen atmosphere was slowly added (trifluoromethyl)-trimethylsilane (2.67 g, 18.78 mmol). The mixture was stirred at 0°C for 15 minutes, and then tetrabutylammonium fluoride (1.0 M in THF, 31.38 mL, 31.38 mmol) was slowly added dropwise, upon which the ice bath was removed, and the reaction was allowed to stir at room temperature overnight (total reaction time 16 hours). The reaction was then poured into water and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-20% EtOAc/hexanes over 20 minutes) to provide the trifluoromethyl alcohol product (2.01 g, 82%).

Step 2: To the trifluoromethyl alcohol prepared in step 1 (1 g, 5.12 mmol) stirring in anhydrous DCM (20 mL) was added Dess-Martin periodinane (2.63 g, 6.14 mmol). The reaction was stirred at room temperature overnight (total reaction time 16 hours). Hexanes were added upon which a precipitate formed. The solid was filtered off and washed with DCM. The filtrate was taken and poured into saturated aqueous sodium bicarbonate and extracted with DCM. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-20% EtOAc/hexanes over 20 minutes) to provide the trifluoromethyl ketone product (0.453 g, 46%).

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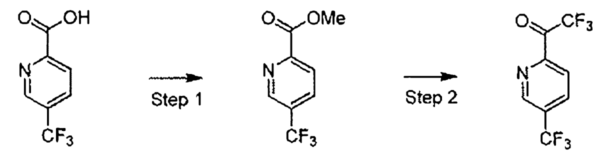
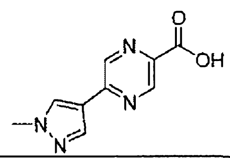
Scheme 11s:



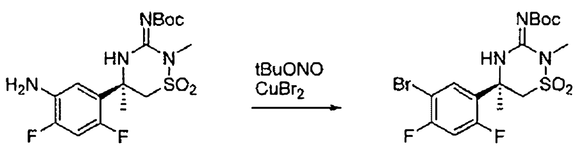
Step 1: The carboxylic acid (1.5 g, 7.84 mmol) was converted to the methyl ester using methods similar to those described in Scheme 11q, Step 1. The crude reaction was evaporated to dryness *in vacuo*, and purified by silica gel chromatography (0-30% EtOAc/hexanes over 20 minutes, 30-40% EtOAc/hexane from 20-30 minutes) to provide the methyl ester product as a solid (1.02 g, 63%).

Step 2: To a mixture of methyl 5-(trifluoromethyl)pyridine-2-carboyxlate prepared above (0.2 g, 0.97 mmol) and (trifluoromethyl)trimethylsilane (0.173 g, 1.22 mmol) stirring at -78°C in pentante (3 mL) under a nitrogen atmosphere was slowly added tetrabutylammonium fluoride (1.0 M in THF, 25 μL, 0.024 mmol). The reaction was allowed to come to room temperature and stirred overnight (total reaction time 16 hours). At that time, 2 N HCl was added, and the mixture was stirred vigorously at room temperature for 2 hours. The solution was extracted with DCM. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-20% EtOAc/hexanes over 20 minutes) to provide the trifluoromethyl ketone product (0.084 g, 35%).

Table IVl: The following pyrazine carboxylic acid was prepared using a procedure similar to that described in Scheme 11e.

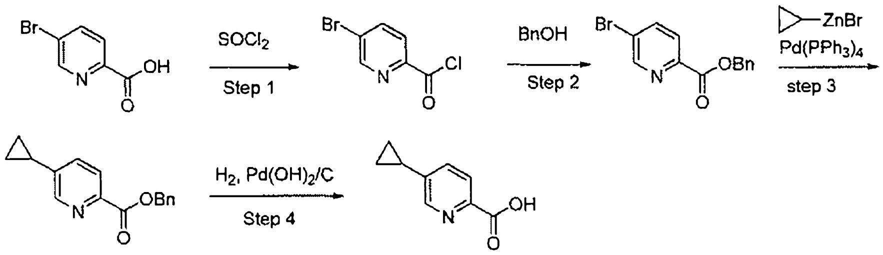
Entry	
1	

Scheme 11t:



A large microwave tube was charged sequentially with MeCN (9 mL), *tert*-butyl nitrite (0.15 mL, 1.2 mmol), and copper(II) bromide (0.331 g, 1.48 mmol). The tube was crimp sealed and immersed in an oil bath at 60 °C. To the resulting black-green mixture was added a solution of 1,1-dimethylethyl [5(R)-(5-amino-2,4-difluorophenyl)dihydro-2,5-dimethyl-1,1-dioxido-2H-1,2,4-thiadiazin-3(4H)-ylidene]carbamate (Table IV, Entry 2, 500 mg, 1.24 mmol) in MeCN (3 mL) via syringe over ~ 2 min. After the addition was complete, the reaction was stirred at 60 °C for 20 min. At that time, the reaction was cooled, diluted with EtOAc, and filtered through Celite. The filtrate was diluted with water and EtOAc. The phases were separated and the aqueous layer was extracted 2X with EtOAc. The organic portions were combined, washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. This crude sample was subjected to column chromatography (80 g silica, 60 mL/min, 0% to 50% EtOAc/hexanes) to give product 1,1-dimethylethyl [5(R)-(5-bromo-2,4-difluorophenyl)dihydro-2,5-dimethyl-1,1-dioxido-2H-1,2,4-thiadiazin-3(4H)-ylidene]carbamate (0.30 g, 52%).

Scheme 11u:



Step 1: To a suspension of 5-bromopicolinic acid (20.2 g, 100 mmol) in 200 mL of toluene was added thionyl chloride (11 mL, 150 mmol). The mixture was stirred at room temperature for 20 min and then heated to reflux for 30 min. The resulting solution was cooled to room temperature and concentrated to dryness. The crude product 5-bromopicolinoyl chloride was used directly in the next step.

Step 2: After addition of THF (200 mL) and Et_3N (42 mL) to the above residue, the mixture was cooled in an ice-water bath. Benzyl alcohol (31.1 mL, 300 mmol) was added slowly. The mixture was warmed up to room temperature and stirred overnight.

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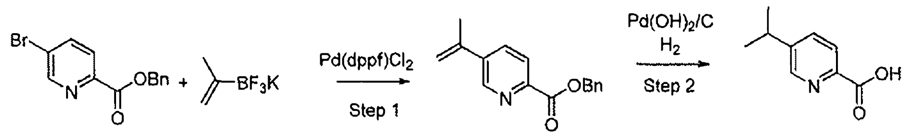
The reaction mixture was diluted with ether, washed with sat. $NaHCO_{3(aq.)}$, H_2O, brine and then dried ($MgSO_4$). After concentration and crystallization, the desired product benzyl 5-bromopicolinate (20.6 g) was obtained.

Step 3: To a solution of benzyl 5-bromopicolinate (876 mg, 3.0 mmol) in THF (10 mL) was added $Pd(PPh_3)_4$ (173 mg, 0.15 mmol) under N_2. After addition of a solution of cyclopropylzinc bromide in THF (0.5 M, 10 mL), the mixture was heated at 80 °C for 3 hours and then cooled to room temperature. The reaction mixture was quenched with sat. NH_4Cl (aq) and extracted with EtOAc (3x). The organic layer was washed with sat. $NaHCO_{3(aq.)}$, brine, and dried ($MgSO_4$). The product benzyl 5-cyclopropylpicolinate (510 mg) was obtained by silica gel chromatography (elution with 0-15% EtOAc/Hex, then 15% EtOAc/Hex).

Step 4: To a solution of benzyl 5-cyclopropylpicolinate in MeOH (15 mL) was added 20% $Pd(OH)_2/C$ (100 mg). The hydrogenolysis with H_2 was carried out at room temperature under a H_2 balloon. The desired product 5-cyclopropylpicolinic acid (305 mg) was obtained after filtration and concentration.

Scheme 11v:



Step 1: A mixture of benzyl 5-bromopicolinate (2.92 g, 10 mmol), potassium isopropenyl trifluoroborate (3.05 g, 21 mmol), $Pd(dppf)Cl_2$ (445 mg, 0.54 mmol), and Et_3N (1.4 mL) in isopropyl alcohol (20 mL) was degassed with N_2 and heated at 80 °C for 7 h. The mixture was cooled to room temperature and diluted with EtOAc. The organic layer was washed with H_2O, 5% citric acid, sat.$NaHCO_{3\,(aq.)}$ and brine, then dried ($MgSO_4$) and concentrated. The product benzyl 5-isopropenylpicolinate (1.27 g) was obtained by silica gel chromatography (elution with 0-16% EtOAc/Hex).

Step 2: A solution of benzyl 5-isopropenylpicolinate (1.27 g, 5 mmol) in MeOH (25 mL) was subjected to hydrogenation with 20% $Pd(OH)_2/C$ (200 mg) with a H_2 balloon for 2h. The product 5-isopropenylpicolinic acid (780 mg) was obtained by filtration and concentration.

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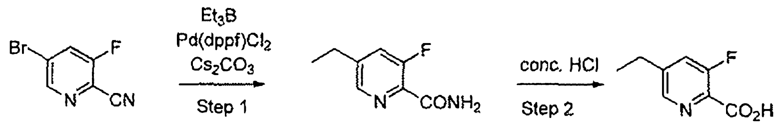
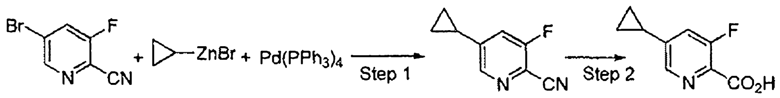
Scheme 11w:



Step 1: A mixture of 5-bromo-3-fluoropicolinonitrile (1.0 g, 5 mmol), Pd(dppf)Cl_2 (82 mg, 0.1 mmol) and cesium carbonate (3.26, 10 mmol) in THF (20 mL) was degassed with N_2. After addition of a solution of triethylborane (1.0 M THF, 10 mL), the mixture was heated at 65 °C for 5 h. The mixture was cooled down to room temperature, and then further cooled down in an ice bath. Into the mixture was added a solution of NaOH (1.2 g) in 20 mL of H_2O, followed by H_2O_2 (30 % aqueous 7 mL). The mixture was stirred at 0°C for 30 min and extracted with ether (4x). The organic layer was washed with brine and dried ($MgSO_4$), and concentrated. The product 5-ethyl-3-fluoropicolinamide (370 mg) was obtained from silica gel chromatography (elution with 0-40% EtOAc/Hex).

Step 2: A mixture of amide (475 mg, 2.8 mmol) in 10 mL of conc. HCl was heated at reflux for 5 h. The mixture was concentrated and dried *in vacuo* to give the product 5-ethyl-3-fluoropicolinic acid.

Scheme 11x:



Step 1: To solution of 5-bromo-3-fluoropicolinonitrile (603 mg, 3.0 mmol) and Pd(PPh_3)$_4$ (173 mg, 0.15 mmol) in 10 mL of THF was added cyclopropyl zinc bromide (0.5 M, 10 mL) under N_2. After being heated 80 °C for 4 h, the mixture was cooled to room temperature and quenched with sat. NH_4Cl (aq). The mixture was extracted with EtOAc (3x) and the combined organic layers were washed with sat. $NaHCO_3$ $_{(aq.)}$ and brine, dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel chromatography (elution with 0-8% EtOAc/Hex) to afford 5-cyclopropyl-3-fluoropicolinonitrile (406 mg).

Step 2: The product of step 1 was heated at reflux in 10 mL of conc. HCl overnight. After concentration, the solid product 5-cyclopropyl-3-fluoropicolinic acid (400 mg) was washed with cold water and dried *in vacuo*.

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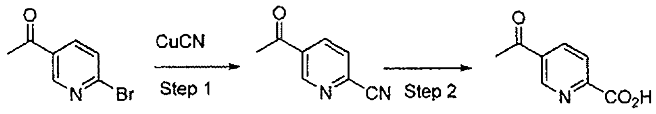
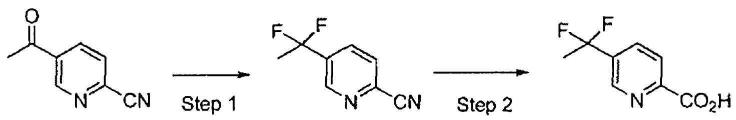
Scheme 11y:



Step 1: A mixture of 1-(6-bromopyridin-3-yl)ethanone (200 mg, 1.0 mmol) and CuCN (179 mg, 2.0 mmol) in anhydrous DMF (5 mL) was heated at 110°C for 18 h under N_2. The mixture was cooled to room temperature and diluted with water. After addition of EtOAc and filtration, the aqueous layer was extracted with EtOAc. The organic layer was washed with sat. $NaHCO_3$ (aq), brine, and then dried ($MgSO_4$) and concentrated. The product 5-acetylpicolinonitrile (120 mg) was obtained by silica gel chromatography (elution with 0-20% EtOAc/Hex).

Step 2: 5-Acetylpicolinonitrile (146 mg, 1.0 mmol) in 5 mL of conc. HCl was heated at reflux for 2.5 h. The mixture was concentrated and dried *in vacuo*. The crude product 5-acetylpicolinic acid was used without further purification.

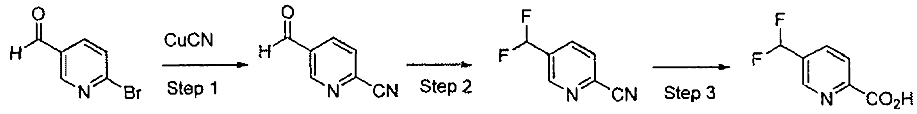
Scheme 11z:



Step 1: A mixture of 5-acetylpicolinonitrile (146 mg, 1.0 mmol) and Deoxo-Fluor™ (1.0 mL, 50% in toluene) was heated at 80 °C for 3h under N_2. The mixture was cooled to room temperature and diluted with DCM. The organic layer was washed with sat. $NaHCO_{3\,(aq.)}$, and brine, dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography (elution with 0-15% EtOAc/Hex) to afford 5-(1,1-difluoroethyl)picolinonitrile (120 mg).

Step 2: 5-(1,1-Difluoroethyl)picolinonitrile (120 mg, 0.71 mmol) in 9 mL of conc. HCl was heated at 110 °C for 5h. The mixture was concentrated. To the residue was added diisopropylethylamine (2 mL) and the mixture was concentrated. The residue was dried *in vacuo* and used without further purification.

Scheme 11aa:

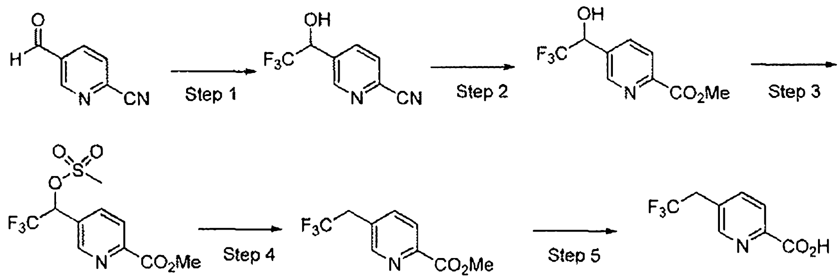


Step 1: A mixture of 6-bromonicotinaldehyde (11.2 g, 60 mmol) and CuCN (8.06 g, 90 mmol) in DMF (100 mL) was heated at 120°C for 3 h under N_2. The mixture was cooled to rt and diluted with EtOAc and filtered through a pad of celite. The organic layer was washed with water and brine and then dried ($MgSO_4$) and concentrated. The product 5-formylpicolinonitrile (4.55 g) was obtained by silica gel chromatography (elution with 0-20% EtOAc/Hex).

Step 2: A mixture of 5-formylpicolinonitrile (132 mg, 1.0 mmol) and Deoxo-Fluor ® (1.0 mL, 50% in toluene) was stirred at room temperature 16 h. After dilution with DCM, the solution was washed with sat. $NaHCO_3$, brine, then dried ($MgSO_4$) and concentrated. The product 5-(difluoromethyl)picolinonitrile (118 mg) was obtained by silica gel chromatography (elution with 0-10% EtOAc/Hex).

Step 3: 5-(Difluoromethyl)picolinonitrile (118 mg, 0.75 mmol) in 9 mL of conc. HCl was heated at 110°C for 2.5 h. The mixture was cooled, concentrated and treated with diisopropylethylamine (2 mL). The mixture was re-concentrated and dried *in vacuo* to give 5-(difluoromethyl)picolinic acid that was used without purification.

Scheme 11ab:



Step 1: To a -78°C solution of 5-formylpicolinonitrile (1.0 g, 7.58 mmol) and tetrabutylammonium triphenyldifluorosilicate (4.9 g, 9.10 mmol) in 60 mL of THF was added a solution of trimethyl(trifluoromethyl)silane (1.62 g, 114 mmol). The mixture was stirred for

20 min at -78°C. Then the cooling bath was changed to an ice bath. After stirring for another 30 min, the reaction was quenched with sat. $NH_4Cl_{(aq.)}$. The mixture was extracted with EtOAc (3x). The organic layer was washed with sat. $NaHCO_{3\,(aq.)}$, brine, then dried ($MgSO_4$) and concentrated. The product 5-(2,2,2-trifluoro-1-hydroxyethyl)picolinonitrile (600 mg) was obtained by silica gel chromatography (elution with 0-40% EtOAc/Hex).

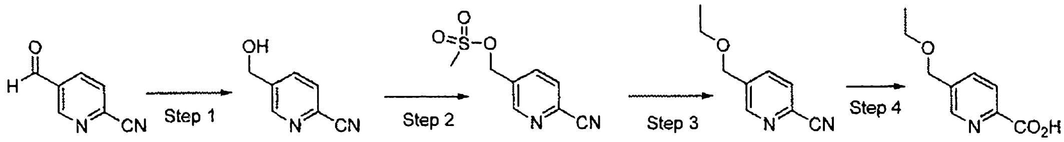
Step 2: A mixture of 5-(2,2,2-trifluoro-1-hydroxyethyl)picolinonitrile (202 mg, 1.0 mmol), conc. HCl (0.5 mL) and conc. H_2SO_4 (0.25 mL) in 10 mL of anhydrous MeOH was heated at reflux for 19 h. The solution was concentrated and neutralized with sat. $NaHCO_{3\,(aq.)}$. Extraction with EtOAc followed by concentration of the organic layer and purification of the residue by silica gel chromatography (elution with 0-45% EtOAc/Hex) afforded methyl 5-(2,2,2-trifluoro-1-hydroxyethyl)picolinate (76 mg).

Step 3: To a solution of methyl 5-(2,2,2-trifluoro-1-hydroxyethyl)picolinate (76 mg, 0.32 mmol) in 3mL of DCM was added triethylamine (0.22 mL), followed by a solution of methanesulfonyl chloride (45 mg, 0.39 mmol) in 1 mL of DCM. The mixture was stirred at room temperature for 7h and then diluted with DCM. The solution was washed with 5% citric acid and sat. $NaHCO_{3\,(aq.)}$, dried ($MgSO_4$), and concentrated. The product methyl 5-(2,2,2-trifluoro-1-(methylsulfonyloxy)ethyl)picolinate (95 mg) was purified by chromatography.

Step 4: To a solution of methyl 5-(2,2,2-trifluoro-1-(methylsulfonyloxy)ethyl)picolinate (95 mg, 0.3 mmol) in 5 mL of MeOH was added 10% Pd/C (45 mg). Hydrogenation with 1 atm H_2 was carried out at room temperature for 2h. After the catalyst was removed by filtration, the filtrated was concentrated. The residue was dissolved in DCM and washed with sat. $NaHCO_{3\,(aq.)}$, and brine. The solution was dried ($MgSO_4$) and concentrated to give methyl 5-(2,2,2-trifluoroethyl)picolinate that was used without purification.

Step 5: A mixture of methyl 5-(2,2,2-trifluoroethyl)picolinate (57 mg, 0.26 mmol) and LiOH (12.5 mg, 0.52 mmol) in 6 mL MeOH/water (5:1) was stirred at room temperature for 3.5 h. The reaction mixture was acidified with 5% citric acid, and then concentrated. The residue was extracted with DCM (4x). The organic layer was washed with brine and dried (Na_2SO_4). After concentration, the product 5-(2,2,2-trifluoroethyl)picolinic acid was dried *in vacuo* and used without further purification.

Scheme 11ac:



Step 1: To a 0°C solution of 5-formylpicolinonitrile (490 mg, 3.71 mmol) in 15 mL of MeOH was added $NaBH_4$ (140 mg, 3.71 mmol). The reaction mixture was stirred at 0°C for 1 h and quenched with 5% citric acid. After most MeOH was removed by concentration, the residue was partitioned between DCM and sat. $NaHCO_{3\ (aq.)}$. The aqueous layer was extracted with DCM (10x). The organic layer was washed with brine and dried (Na_2SO_4). The product 5-(hydroxymethyl)picolinonitrile (431 mg) was obtained by concentration under vaccum.

Step 2: To a solution of 5-(hydroxymethyl)picolinonitrile (1.59 g, 11.9 mmol) in 80 mL of DCM was added diisopropylethylamine (3.2 mL), followed by a solution of methanesulfonyl chloride (1.49g, 13.0 mmol) in 20 mL of DCM at 0°C. The solution was stirred at 0°C for 40 min and washed with 5% citric acid, sat. $NaHCO_{3\ (aq.)}$ and brine. After concentration, the residue was purified by silica gel chromatography (elution with 0-30% EtOAc/Hex) to afford (6-cyanopyridin-3-yl)methyl methanesulfonate (2.33 g).

Step 3: (6-Cyanopyridin-3-yl)methyl methanesulfonate (199 mg, 0.94 mmol) in 2 mL anhydrous EtOH was heated at 85 °C in a sealed tube for 3.5 h. The mixture was concentrated and purified by silica gel chromatography (elution with 0-25% EtOAc/Hex) to afford 5-(ethoxymethyl)picolinonitrile (104 mg).

Step 4: A solution of 5-(ethoxymethyl)picolinonitrile (104 mg) in 10 mL of conc. HCl was heated at reflux for 3.5 h. After concentration, diisopropylethylamine (3mL) was added into the residue. The mixture was concentrated and dried *in vacuo*. The product 5-(ethoxymethyl)picolinic acid was used without further purification.

Table IVm: The following acids were prepared using similar procedures described in Scheme 11ac, substituting the appropriate alcohol in Step 3.

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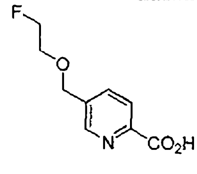
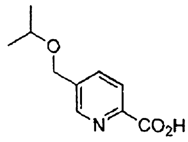
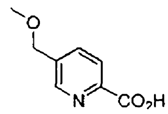
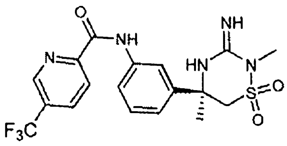
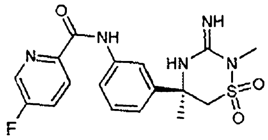
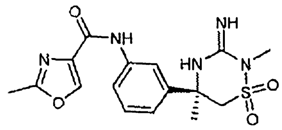
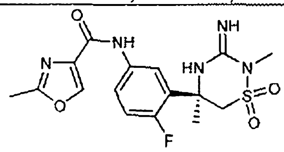
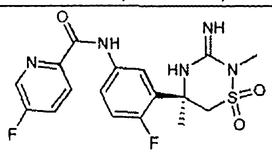
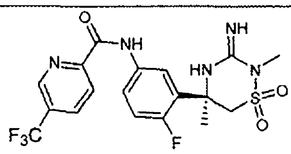
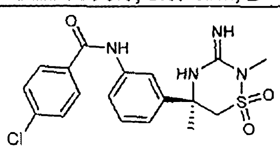
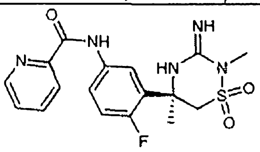
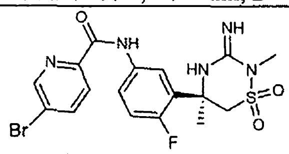
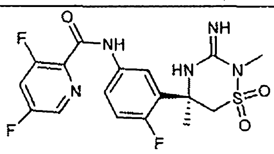
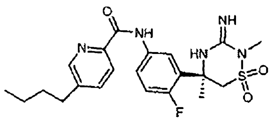
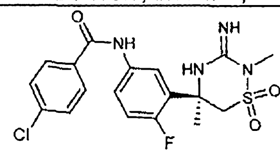
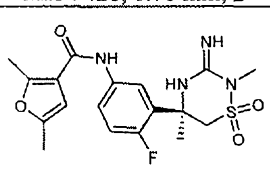
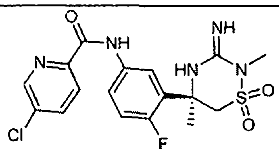
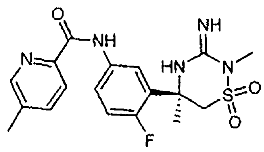
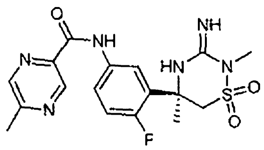
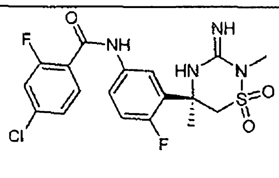
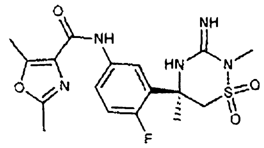
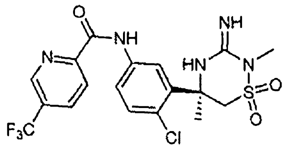
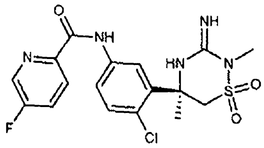
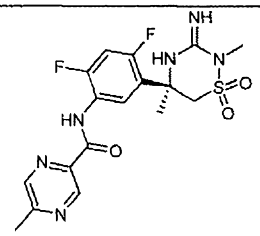
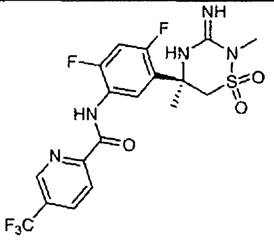
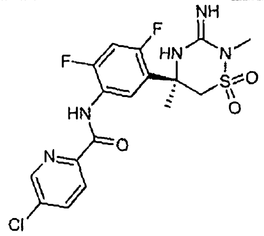
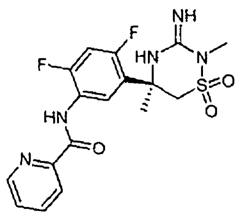
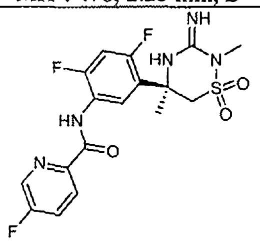
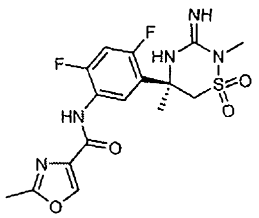
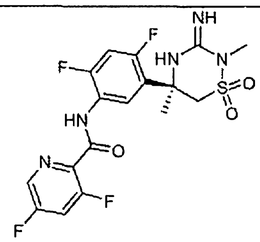
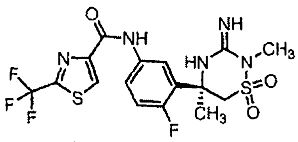
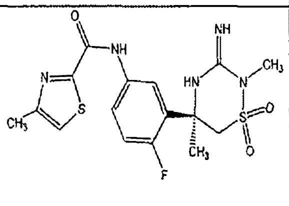
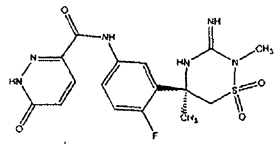
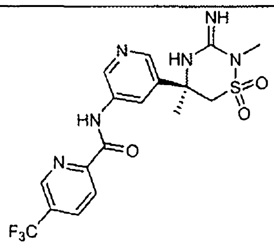
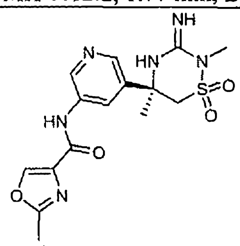
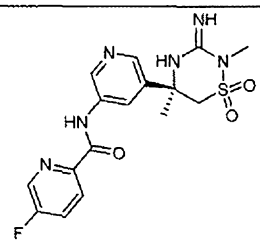
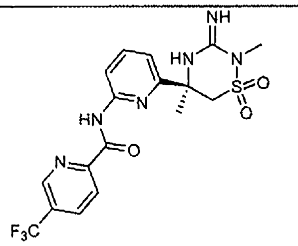
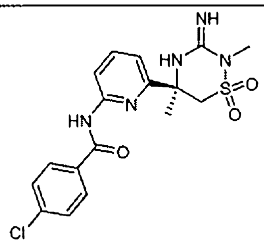
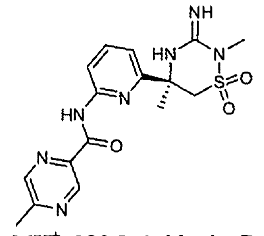
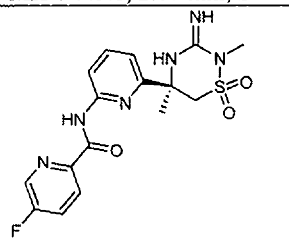
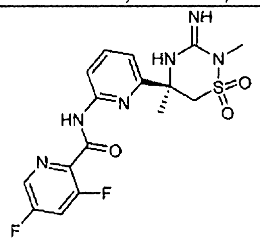
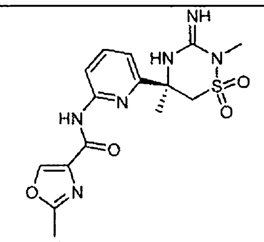
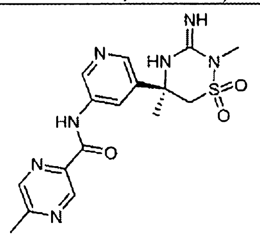
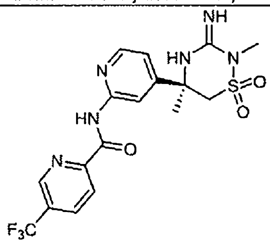
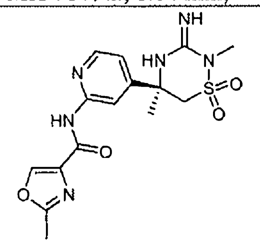
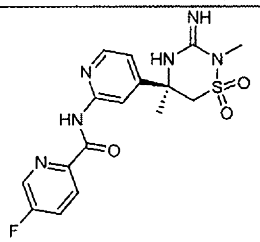
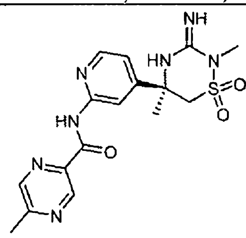
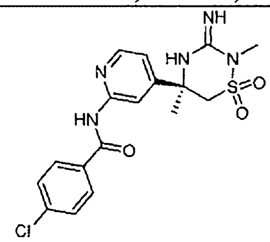
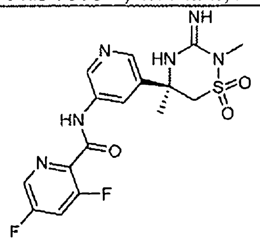
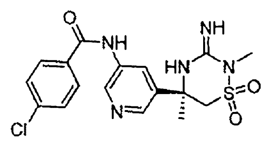
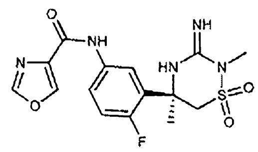
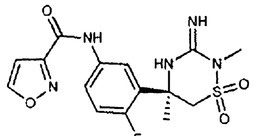
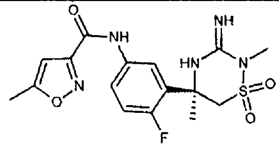
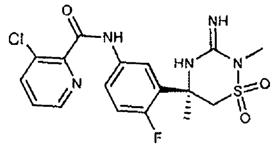
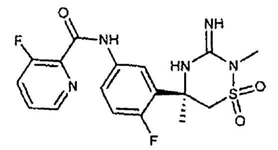
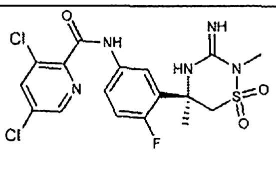
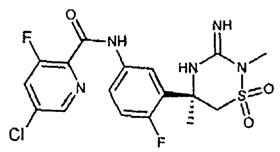
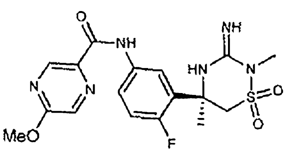
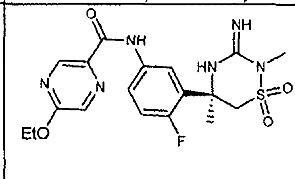
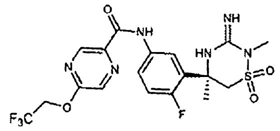
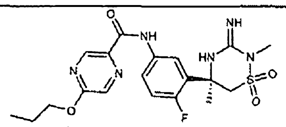
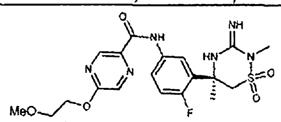
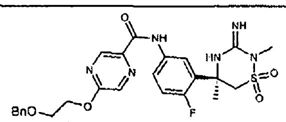
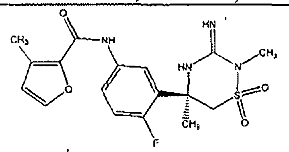
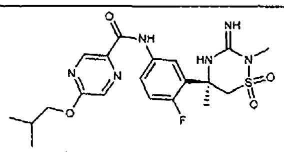
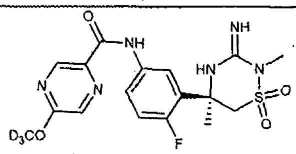
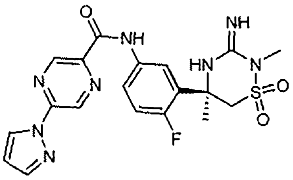
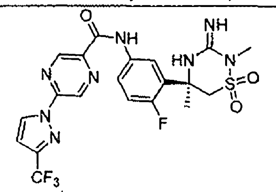
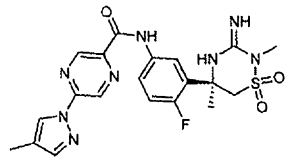
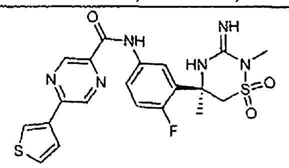
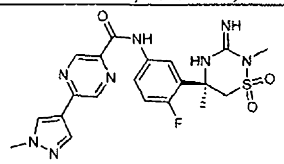
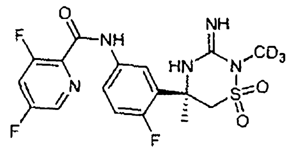
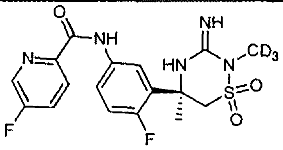
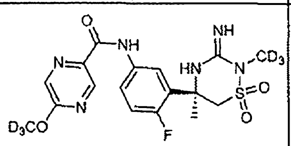
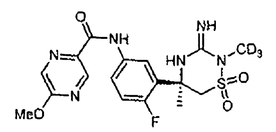
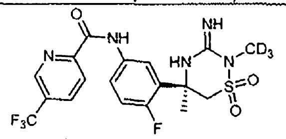
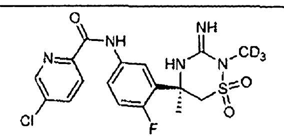
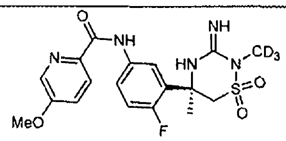
Entries		
 1	 2	 3

Table V: The following examples were prepared using a procedure similar to that described in Scheme 11b using the appropriate aryl amines and carboxylic acids.

Examples (LCMS data listed with each compound: observed MH^+, HPLC retention time and LCMS method)					
21	 MH^+: 442, 1.89 min, D	22	 MH^+: 392, 1.76 min, D	23	 MH^+: 378, 1.64 min, D
24	 MH^+: 396.0, 1.69 min, D	25	 MH^+: 410.0, 1.79 min, D	26	 MH^+: 460.0, 1.90 min, D
27	 MH^+: 407, 1.86 min, D	28	 MH^+: 392, 1.76 min, D	29	 MH^+: 470.0, 1.87 min, D
30	 MH^+: 428, 1.76 min, D	31	 MH^+:448.2, 2.02 min, D	32	 MH^+: 426, 1.88 min, D
33	 MH^+: 409.2, 1.68 min, D	34	 MH^+: 426.2, 3.25 min, A	35	 MH^+: 406.2, 1.8 min, D

36	 MH+: 407.2, 1.71 min, D	**37**	 MH+: 444, 1.86 min, D	**38**	 MH+: 410.2, 1.78 min, D
39	 MH+: 476.0, 1.91 min, D	**40**	 MH+: 426.0, 1.83 min, D	**40a**	 MH+: 425.1, 1.91 min, B
40b	 MH+: 478, 2.25 min, B	**40c**	 MH+: 443.9, 2.18 min, B	**40d**	 MH+: 410.2, 2.02 min, B
40e	 MH+: 428, 2.06 min, B	**40f**	 MH+: 414.1, 1.86 min, B	**40g**	 MH+: 446.0, 2.01 min, B
40h	 MH+:466.2, 1.84 min, D	**40i**	 MH+:412.2, 1.77 min, D	**40j**	 MH+:409.3, 1.55 min, D
40k	 MH+: 443.1, 1.94 min, B	**40l**	 MH+: 379.1, 1.49 min, B	**40m**	 MH+: 393, 1.73 min, B

40n	 MH⁺: 443.1, 2.07 min, B	**40o**	 MH⁺: 408.1, 2.03 min, B	**40p**	 MH⁺: 390.2, 1.66 min, B
40q	 MH⁺: 393.1, 1.86 min, B	**40r**	 MH⁺: 411.1, 1.79 min, B	**40s**	 MH⁺: 379.2, 1.64 min, B
40t	 MH⁺: 390.1, 1.46 min, B	**40u**	 MH⁺: 443.0, 1.94 min, B	**40v**	 MH⁺: 379.1, 1.55 min, B
40w	 MH⁺: 393.1, 1.77 min, D	**40x**	 MH⁺: 390.2, 1.53 min, B	**40y**	 MH⁺: 408.0, 1.85 min, B
40z	 MH⁺: 411.0, 1.69 min, B	**40aa**	 MH⁺: 408.1, 1.76 min, B	**40ab**	 MH⁺:382.2, 1.61 min, D
40ac	 MH⁺:382.2, 1.65 min, D	**40ad**	 MH⁺:396.1, 1.49 min, F	**40ae**	 MH⁺:426.2, 1.73 min, D

40af	 MH+:410.2, 1.71 min, D	**40ag**	 MH+:460.2, 1.82 min, D	**40ah**	 MH+:444.2, 1.78 min, D
40ai	 MH+:423.2, 1.76 min, D	**40aj**	 MH+:437.2, 1.85 min, D	**40ak**	 MH+:491.2, 1.91 min, D
40al	 MH+:451.3, 1.93 min, D	**40am**	 MH+:467.2, 1.79 min, D	**40an**	 MH+:543.1, 2.01 min, D
40ao	 MH+:395.2, 1.81 min, D	**40ap**	 MH+:465.2, 1.99 min, D	**40aq**	 MH+:426.0, 1.75 min, D
40ar	 MH+:459.0, 1.86 min, D	**40as**	 MH+:527.0, 2.01 min, D	**40at**	 MH+:473.0, 1.93 min, D
40au	 MH+:475.0, 1.93 min, D	**40av**	 MH+:473.0, 1.78 min, D	**40aw**	 MH+:431.2, 1.75 min, D
40ax	 MH+:413.0, 1.81 min, D	**40ay**	 MH+:429.0, 1.78 min, D	**40az**	 MH+:426.0, 1.78 min, D
40ba	 MH+:463.2, 1.91 min, D	**40bb**	 MH+:429.0, 1.87 min, D	**40bc**	 MH+:425.2, 1.84 min, D

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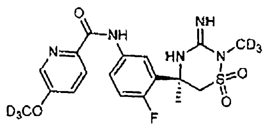
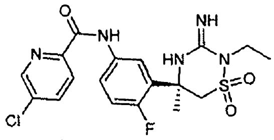
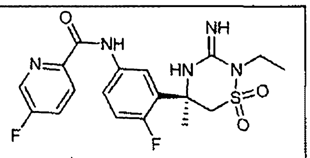
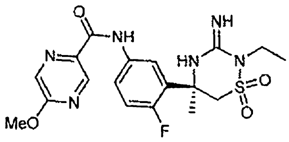
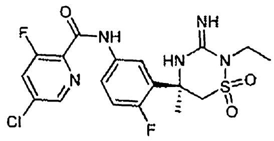
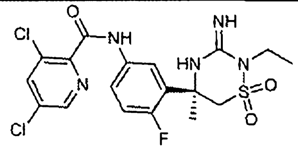
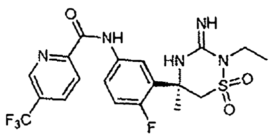
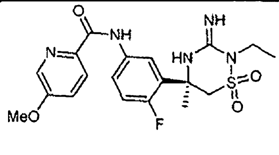
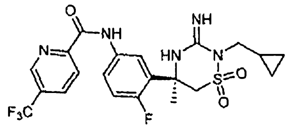
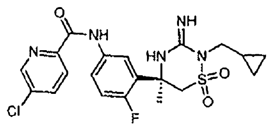
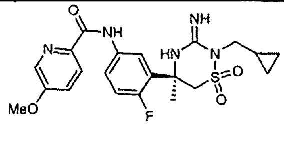
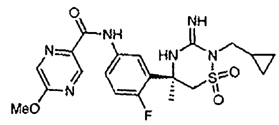
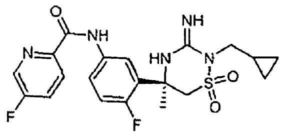
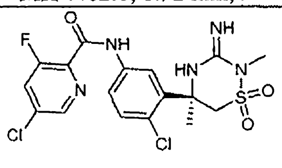
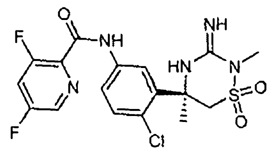
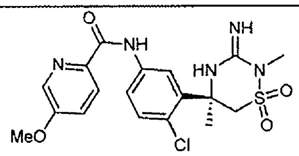
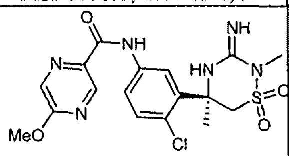
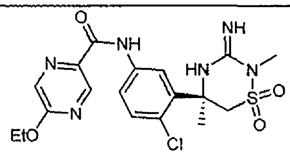
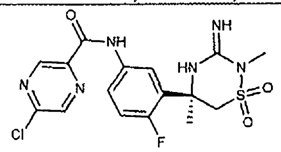
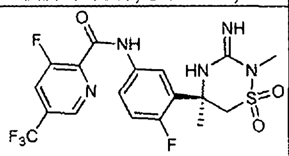
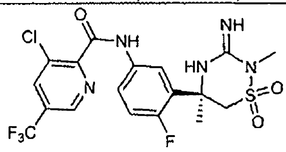
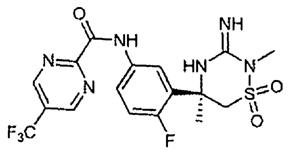
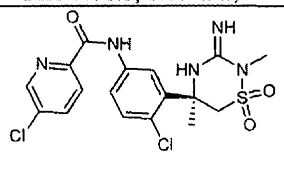
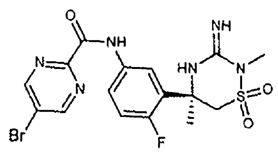
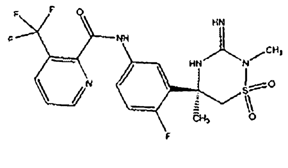
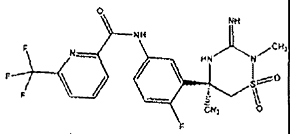
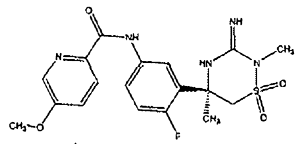
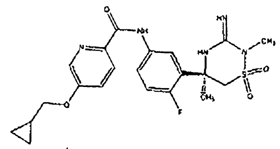
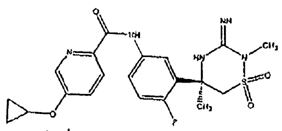
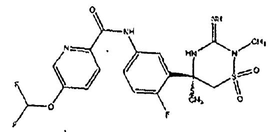
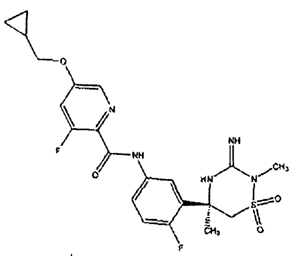
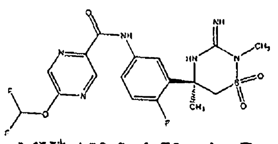
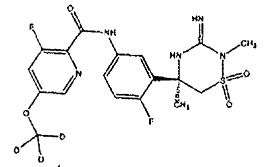
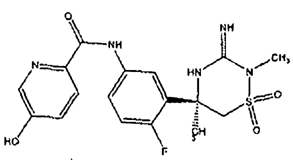
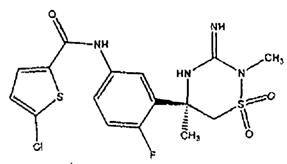
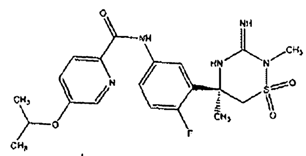
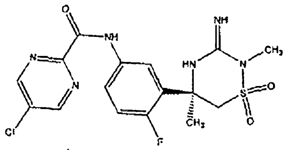
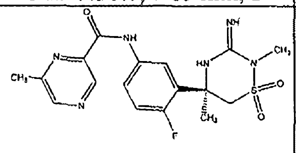
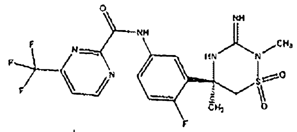
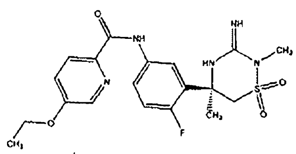
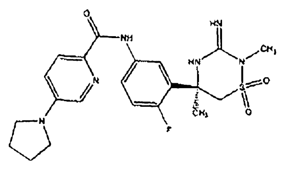
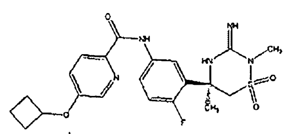
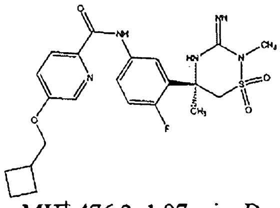
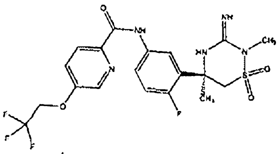
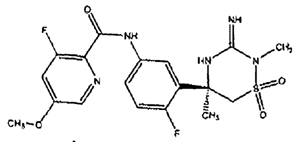
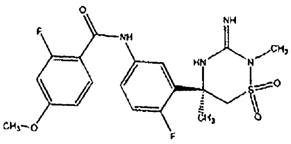
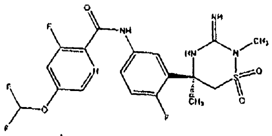
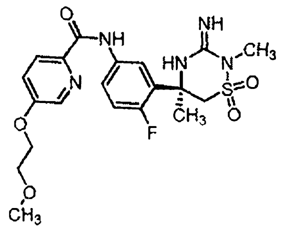
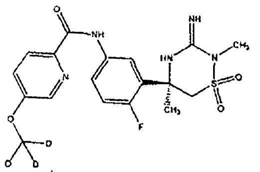
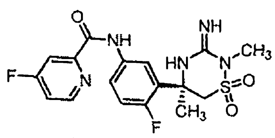
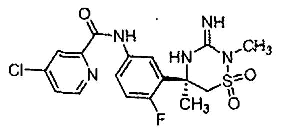
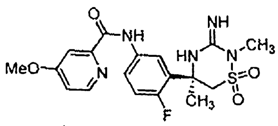
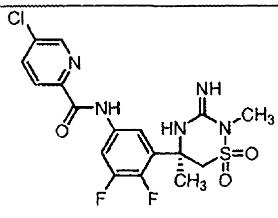
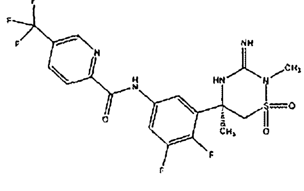
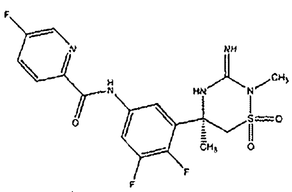
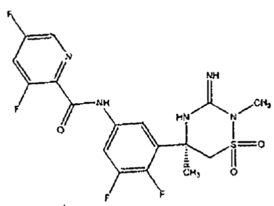
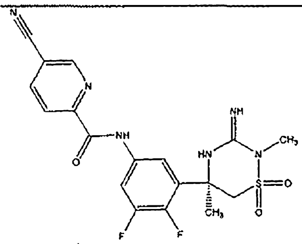
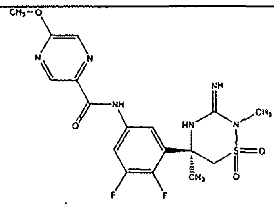
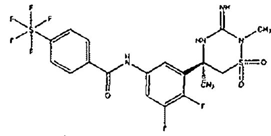
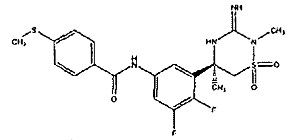
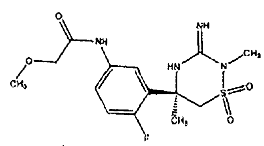
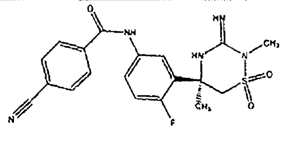
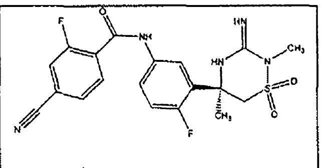
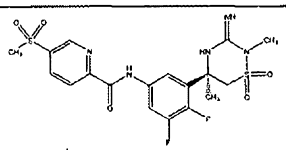
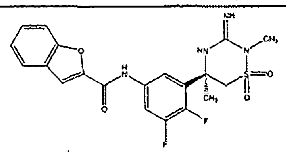
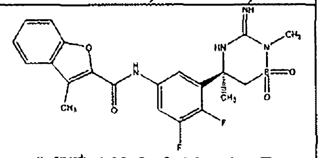
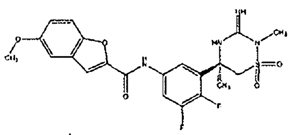
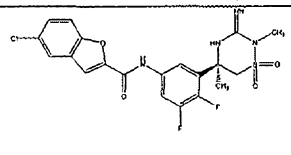
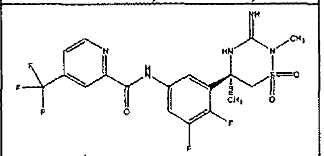
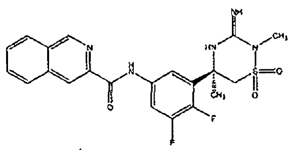
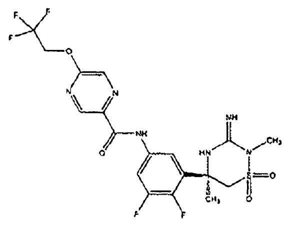
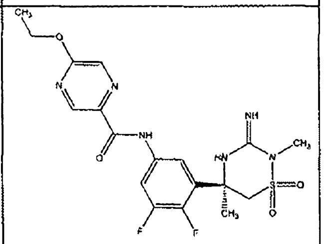
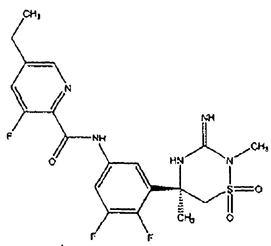
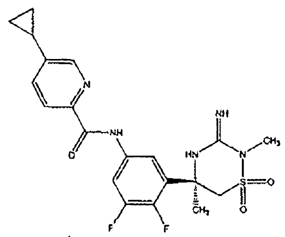
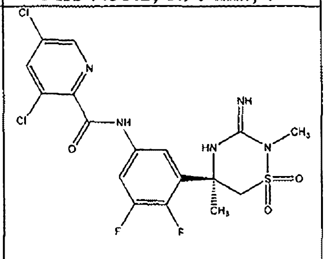
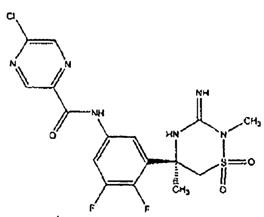
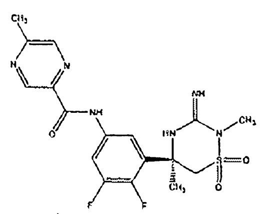
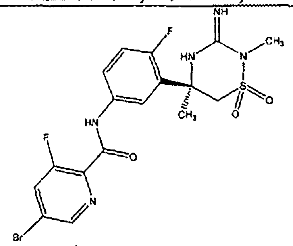
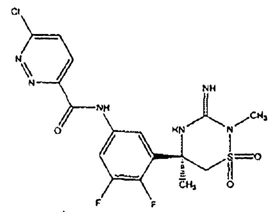
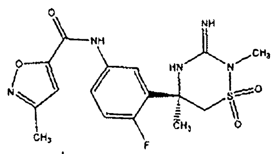
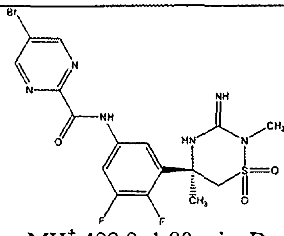
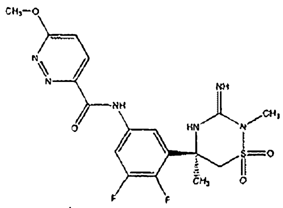
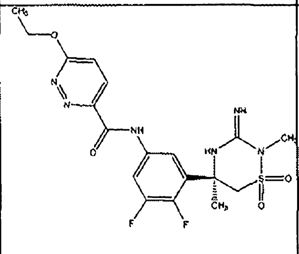
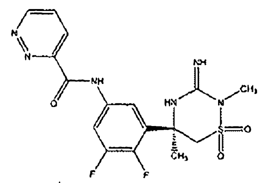
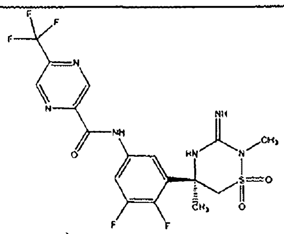
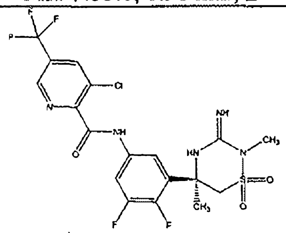
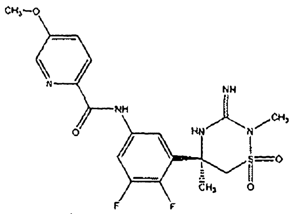
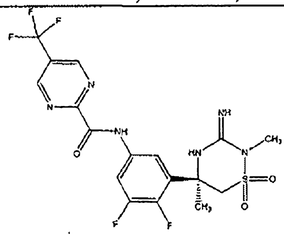
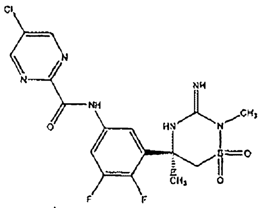
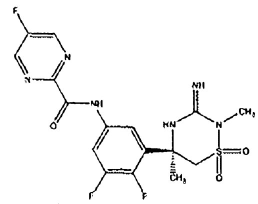
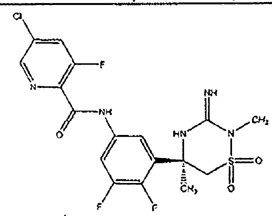
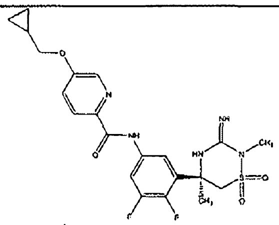
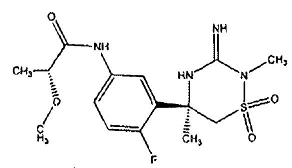
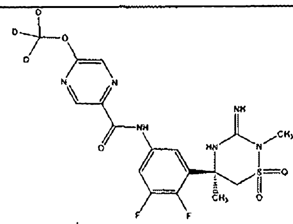
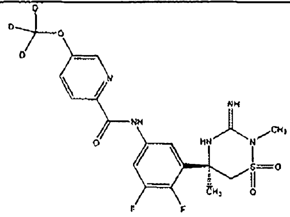
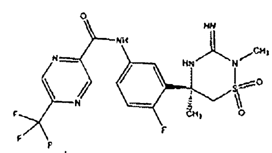
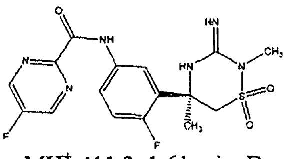
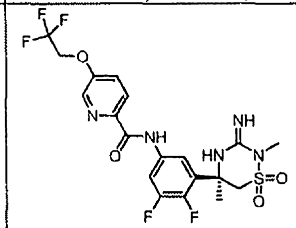
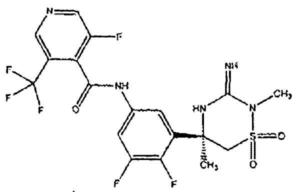
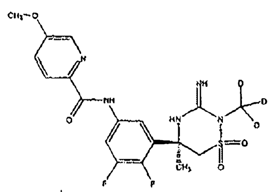
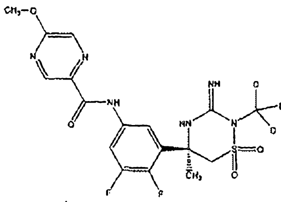
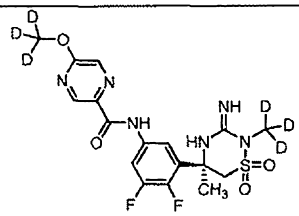
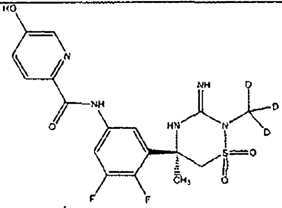
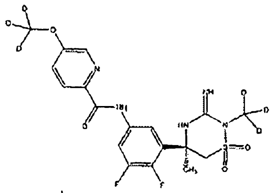
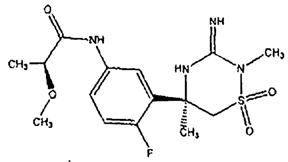
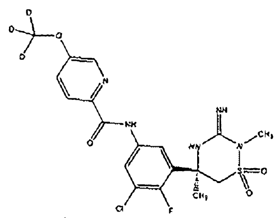
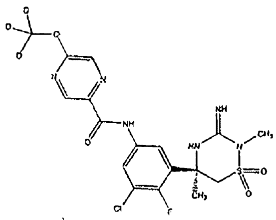
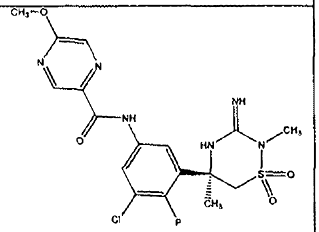
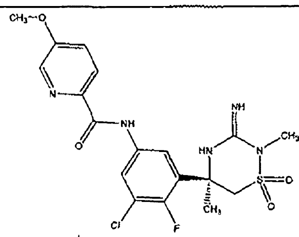
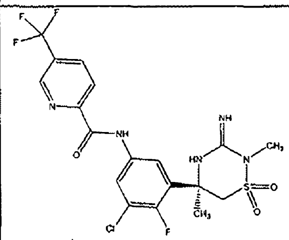
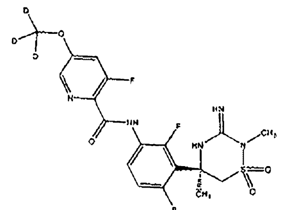
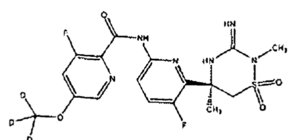
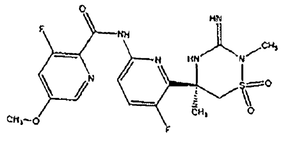
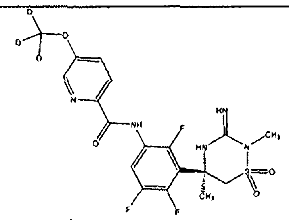
40bd	 MH^+:428.2, 1.78 min, D	**40be**	 MH^+:440.0, 1.88 min, D	**40bf**	 MH^+:424.0, 1.82 min, D
40bg	 MH^+:437.0, 1.82 min, D	**40bh**	 MH^+:458.0, 1.87 min, D	**40bi**	 MH^+:474.0, 1.87 min, D
40bj	 MH^+: 474.2, 1.95 min, D	**40bk**	 MH^+:436.0, 1.85 min, D	**40bl**	 MH^+:500.0, 1.98 min, D
40bm	 MH^+:466.0, 1.95 min, D	**40bn**	 MH^+:462.0, 1.92 min, D	**40bo**	 MH^+:463.0, 1.90 min, D
40bp	 MH^+:450.0, 1.91 min, D	**40bq**	 MH^+:460.0, 1.87 min, D	**40br**	 MH^+:444.0, 1.81 min, D
40bs	 MH^+:438.0, 1.86 min, D	**40bt**	 MH^+:439.0, 1.83 min, D	**40bu**	 MH^+:453.0, 1.92 min, D
40bv	 MH^+:427.0, 1.79 min, D	**40bw**	 MH^+:478.0, 1.87 min, D	**40bx**	 MH^+:494.2, 1.81 min, D
40by	 MH^+:461.2, 1.73 min, D	**40bz**	 MH^+:442.0, 1.86 min, D	**40ca**	 MH^+:473.0, 1.71 min, D

40cb	 MH+:460.2, 1.78 min, D	**40cc**	 MH+:460.2, 1.87 min, D	**40cd**	 MH+:422.2, 1.79 min, D
40ce	 MH+:484.2, 1.90 min, D	**40cf**	 MH+:448.0, 1.88 min, D	**40cg**	 MH+:458.0, 1.59 min, F
40ch	 MH+:480.0, 1.92 min, D	**40ci**	 MH+:459.2, 1.73 min, D	**40cj**	 MH+:443.0, 1.79 min, D
40ck	 MH+:408.2, 1.69 min, D	**40cl**	 MH+:431.0, 1.85 min, D	**40cm**	 MH+:450.2, 1.88 min, D
40cn	 MH+:427.0, 1.67 min, D	**40co**	 MH+:407.0, 1.72 min, D	**40cp**	 MH+:461.0, 1.75 min, D
40cq	 MH+:436.2, 1.84 min, D	**40cr**	 MH+:461.4, 1.83 min, D	**40cs**	 MH+:462.0, 1.92 min, D

40ct	 MH^{+}:476.2, 1.97 min, D	**40cu**	 MH^{+}:490.0, 1.92 min, D	**40cv**	 MH^{+}:440.0, 1.76 min, D
40cw	 MH^{+}:439.0, 1.79 min, D	**40cx**	 MH^{+}:476.0, 1.72 min, D	**40cy**	 MH^{+}:466.0, 1.82 min, D
40cz	 MH^{+}:425.0, 1.80 min, D	**40da**	 MH^{+}:410, 1.79 min, D	**40db**	 MH^{+}:426.0, 1.83 min, D
40dc	 MH^{+}:422.0, 1.71 min, D	**40dd**	 MH^{+}:444.0, 1.94 min, D	**40de**	 MH^{+}:478.0, 2.04 min, D
40df	 MH^{+}:428.0, 1.89 min, D	**40dg**	 MH^{+}:446.0, 1.85 min, D	**40dh**	 MH^{+}:435.0, 1.87 min, D
40di	 MH^{+}:441.0, 1.85 min, D	**40dj**	 MH^{+}:534.8, 2.04 min, D	**40dk**	 MH^{+}:455.0, 1.95 min, D

40dl	 MH+359.0, 1.58 min, D	**40dm**	 MH+:416.0, 1.75 min, D	**40dn**	 MH+:434.0, 1.75 min, D
40do	 MH+:488.0, 1.81 min, D	**40dp**	 MH+:449.0, 1.93 min, D	**40dq**	 MH+:463.0, 2.02 min, D
40dr	 MH+:479.0, 1.94 min, D	**40ds**	 MH+:483.0, 2.01 min, D	**40dt**	 MH+:478.0, 1.97 min, D
40du	 MH+:460, 1.96 min, D	**40dv**	 MH+:509.0, 2.11 min, D	**40dw**	 MH+:455.2, 1.90 min, D
40dx	 MH+:456.2, 1.92 min, D	**40dy**	 MH+:450.2, 1.95 min, D	**40dz**	 MH+:478.0, 1.92 min, D
40ea	 MH+:445.0, 1.87 min, D	**40eb**	 MH+:425.0, 1.81 min, D	**40ec**	 MH+:490.0 1.90 min, D

40ed	 MH+:445.0, 1.84 min, D	**40ee**	 MH+:396.2, 1.67 min, D	**40ef**	 MH+:488.8, 1.80 min, D
40eg	 MH+:441.0 1.84 min, D	**40eh**	 MH+:455.0, 1.91 min, D	**40ei**	 MH+:411.0, 1.76 min, D
40ej	 MH+:479.0, 1.95 min, D	**40ek**	 MH+:422.0, 1.71 min, D	**40el**	 MH+:440.0, 1.88 min, D
40em	 MH+:422.0, 1.71 min, D	**40en**	 MH+:445.0, 1.79 min, D	**40eo**	 MH+:429.0, 1.73 min, D
40ep	 MH+:462.0, 1.90 min, D	**40eq**	 MH+:480.0, 1.98 min, D	**40er**	 MH+:373.2, 1.64 min, D
40es	 MH+:444.2, 1.84 min, D	**40et**		**40eu**	 MH+:461.2, 1.83 min, D

			MH+:443.0, 1.88 min, D		
40ev	 MH+:411.2, 1.61 min, D	**40ew**	 MH+:508.0, 1.99 min, D	**40ex**	 MH+:496.0, 1.88 min, D
40ez	 MH+:443.0, 1.85 min, D	**40fa**	 MH+:444.0, 1.84 min, D	**40fb**	 MH+:447.0, 1.83 min, D
40fc	 MH+:429.0, 1.75 min, D	**40fd**	 MH+:446.0, 1.84 min, D	**40fe**	 MH+:373.4, 1.66 min, D
40ff	 MH+:459.3, 1.78 min, A	**40fg**	 MH+:460.3, 2.72 min, A	**40fh**	 MH+:457.3, 2.71 min, A
40fi	 MH+:456.3, 2.76 min, A	**40fj**	 MH+:494.3, 3.08 min, A	**40fk**	 MH+:461.3, 2.83 min, A
40fl	 MH+:444.2, 2.87 min, A	**40fm**	 MH+:441.2, 2.80 min, A	**40fn**	 MH+:461.3, 2.88 min, A

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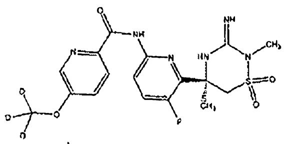
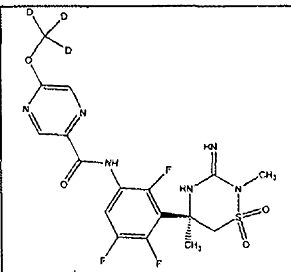
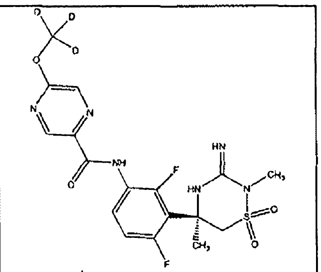
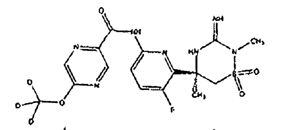
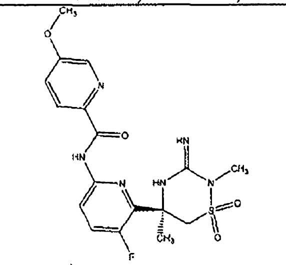
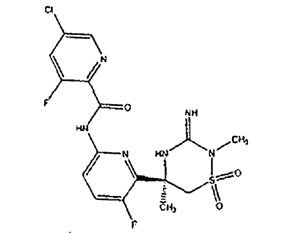
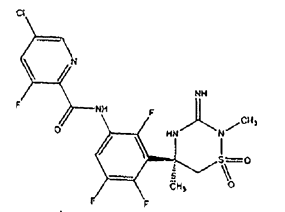
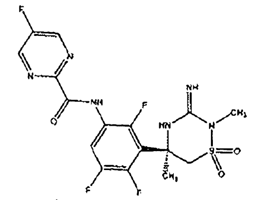
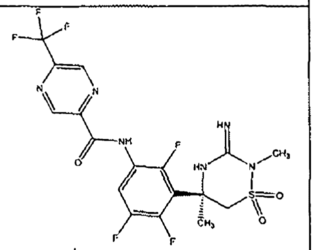
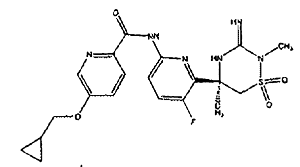
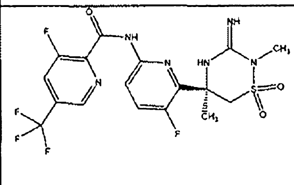
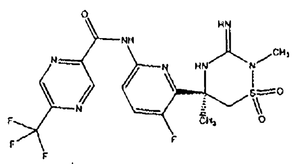
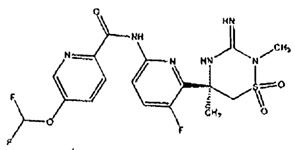
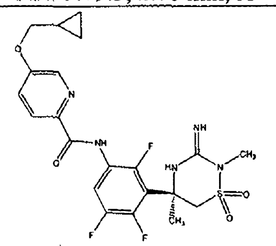
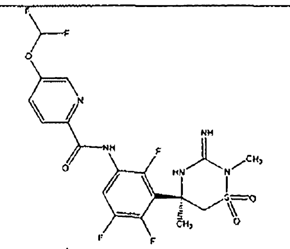
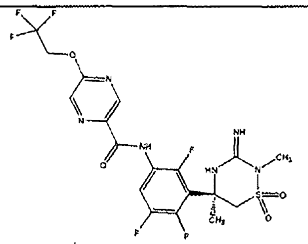
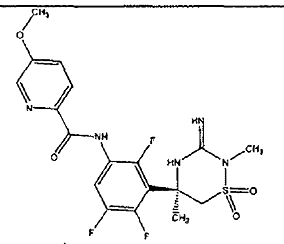
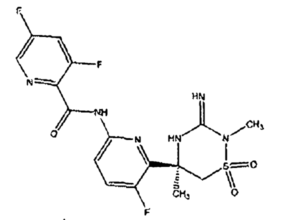
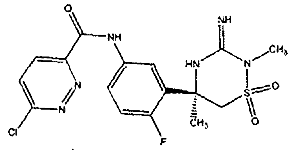
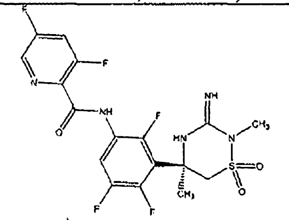
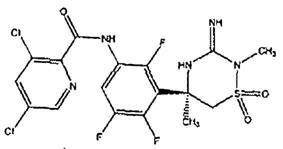
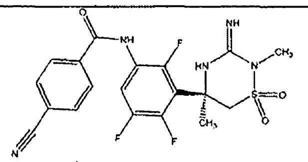
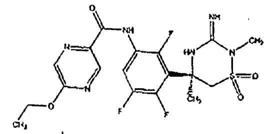
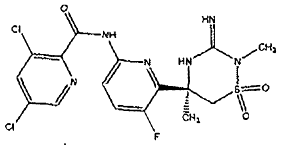
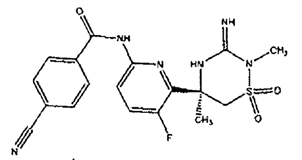
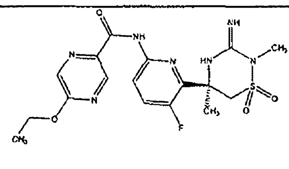
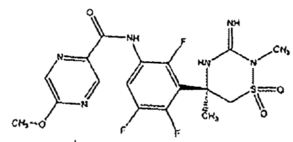
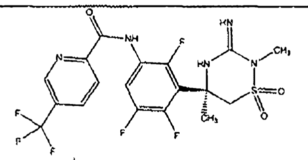
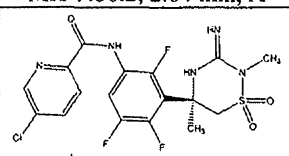
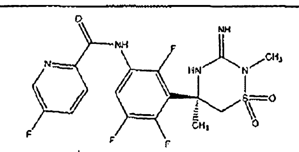
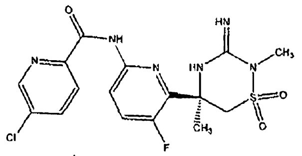
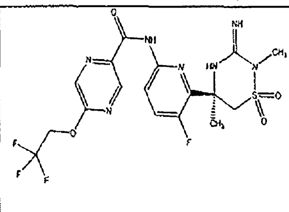
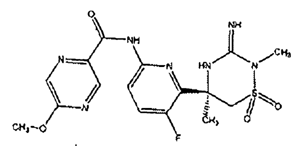
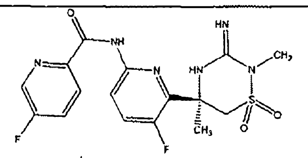
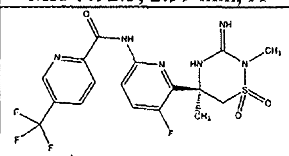
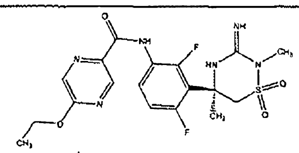
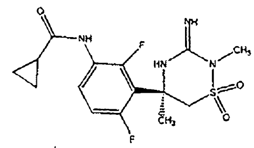
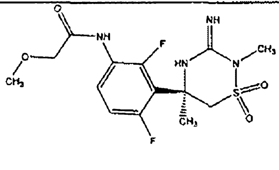
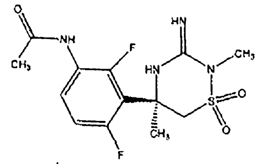
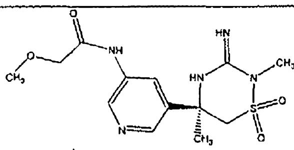
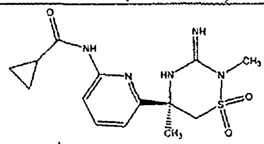
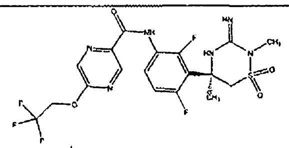
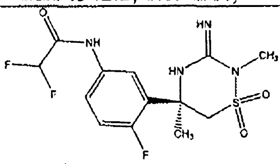
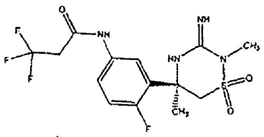
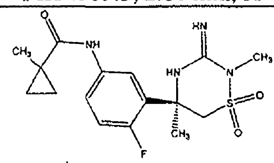
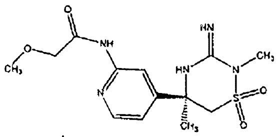
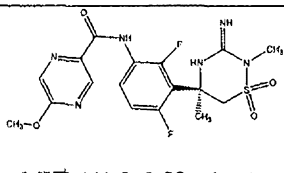
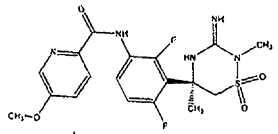
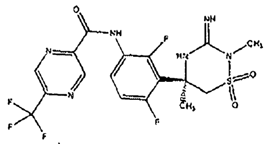
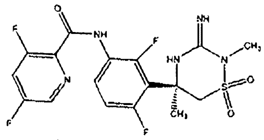
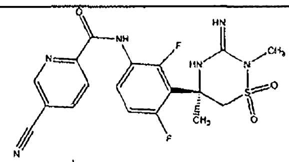
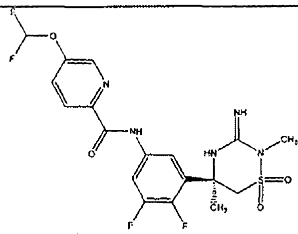
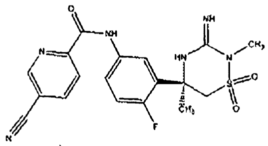
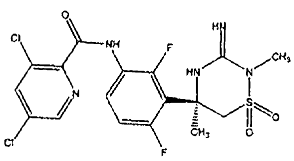
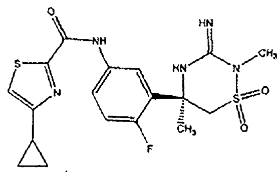
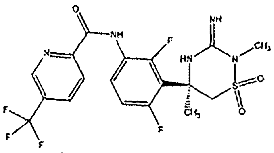
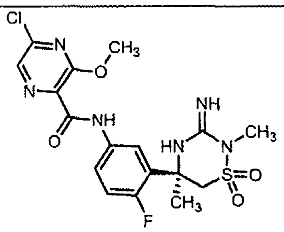
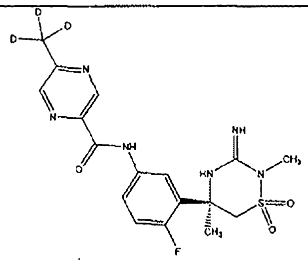
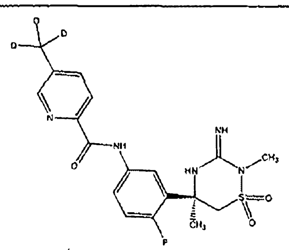
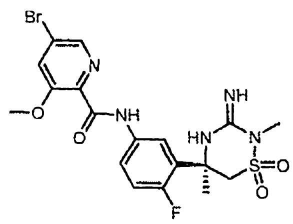
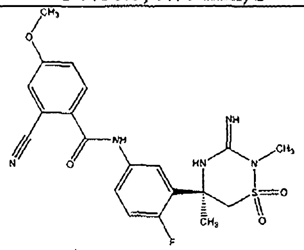
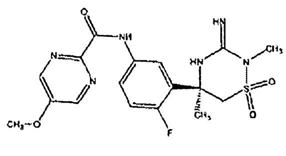
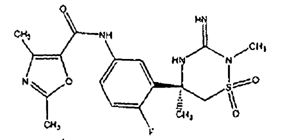
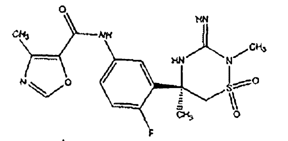
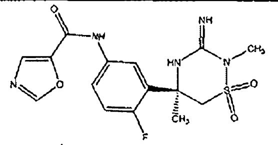
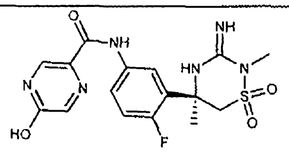
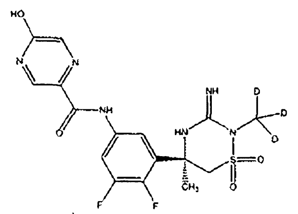
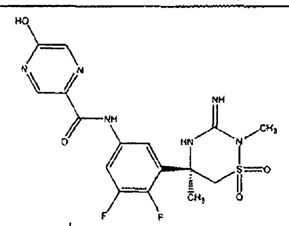
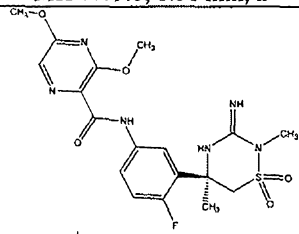
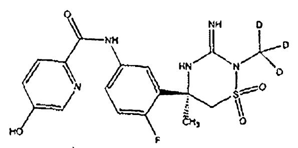
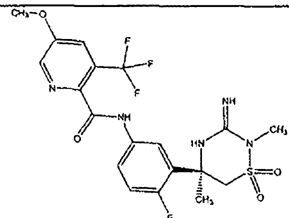
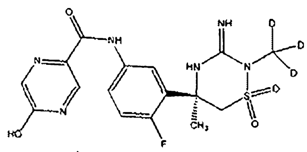
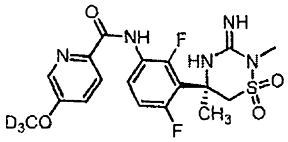
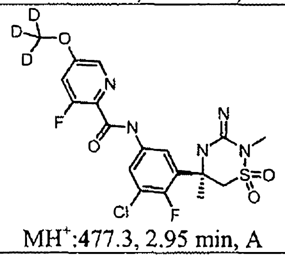
40fo		MH$^+$:426.2, 2.68 min, A
40fp		MH$^+$:462.3, 3.09 min, A
40fq		MH$^+$:444.2, 2.82 min, A
40fr		MH$^+$:427.2, 2.85 min, A
40fs		MH$^+$:423.2, 2.46 min, A
40ft		MH$^+$:445.2, 3.04 min, A
40fu		MH$^+$:480.3, 2.68 min, A
40fv		MH$^+$:447.2, 2.04 min, A
40fw		MH$^+$:497.3, 2.84 min, A
40fx		MH$^+$:464.3, 2.90 min, A
40fy		MH$^+$:479.3, 2.70 min, A
40fz		MH$^+$:462.3, 2.68 min, A
40ga		MH$^+$:459.3, 2.67 min, A
40gb		MH$^+$:498.3, 3.83 min, A
40gc		MH$^+$:494.3, 3.46 min, A

40gd	 MH^+:527.3, 3.75 min, A	**40ge**	 MH^+:458.3, 3.23 min, A	**40gf**	 MH^+:429.2, 2.51 min, A
40gg	 MH^+:427.3, 1.71 min, D	**40gh**	 MH^+:464.3, .2.68 min, A	**40gi**	 MH^+:496.3, 3.04 min, A
40gj	 MH^+:452.2, 2.99 min, A	**40gk**	 MH^+:473.3, 3.42 min, A	**40gl**	 MH^+:461.3, 3.21 min, A
40gm	 MH^+:417.2, 2.48 min, A	**40gn**	 MH^+:438.2, 2.64 min, A	**40go**	 MH^+:459.3, 2.58 min, A
40gp	 MH^+: 496.3, 2.96 min, A	**40gq**	 MH^+:462.3, 2.79 min, A	**40gr**	 MH^+:446.2, 2.60 min, A
40gs	 MH^+:427.2, 2.74 min, A	**40gt**	 MH^+:492.3, 2.99 min, A	**40gu**	 MH^+:424.2, 2.92 min, A
40gv	 MH^+:411.2 2.89 min, A	**40gw**	 MH^+:461.3, 3.40 min, A	**40gx**	 MH^+:455.3, 2.61 min, A

40gy		**40gz**		**40ha**	
	MH$^+$:373.2, 2.24 min, A		MH$^+$:377.2, 1.96 min, A		MH$^+$:347.2, 1.76 min, A
40hb		**40hc**		**40hd**	
	MH$^+$:342.2, 1.19 min, A		MH$^+$:338.2, 2.02 min, A		MH$^+$:509.3, 2.86 min, A
40he		**40hf**		**40hg**	
	MH$^+$:365.0, 1.62 min, D		MH$^+$:397.0, 1.71 min, D		MH$^+$:369.0, 1.71 min, D
40hh		**40hi**		**40hj**	
	MH$^+$:342.2, 1.62 min, A		MH$^+$:441.2, 2.88 min, A		MH$^+$:440, 2.07 min, D
40hk		**40hl**		**40hm**	
	MH$^+$:478.3, 2.72 min, A		MH$^+$:446.2, 2.33 min, A		MH$^+$:435.2, 2.39 min, A
40hn		**40ho**		**40hp**	
	MH$^+$:476.0, 1.92 min, D		MH$^+$:417.2, 1.73 min, D		MH$^+$:478.3, 2.68 min, A
40hq		**40hr**		**40hs**	
	MH$^+$:438.0, 1.89 min, D		MH$^+$:478.3, 1.99 min, A		MH$^+$:457.0, 1.79 min, D

40ht	 MH+:410.0, 1.71 min, D	40hu	 MH+:409.2, 1.79 min, D	40hv	 MH+:500.0, 1.81 min, D
40hw	 MH+:446.0, 1.79 min, D	40hx	 MH+:423.0, 1.68 min, D	40hy	 MH+:410.2, 1.69 min, D
40hz	 MH+:396.2, 1.65 min, D	40ia	 MH+:382.2, 1.58 min, D	40ib[a]	 MH+:409.0, 1.58 min, D
40ic[a]	 MH+:430.0, 1.66 min, D	40id[a]	 MH+:427.0, 1.68 min, D	40ie	 MH+:453.2, 1.60 min, D
40if	 MH+:411.0, 1.83 min, D	40ig	 MH+:490.0, 1.96 min, D	40ih[a]	 MH+:412.0, 1.72 min, D
40ii	 MH+:443.2, 2.57 min, A	40ij	 MH+:477.3, 2.95 min, A		

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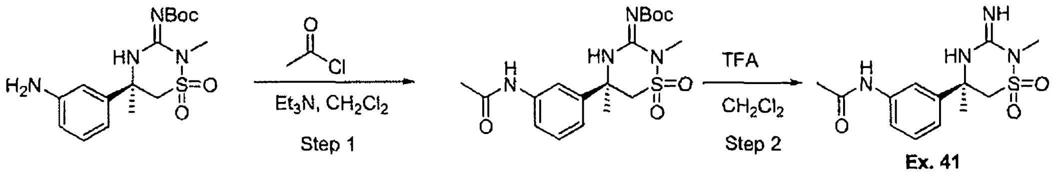
[a] The hydroxypyrazine amides were formed using the cyclopropylmethylether pyrazine acid (Entry 5, Table IVb) instead of 1,3-oxazole-4-carboxylic acid in step 1 of Scheme 11b.

Scheme 12:

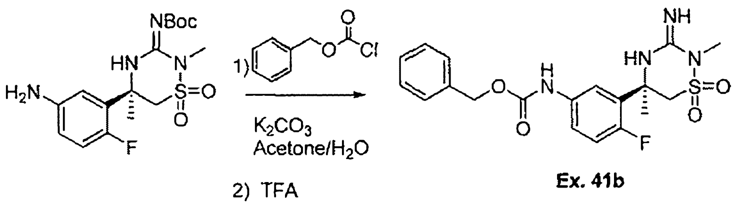


Ex. 41

Step 1: To a solution of the aniline from Table IV entry 1 (80 mg) and Et_3N (50 μL) in CH_2Cl_2 (2 mL) was added acetyl chloride (1.2 eq.). The resulting solution was stirred at RT for 2 hours. Water was added and the aqueous layer was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via flash chromatography (SiO_2: 0 to 60% EtoAc in hex).

Step 2: Example 41 was prepared as the TFA salt from the product of step 1 using a method similar to that described in Scheme 11b step 2. LCMS data: (method D): t_R = 0.91 min, *m/e* = 311 (M+H).

Scheme 12b:



Ex. 41b

To a mixture of the aniline from Scheme 10 (50 mg, 0.13 mmol) and potassium carbonate (18 mg, 0.13 mmol) in 1:1 acetone:water (4 mL) was added benzyl chloroformate (0.028 mL, 0.19 mmol). The mixture was stirred at RT for 30 min. Water was added and the mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 70:30 hexanes:EtOAc) to afford the carbamate.

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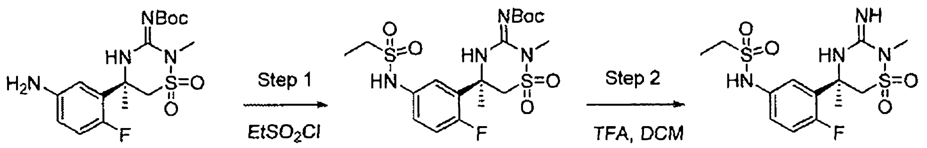
Example 41b was prepared as its TFA salt from the above carbamate using a method similar to that described in Scheme 11b step 2. LCMS data: (method D): t_R = 1.88 min, *m/e* = 421.0 (M+H).

Scheme 12c:



Ex. 41c

Step 1: To a mixture of the aniline (200 mg, 0.517 mmol, Scheme 10) and DIEA (0.36 mL, 2.07 mmol) in CH_2Cl_2 (2 mL) at RT was added dropwise ethylsulfonyl chloride (0.074 mL, 0.775 mmol). After 18 h, the reaction was quenched with 1 M HCl and the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure.

Step 2: Example 41c was prepared from the above material using a method similar to that described in Scheme 11b step 2. After deprotection, the resulting residue was purified by reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:TFA) to provide **Example 41c** as its TFA salt. LCMS (conditions D): t_R = 1.64 min, *m/e* = 379.0 (M+H).

Table Va: The following examples were prepared using a method similar to that described in Scheme 12c.

Examples (LCMS data listed with each compound: observed MH^+, HPLC retention time and LCMS method)

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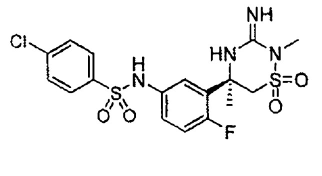
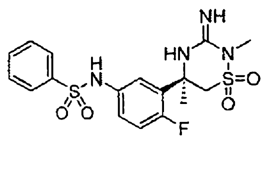
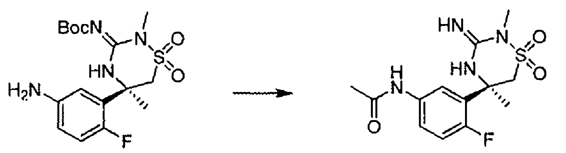
41d	MH$^+$:460.8, 1.86 min, D	**41e**	MH$^+$:427.0, 1.78 min, D





Scheme 12d:

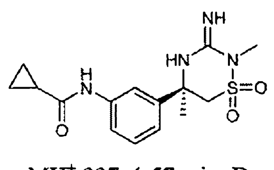


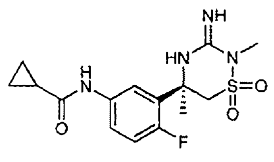
Example 41f

To the aniline (Scheme 10, 70 mg, 0.18 mmol) in 2 mL DCM was added acetic anhydride (19 μL, 0.2 mmol) and triethylamine (29 μL, 0.2 mmol). The reaction was stirred for 3 hours at room temperature, then poured into water. The mixture was extracted with DCM. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-50% EtOAc/hexanes over 30 minutes) to provide a methyl amide product. This material was stirred in 2 mL 20% TFA/DCM for 1 hr and then concentrated *in vacuo* to provide **Example 41f** as a trifluoroacetate salt (0.041g, 69%). LCMS data: (method A): t_R = 2.96 min, *m/e* = 379.2 (M+H).

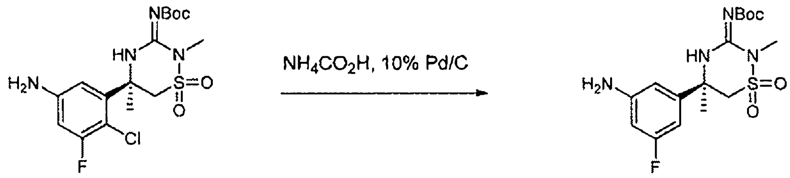
Table VI: The following examples were prepared using a method similar to that described in Scheme 12 using the appropriate acid chlorides and aryl amines.

Examples (LCMS data listed with each compound: observed MH$^+$, HPLC retention time and LCMS method)			
42	MH$^+$:337, 1.57 min, D	**42a**	MH$^+$:335.0, 1.66 min, D



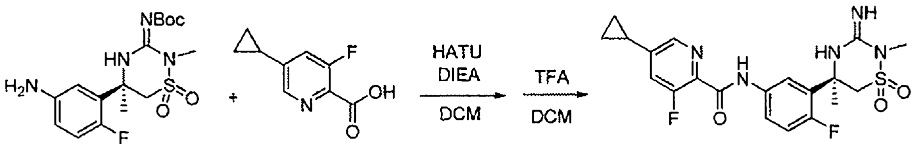


Scheme 12e:



A mixture of 2-chloro-3-fluoro aniline (252 mg, 0.60 mmol), ammonium formate (5.0 g, 79 mmol) in 25 mL of isopropanol was heated at 70 °C overnight. After filtration and concentration, the residue was purified by silica gel chromatography (elution with 0-30% EtOAc/Hex) to afford the 3-fluoro aniline product (150 mg).

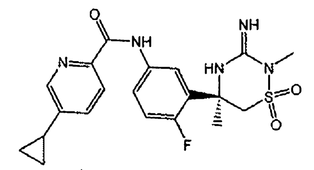
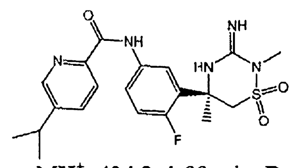
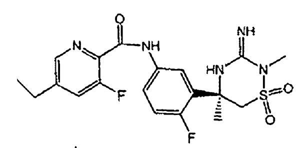
Scheme 12f:



Example 42b

A mixture of aniline (96 mg, 0.25 mmol, Scheme 10), the acid (Scheme 11x, 81 mg, 0.45 mmol), HATU (230 mg, 0.60 mmol), and DIEA (0.36 mL, 2.0 mmol) in 5 mL of DCM was stirred at room temperature overnight. The reaction mixture was diluted with DCM, washed with 5% citric acid, sat. $NaHCO_3$, and brine. After drying ($MgSO_4$) and concentration, the residue was subjected to silica gel chromatograpy (elution with 0-25% EtOAc/Hex). The resulting product was dissolved in 6 mL of 25% of TFA/DCM and stirred at room temperature for 1 h. Concentration and drying *in vacuo* provided **Example 42b** (143 mg) as a TFA salt. LCMS (conditions D): t_R = 1.91 min, *m/e* = 450.2 (M+H).

Table VIb: The following examples were prepared from the corresponding aniline and carboxylic acid using a procedure similar to that described in Scheme 12f.

Examples (LCMS data listed with each compound: observed MH^+, HPLC retention time and LCMS method)					
42c	 MH^+: 432.2, 1.95 min, D	**42d**	 MH^+: 434.2, 1.99 min, D	**42e**	 MH^+: 438.2, 1.91 min, D

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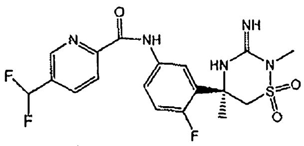
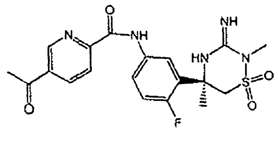
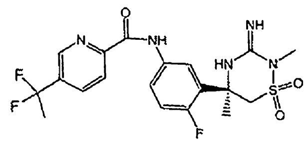
<td>42f</td>
<td>
MH$^+$: 442.2, 0.81 min, E</td>
<td>42g</td>
<td>
MH$^+$: 434.2, 0.76 min, E</td>
<td>42h</td>
<td>
MH$^+$: 432.2, 1.95 min, D</td>
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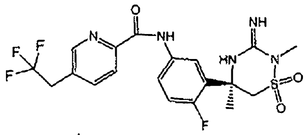
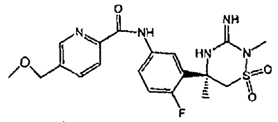
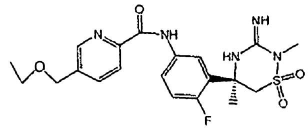
<td>42i</td>
<td>
MH$^+$: 474.0, 0.84 min, E</td>
<td>42j</td>
<td>
MH$^+$: 436.0, 0.77 min, E</td>
<td>42k</td>
<td>
MH$^+$: 450.0, 0.84 min, E</td>
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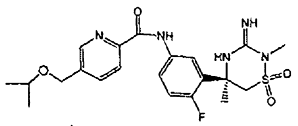
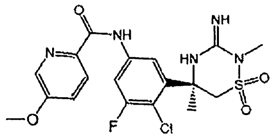
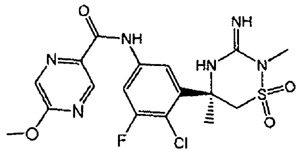
<td>
MH$^+$: 464.0, 0.88 min, E</td>
<td>42m</td>
<td>
MH$^+$: 456.0, 1.87 min, D</td>
<td>42n</td>
<td>
MH$^+$: 457.0, 0.84 min, E</td>
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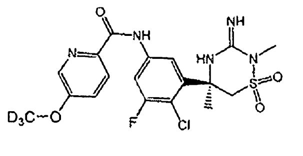
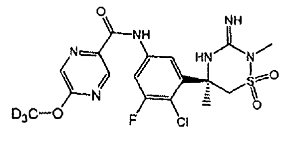
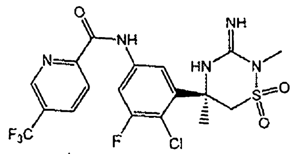
<td>
MH$^+$: 459.0, 0.84 min, E</td>
<td>42p</td>
<td>
MH$^+$: 460.0, 0.84 min, E</td>
<td>42q</td>
<td>
MH$^+$: 493.9, 0.88 min, E</td>
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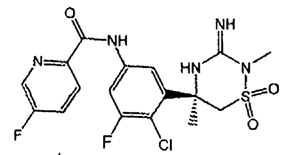
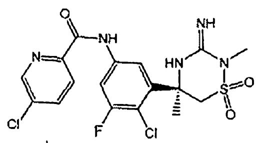
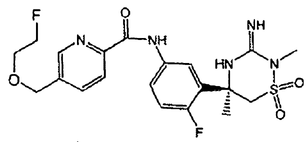
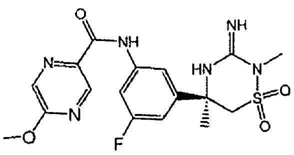
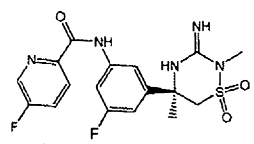
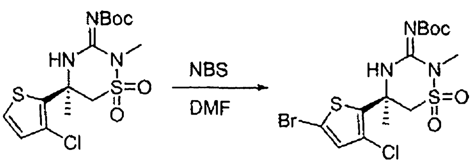
<td>42r</td>
<td>
MH$^+$: 444.0, 0.82 min, E</td>
<td>42s</td>
<td>
MH$^+$: 459.9, 0.88 min, E</td>
<td>42t</td>
<td>
MH$^+$: 468.0, 0.79 min, E</td>
</tr>
<tr>
<td>42u</td>
<td>
MH$^+$: 432.0, 0.78 min, E</td>
<td>42v</td>
<td>
MH$^+$: 410.0, 0.79 min, E</td>
<td></td>
<td></td>
</tr>
</table>

Scheme 13:



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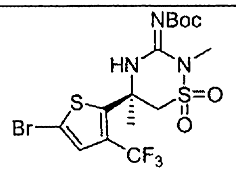
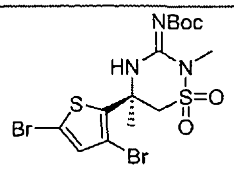
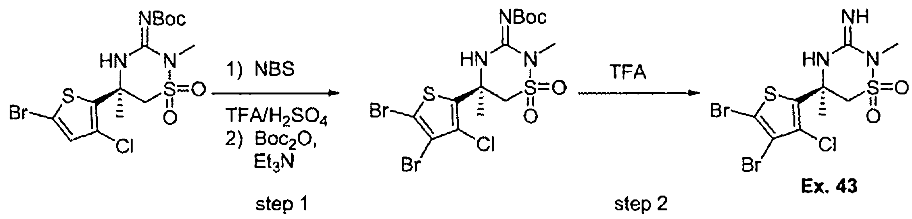
To a solution of the thiophene from Table IIb Entry 3 (2.2 g, 5.6 mmol) in DMF in an aluminum foil wrapped round bottom flask under an atmosphere of N_2 was added NBS (2.7 g, 15 mmol). The resultant solution was heated to 50°C with stirring for 8 hours. The solution was cooled to RT. To the solution was added an aqueous solution of $NaHCO_3$ and $Na_2S_2O_5$. The aqueous layer was extracted with EtOAc. The organic layer was washed with sat $NaHCO_{3\ (aq.)}$ (2x). The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 83:17 hexanes:EtOAc) to afford the bromothiophene (1.7 g, 63% yield).

Table VII: The following compounds were prepared using a procedure similar to that described in Scheme 13 using the appropriate starting material.

Entry	2-bromothiophene	Entry	2-bromothiophene
1		2	

Scheme 14:

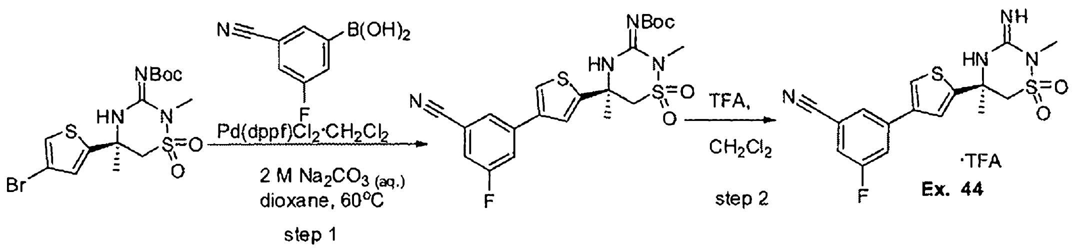


Step 1: To a solution of the thiophene from Scheme 13 (100 mg, 0.21 mmol) in TFA (ca. 2 mL) was added NBS (94 mg, 0.53 mmol) and H_2SO_4 (4 drops). The solution was allowed to stir at RT for 30 min. After that time, additional NBS (80 mg) was added and the solution was stirred for an additional 30 min. The mixture was then quenched with sat. $NaHCO_{3\ (aq.)}$ and $Na_2S_2O_{5\ (s)}$. The aqueous layer was extracted with EtOAc. The organic layer was washed with sat. $NaHCO_{3\ (aq.)}$ (2x), dried over Na_2SO_4, filtered and concentrated. The crude product was slurried in CH_2Cl_2. To this mixture was added di-*tert*-butyldicarbonate (96 mg, 0.21 mmol) and Et_3N (25 mg, 0.23 mmol). The resultant mixture was stirred at RT overnight. The

solution was then concentrated and the crude residue was purified via prep TLC (SiO_2: 3:1 hexanes:EtOAc) to afford the dibromothiophene (49 mg).

Step 2: **Example 43** was prepared using a method similar to that described in Scheme 11b Step 2. LCMS (conditions A): t_R = 3.07 min, *m/e* = 452.2 (M+H).

Scheme 15:

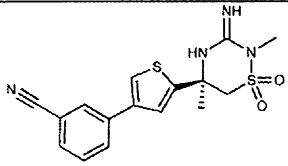
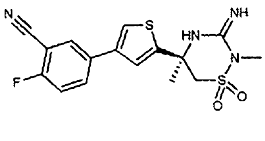
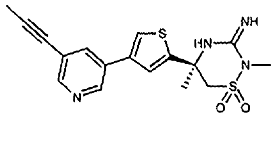
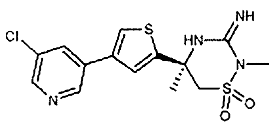
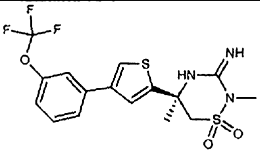
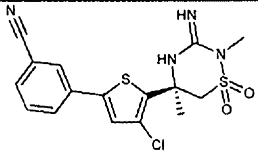
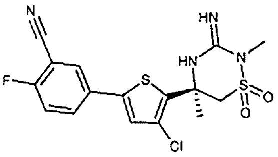
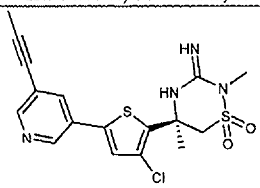
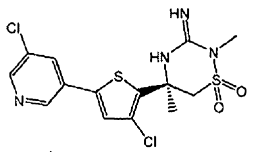
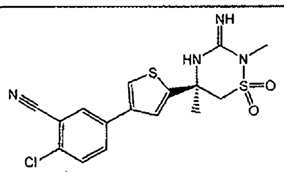
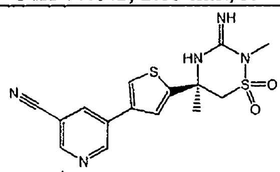
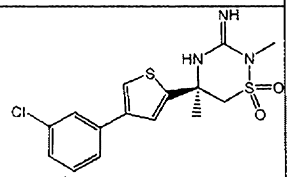
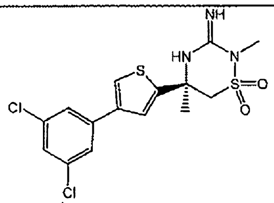
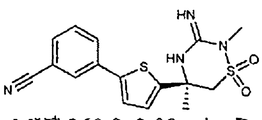
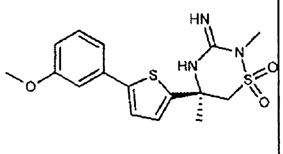
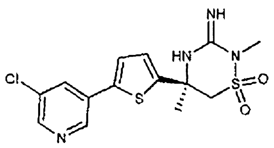
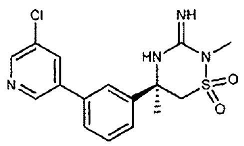
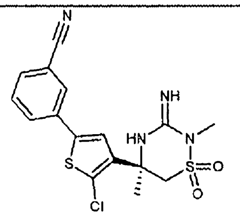
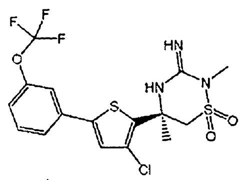
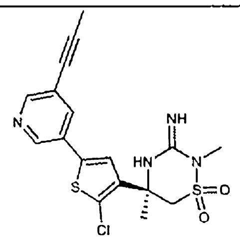
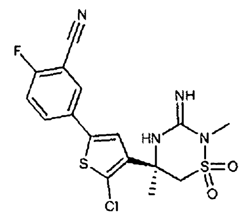


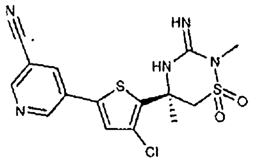
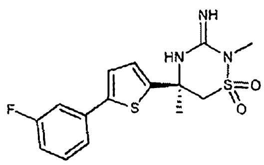
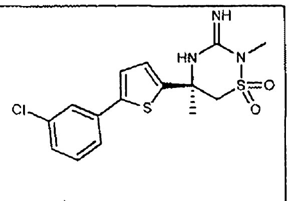
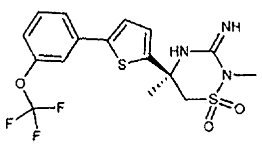
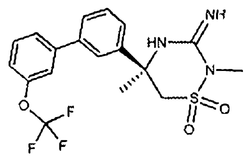
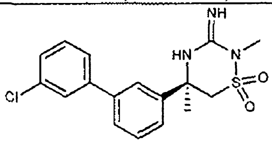
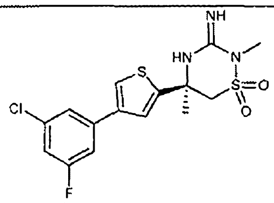
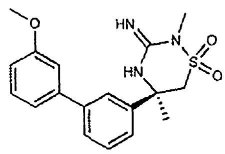
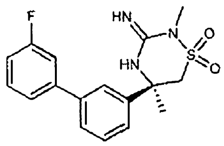
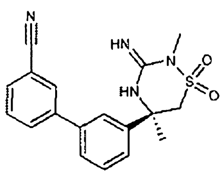
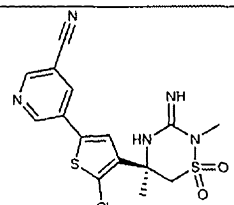
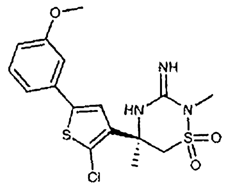
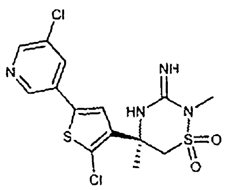
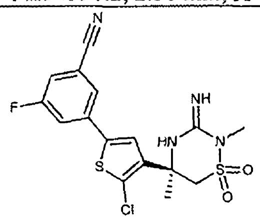
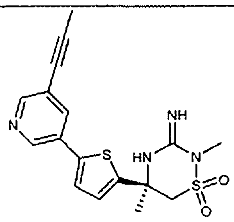
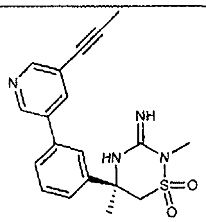
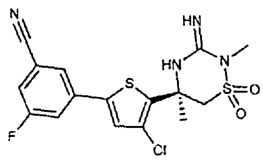
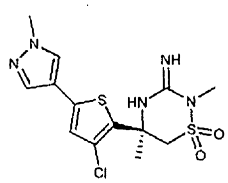
Step 1: To a microwave vial containing the thiophene bromide (Scheme 3) (149 mg, 0.34 mmol) was added 3-cyano-5-fluorophenyl boronic acid (146 mg, 0.88 mmol), 2 M Na_2CO_3 (aq.) (0.31 mL) and dioxane (2.5 mL). The mixture was degassed by bubbling N_2 through it for 5 min. To this mixture was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (60mg, 0.074 mmol). The vial was capped and the atmosphere was purged with nitrogen. The mixture was heated to 60°C with stirring for 2 hours. The mixture was cooled to RT and diluted with EtOAc. The mixture was then filtered through Celite. The organic layer was washed with brine. The aqueous layer was back extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via preperative TLC (SiO_2: 3:1 hexanes:EtOAc) to afford the biaryl compound (105 mg).

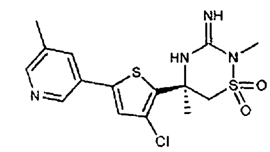
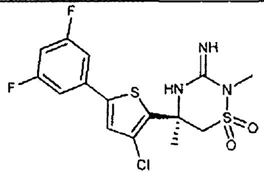
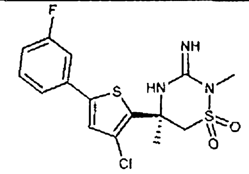
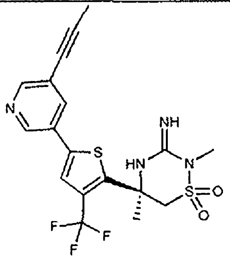
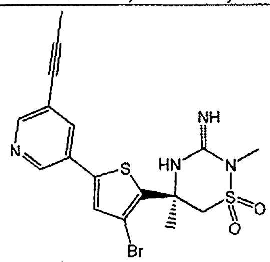
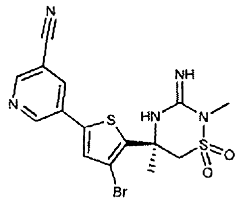
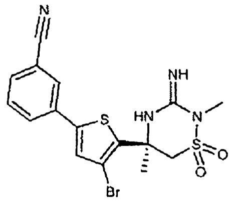
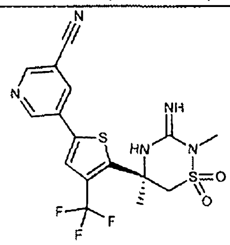
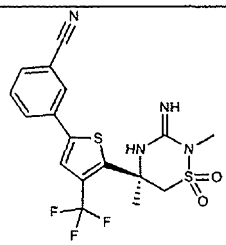
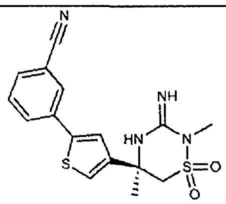
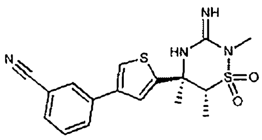
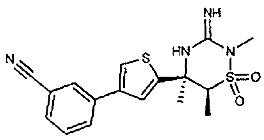
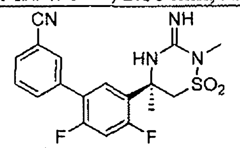
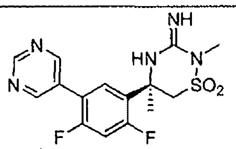
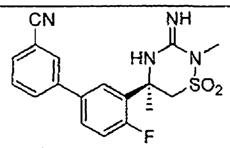
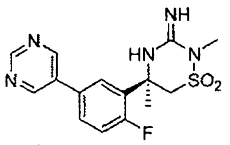
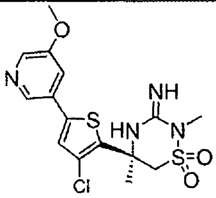
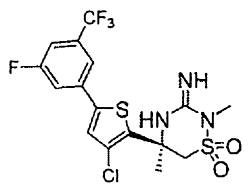
Step 2: To a solution of the biaryl compound from step 1 in CH_2Cl_2 (1.0 mL) was added TFA (1.0 mL). The resultant solution was stirred at RT for 1.5 hours. The solvent was removed *in vacuo* to afford **Example 44** as the trifluoroacetate salt. LCMS data: (method A): t_R = 2.96 min, *m/e* = 379.2 (M+H).

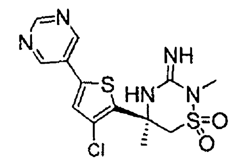
Table VIII: The following examples were prepared using a procedure similar to that described in Scheme 15 using the appropriate aryl bromide and boronic acid/ester.

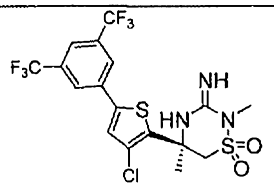
Examples (LCMS data listed with each compound: observed MH^+, HPLC retention time and LCMS method)

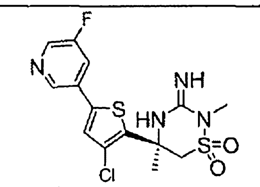
45	 MH+:361.2, 2.66 min, A	**46**	 MH+:379.2, 3.43 min, A	**47**	 MH+:375.2, 2.90 min, A
48	 MH+:371.2, 3.11 min, A	**49**	 MH+:420.2, 3.33 min, A	**50**	 MH+:395.2, 2.99 min, A
51	 MH+:413.2, 3.11 min, A	**52**	 MH+:409.2, 2.83 min, A	**53**	 MH+:405.2, 2.80 min, A
54	 MH+:395.2, 3.00 min, A	**55**	 MH+:362.2, 2.37 min, A	**56**	 MH+:370.2, 3.15 min, A
57	 MH+:404.2, 3.27 min, A	**58**	 MH+:360.8, 2.09 min, B	**59**	 MH+:365.9, 2.19 min, B
60	 MH+:370.9, 1.95 min, B	**61**	 MH+:364.9, 1.98 min, B	**62**	 MH+:361.2, 2.66 min, A
63	 MH+:454.2, 3.36 min, A	**64**	 MH+:409.2, 2.87 min, A	**65**	 MH+:413.2, 3.16 min, A

66	 MH+:396.2, 2.49 min, A	**67**	 MH+:353.9, 2.20 min, B	**68**	 MH+:369.9, 2.27 min, B
69	 MH+:419.9, 2.36 min, B	**70**	 MH+:413.9, 2.42 min, B	**71**	 MH+:363.9, 2.28 min, B
72	 MH+:386.2, 3.09 min, A	**73**	 MH+:359.2, 2.17 min, B	**74**	 MH+:348.0, 2.38 min, B
75	 MH+:355.0, 2.30 min, B	**76**	 MH+:396.2, 2.56 min, A	**77**	 MH+:400.2, 3.10 min, A
78	 MH+:406.2, 2.88 min, A	**79**	 MH+:413.2, 3.17 min, A	**80**	 MH+:375.0, 1.94 min, B
81	 MH+:369.0, 1.95 min, B	**82**	 MH+:413.2, 2.96 min, A	**83**	 MH+:374.2, 2.59 min, A

84	 MH+:385.2, 1.92 min, A	**85**	 MH+:406.2, 3.22 min, A	**86**	 MH+:388.2, 3.15 min, A
87	 MH+:442.9, 2.06 min, B	**88**	 MH+:455.3, 2.99 min, A	**89**	 MH+:440.2, 2.77 min, A
90	 MH+:441.2, 3.10 min, A	**91**	 MH+:361.2, 2.66 min, B	**92**	 MH+:428.9, 2.34 min, B
93	 MH+:361.2, 2.80 min, A	**94**	 MH+:375.2, 2.84 min, A	**95**	 MH+:375.2, 2.94 min, A
95a	 MH+:391.0, 3.09 min, C	**95b**	 MH+:368.0, 2.32 min, C	**95c**	 MH+:373.0, 2.98 min, C
95d	 MH+:350.0, 2.15 min, C	**95e**	 MH+:401.0, 1.78 min, D	**95f**	 MH+:456.0, 2.16 min, D

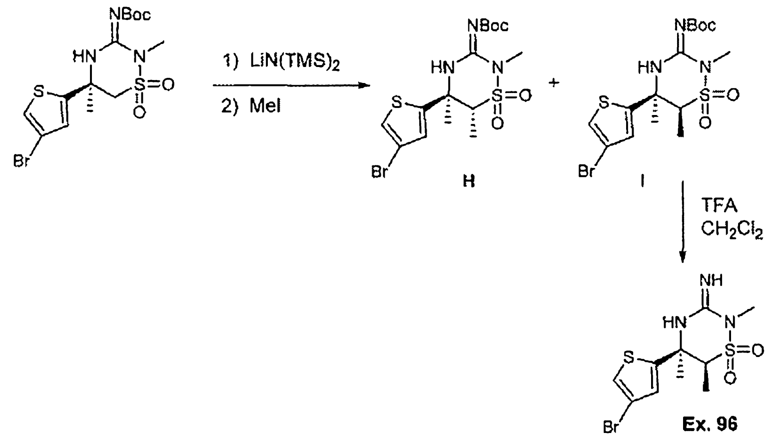






95g	MH$^+$:372.0, 1.77 min, D	**95h**	MH$^+$:506.0, 2.23 min, D	**95i**	MH$^+$:389.0, 1.90 min, D

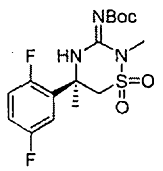
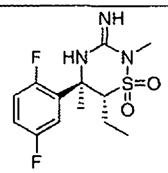
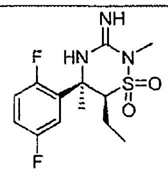
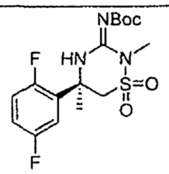
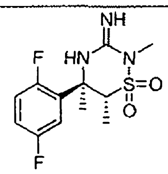
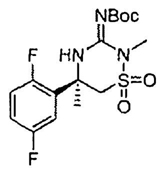
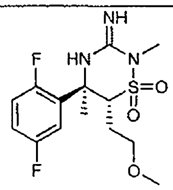
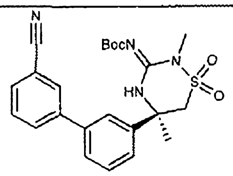
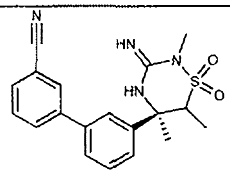
Scheme 16:



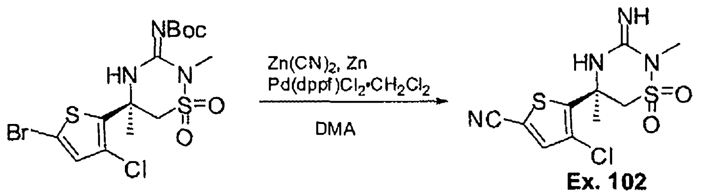
Step 1: To a solution of the thiophene (Scheme 3) (238 mg, 0.54 mmol) in anhydrous THF (2.5 mL) at -78°C was added a solution of LHMDS (1.0 M in THF, 1.63 mL). The resultant solution was stirred at -78°C for 1 hour. To this solution was added methyl iodide (0.086 mL, 1.36 mmol). The resultant solution was stirred at -78°C for an additional 1.25 hours. After that time, water was added and the mixture was allowed to warm to RT. The aqueous layer was then extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 80:20 hexanes:EtOAc) to afford the faster eluting *trans* isomer **H** (20 mg, 8.1 %) and the slower eluting *cis* isomer **I** (168 mg, 68%).

Step 2: To a solution of **I** (16 mg, 0.035 mmol) in CH_2Cl_2 (1 mL) was added TFA (1 mL). The resultant solution was stirred at RT for 1.5 hours. The solution was concentrated to afford **Example 96** (15 mg) as the trifluoroacetate salt. LCMS data: (method A): t_R = 2.79 min, *m/e* = 354.2 (M+H).

Table IX: The following examples were prepared using a method similar to that described in Scheme 16 except NaHMDS was used instead of LHMDS in step 1.

Core	Alkyl halide	Examples		LCMS Obser. MH^+	LCMS Ret time (min)	lcms method
		**97**		318.1	2.02	B
		98		318.0	2.44	B
	MeI	**99**		304.0	1.77	B
		**100**		348.1	2.12	B
	MeI	**101**		369.0	2.16	B

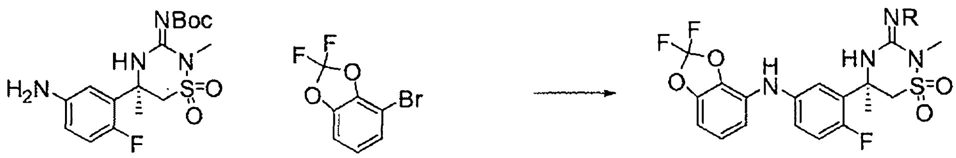
Scheme 17:



Ex. 102

A sealed microwave vial containing a slurry of the thiophene from Scheme 13 (74 mg, 0.16 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (19 mg, 0.023 mmol) , zinc (8.2 mg, 0.12 mmol), zinc cyanide (11 mg, 0.094 mmol) in N,N-dimethylacetamide (2.0 mL) was degassed by bubbling N_2 through the mixture for 5 min. The mixture was then heated to 85°C with stirring for 2 hours. The mixture was cooled to RT and diluted with Et_2O. The organic layer was washed with water (2x), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by preperative TLC (SiO_2: 95:5 CH_2Cl_2:MeOH) to afford **Example 102** (15 mg). LCMS data: (method A): t_R = 2.22 min, *m/e* = 319.2 (M+H).

Scheme 18:



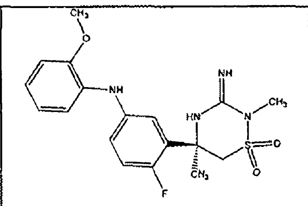
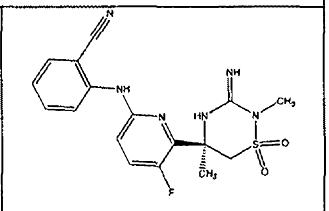
J

K R = Boc
Ex. 103 R = H

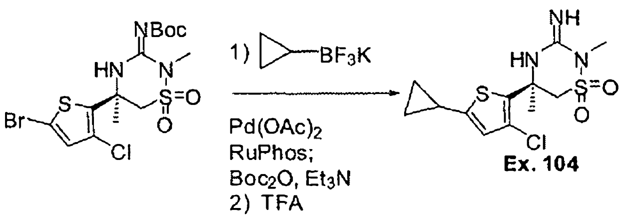
A 20 mL microwave vessel was flame-dried and cooled under vacuum, then backfilled with N_2, followed by two cycles of vacuum/N_2 backfill. The aniline (Scheme 10) (55 mg, 142 µmol), Pd_2dba_3-$CHCl_3$ (17 mg, 19 µmol), di-*tert*-butylphosphinyl-2-biphenyl (15 mg, 50 µmol), sodium *tert*-butoxide (31 mg, 322 µmol) and 4-bromo-2,2-difluorobenzo[d][1,3]dioxole **J** (48 mg, 202 µmol) were suspended in anhydrous toluene (2 mL), the microwave vial was sealed and placed in a preheated 65°C oil bath. After stirring for 18 h, the reaction mixture was diluted with EtOAc, washed with sat. aqueous $NaHCO_3$ (1x), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellow oil, which was subjected to silica-gel chromatography using 0→20 % EtOAc/hexanes as eluent to give intermediate **K** as a film (39 mg). This intermediate was deprotected with TFA (2 mL) in CH_2Cl_2 (3 mL) at RT, then diluted with toluene (5 mL), concentrated under reduced pressure, and subjected to RP-HPLC (C18, 30 ml/min, 10%-100% MeCN/H_2O) with 0.1% TFA) to give

Example 103 in 32% yield (24.9 mg, TFA salt). LCMS (conditions C): t_R = 3.44 min, *m/e* = 443.2 (M+H).

Table IXa: The following Examples were made using methods described in Scheme 18, with the following modification: The coupling reaction was run at 80 °C:

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)			
103a	 MH^+:393, 2.01 min, D	**103b**	 MH^+:389, 1.88 min, D

Scheme 19:



Step 1: To a microwave vial containing 3 mL toluene/water (3:1) was added the bromothiophene from Scheme 13 (50 mg, 0.11 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol), RuPhos (21 mg, 0.04 mmol), potassium cyclopropyl trifluoroborate (17 mg, 0.12 mmol) and Cs_2CO_3 (108 mg, 0.33 mmol). The vial was sealed and the vial was purged with N_2. The mixture was then heated at 70°C for 12 hours. Additional $Pd(OAc)_2$ (5 mg, 0.02 mmol), RuPhos (21 mg, 0.04 mmol), potassium cyclopropyl trifluoroborate (17 mg, 0.12 mmol) were added and the mixture was heated under an atmosphere of N_2 to 70°C for an additional 12 hours. The mixture was cooled to RT, filtered through celite and extracted with CH_2Cl_2. The aqueous layer was dried over Na_2SO_4, filtered and concentrated. The crude mixture was then dissolved in CH_2Cl_2. To this solution was added Boc_2O (24 mg, 0.11 mmol) and Et_3N (13 mg, 0.13

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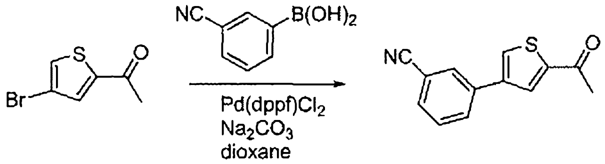
mmol). The resultant solution was stirred overnight at RT. The solution was concentrated and the crude product was purified via preparative TLC (SiO_2; 70:30 hexanes:EtOAc).

Step 2: Example 104 was prepared from the above material using a method similar to that described in Scheme 11b step 2. LCMS data: (method A): t_R = 2.85 min, *m/e* = 334.2 (M+H).

Scheme 20:



The biaryl ketone was formed using a method similar to that described in Scheme 15 step 1.

Table X: The following examples were formed using methods similar to that described in Scheme 1a starting from the ketone in Scheme 20 and the appropriate sulfonamide from Table I.

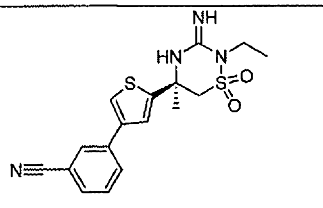
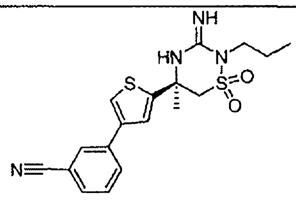
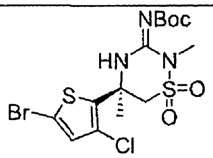
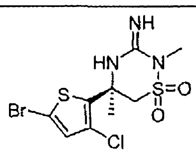
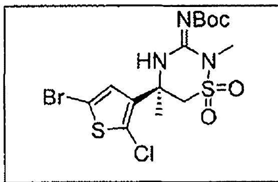
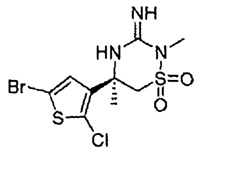
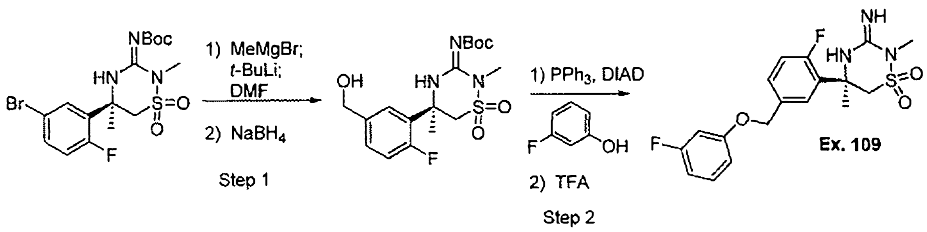
Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)			
105	 MH^+:374.9, 2.13 min, B	**106**	 MH^+:388.9, 2.22 min, B

Table XI: The following examples were prepared using a method similar to that described in Scheme 11b step 2.

Carbamate	**Examples**		**LCMS Obser. MH^+**	**LCMS Ret. time (min)**	**LCMS method**
	**107**		374.2	2.81	A

	**108**		374.2	2.69	A

Scheme 21:



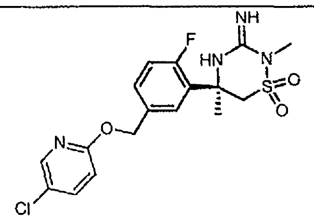
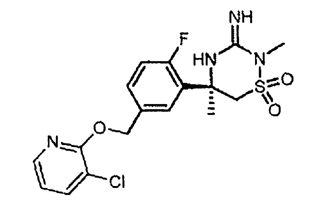
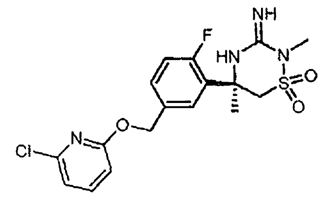
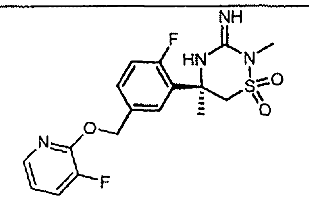
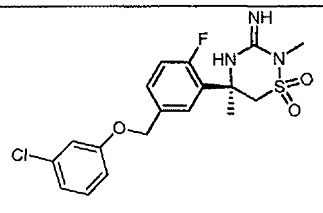
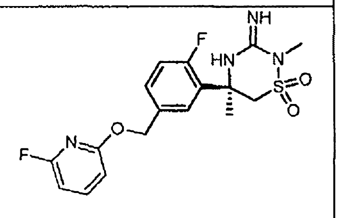
Step 1: To a solution of the bromide (Table IIb, entry 14) (500 mg, 1.11 mmol) in THF (7 mL) at -20^{0}C was added a solution of MeMgBr (3 M in Et_2O, 0.48 mL, 1.4 mmol). The solution was stirred for 30 min at -20^{o}C. The solution was then cooled to -78^{o}C. To the solution was added *t*-BuLi (1.7 M in pentane, 1.6 mL, 2.8 mmol). The solution was stirred for 2 h at -78^{o}C. To the solution was added DMF (0.13 mL, 1.7 mmol). The solution was allowed to slowly warm to RT over 2.5 hours. To the solution was then added sat. NH_4Cl (aq.) (20 mL) and the mixture was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: 3:1 heptane:EtOAc) to afford the aldehyde (237 mg, 54%).

To a solution of the aldehyde (1.04 g, 2.60 mmol) in MeOH (10 mL) at 0^{o}C was added portionwise over 3 min $NaBH_4$ (197 mg, 5.21 mmol). The resultant mixture was stirred for 20 min. To the solution was then added sat. NH_4Cl (aq.) (30 mL) and the mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (SiO_2: 1:1 heptane:EtOAc) to afford the alcohol (949 mg, 91%).

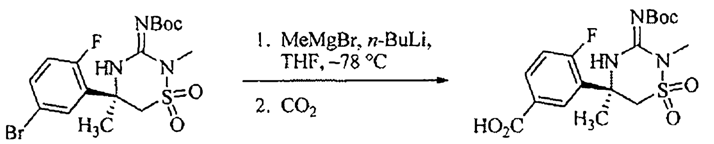
Step 2: To a solution of the alcohol from step 1 (105 mg, 0.26 mmol) and triphenylphosphine (102 mg, 0.39 mmol) in THF (3 mL) was added 3-fluorophenol (0.030 mL, 0.33 mmol). To this solution was added dropwise DIAD (0.075 mL, 0.39 mmol) and the resultant solution was stirred for 2 hours. The reaction was loaded onto a SiO_2 flash column and purified (gradient elution 100:0 to 0:100 heptane:EtOAc) to afford the ether (73 mg, 56%).

Ex. 109 was prepared from the above material using a method similar to that described in Scheme 11b step 2. LCMS (conditions B): t_R = 2.10 min, *m/e* = 396.0 (M+H).

Table XII: The following examples were prepared from the benzylic alcohol described in Scheme 21 step 1 using a method similar to that described in Scheme 21 step 2 using the appropriate aryl alcohol.

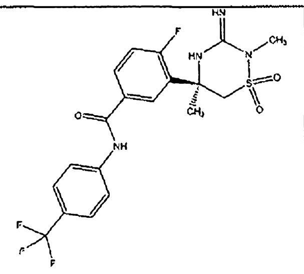
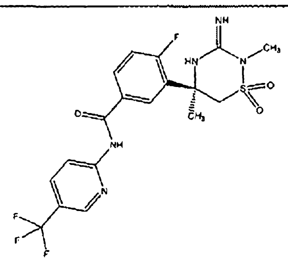
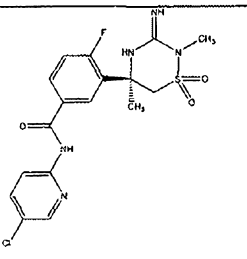
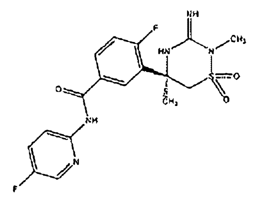
Examples (LCMS data listed with each compound: observed MH^+, HPLC retention time and LCMS method)					
110	 MH^+:412.0, 2.17 min, B	**111**	 MH^+:413.0, 2.02 min, B	**112**	 MH^+:397.0, 1.99 min, B
113	 MH^+:396.0, 2.06 min, B	**114**	 MH^+:397.1, 1.96 min, B	**115**	 MH^+:412.9, 2.08 min, B

Scheme 22:

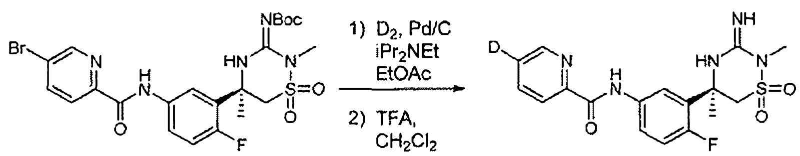


To a stirred solution of the bromide (Table IIb, entry 14, 2.55 g, 5.66 mmol) in anhydrous THF (45 mL) was added a MeMgBr solution (3 M in Et_2O, 2.4 mL, 7.20 mmol) at -78 °C under nitrogen. After addition was completed, the reaction mixture was stirred for 20 min. After that time, a solution of *n*-BuLi solution (2.5 M in hexanes, 5.1 mL, 12.8 mmol) was added dropwise over 5 min. The reaction mixture was then stirred for 50 min at –78 °C and the cooling bath was removed. CO_2 gas was bubbled into the reaction mixture for 50 min. After this time, the reaction was quenched with saturated aqueous NH_4Cl (50 mL) and 1 N hydrochloric acid (aq) (100 mL). The resulting mixture was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 10% methanol/methylene chloride) to afford the carboxylic acid (1.49 g, 53%).

Table XIII: The following examples were prepared using a procedure similar to that described in Scheme 11b using the acid from Scheme 22 and the appropriate aryl amine. The molar ratios used for the acid, amine and BOPCl were 1:1.3:1.5 respectively.

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)			
116	 MH^+:459.0, 2.35 min, B	**117**	 MH^+:460.1, 2.02 min, B
118	 MH^+:426.1, 1.86 min, B	**119**	 MH^+:410.1, 1.74 min, B

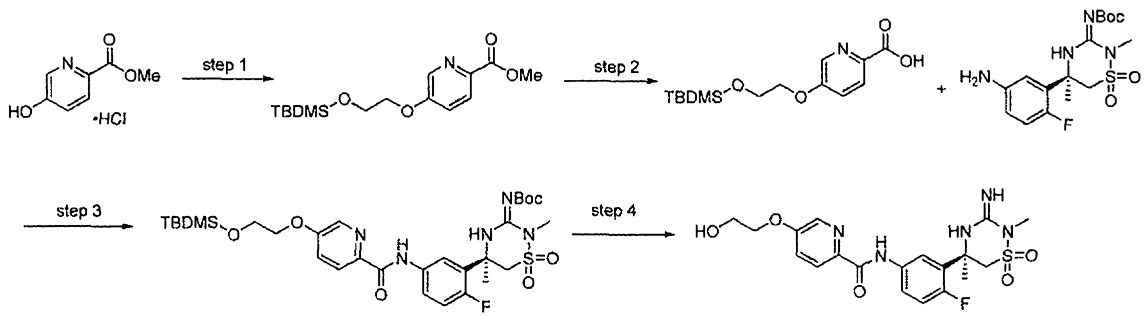
Scheme 23:



Ex. 120

To a sealed round bottom flask containing a solution of the bromide (Table V: Boc intermediate for Ex. 29) (48 mg, 0.084 mmol) in EtOAc (4 mL) under an atmosphere of N_2 was added iPr_2NEt (22 μL, 0.13 mmol) and 10% Pd/C, Degussa type (9.0 mg, 0.0042 mmol). The flask was evacuated and backfilled with D_2 (3x). The mixture was stirred under an atmosphere of D_2 for 4.5 hours. The mixture was purged with N_2, filtered and concentrated. The residue was partitioned between EtOAc and 1/2 sat. $NaHCO_3$ (aq.). The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford the deuterate (38 mg, 92%) as a white solid. **Example 120** was prepared as its TFA salt from the above material using a procedure similar to that described in Scheme 11b step 2. LCMS data: (method D): t_R = 1.76 min, *m/e* = 393.0 (M+H).

Scheme 24:



Ex. 121

Step 1: To the methyl 5-hydroxypicolinate hydrochloride prepared in scheme 11h (0.40 g, 2.1 mmol) in DMF (1 mL) was added potassium carbonate (0.88 g, 6.3 mmol) and (2-bromoethoxy)-*tert*-butyldimethylsilane (0.68 mL, 3.2 mmol). The reaction was warmed to 70 °C and stirred for 18 h. Another equivalent of (2-bromoethoxy)-*tert*-butyldimethylsilane was added and the reaction stirred for an additional 1.5 h at 90 °C. The reaction was cooled to room temperture and water was added. The mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-30% EtOAc/hex) over 30 minutes to provide product (0.31 g, 47%).

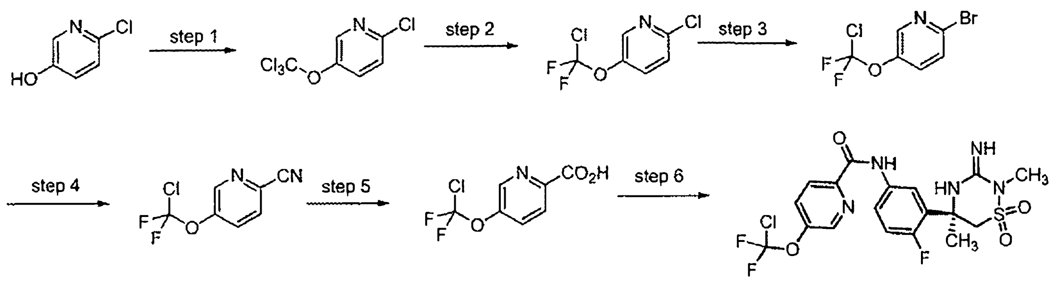
Step 2: To the compound prepared in step 1 (0.31 g, 1.0 mmol) in THF (1.5 mL) was added 2N LiOH (1.5 mL, 3 mmol). The reaction was stirred at room temperature for 4 h. The reaction pH was adjusted to pH~4 using saturated aqueous citric acid. The mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the carboxylic acid (0.18 g, 60%).

Step 3: To the aniline prepared in scheme 10 (0.15 g, 0.39 mmol) in pyridine (1.5 mL) was added the carboxylic acid prepared in step 2 (0.17 g, 0.58 mmol) followed by BOP Cl (0.23 g, 0.89 mmol). The reaction was stirred at room temperature for 4.5 h. The reaction was then concentrated *in vacuo* and the residue was taken up into EtOAc and washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-30% EtOAc/hex over 30 minutes) to provide the amide product (0.14 g, 54%).

Step 4: To the product from step 3 (0.20 g, 0.30 mmol) in THF (1 mL) was added TBAF (1.0 M in THF, 0.33 mL, 0.33 mmol). The reaction was stirred at room temperature for 24h. EtOAc was added to the reaction mixture and the mixture was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-70% EtOAc/hex over 30 minutes) to yield the alcohol (0.14 g, 85%).

To that product (0.14 g, 0.25 mmol) in DCM (2 mL) was added TFA (2 mL). The reaction was stirred at room temperature for 1 h and concentrated *in vacuo*. The reaction was then stirred for 1 h with methanol (1 mL) and 7N NH_3/MeOH (0.5 mL). The reaction was then concentrated *in vacuo* and taken up into EtOAc. The mixture was washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide **Example 121** (0.10 g, 88%). LCMS data: (method D): t_R = 1.68 min, *m/e* = 452.0 (M+H).

Scheme 25



Ex. 122

Step 1: To 2-chloro-5-hydroxypyridine (10 g, 80 mmol) in 1.5 M $NaOH_{(aq)}$ (67 mL) at 0 °C was added thiophosgene (6.0 mL, 79 mmol) in chloroform (46 mL) dropwise. After addition, the reaction was stirred for 2 h. The mixture was then extracted with $CHCl_3$. The combined $CHCl_3$ layers were washed with 1N HCl (aq) and water, dried ($MgSO_4$), and filtered. Into this solution was bubbled Cl_2 gas until the reaction became warm (~1 minute). The reaction was stirred at room temperature for 2h and then Cl_2 gas was bubbled through the mixture again. The reaction was then stirred for 18 h. Nitrogen gas was then bubbled through the reaction mixture to remove residual Cl_2 gas. The reaction was then concentrated *in vacuo*. The residue was purified by reverse phase chromatography [C18 (800g) 5% (2 column volumes (CV), 5-100% (10 CV), 100 (2 CV); 0.1% formic acid/water//0.1% formic acid/acetonitrile] to provide the trichloromethyl ether (4.0 g, 21%).

Step 2: To antimony trifluoride (4.1 g, 22.7 mmol) and antimony pentachloride (0.22 mL, 1.7 mmol) at 120 °C was added the trichloromethylether prepared in step 1 (2.8 g, 11.3 mmol). The mixture was warmed to 150 °C, stirred for 1 h and then cooled to room temperature. DCM and saturated $NaHCO_3$ (aq) were added and the aqueous laywer was extracted with DCM. The combination was washed with 20% $KF_{(aq)}$, water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide product (2.0 g, 83%).

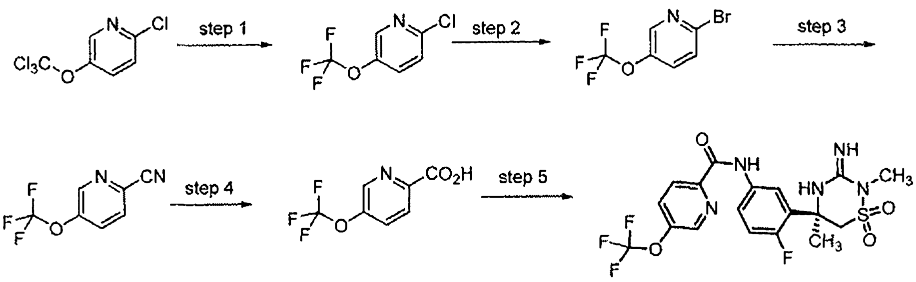
Step 3: To the chlorodifluoromethylether prepared in step 2 (2.0 g, 9.3 mmol) in propanenitrile (11 mL) was added bromotrimethylsilane (2.8 mL, 21 mmol). The reaction was warmed to 100 °C and stirred for 6.5 h. The reaction was cooled to room temperature and saturated $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a product (2.1 g) which was used in the next step without further purification.

Step 4: To the bromopyridine prepared in step 3 (0.33 g, 1.3 mmol) in DMF (2.7 mL) in a microwave reaction vial was bubbled N_2 gas for 5 minutes. $Zn(CN)_2$ (0.22 g, 1.9 mmol) was added and nitrogen was bubbled through the reaction mixture for 5 minutes. $Pd(PPh_3)_4$ (0.078 g, 0.07 mmol) was added and nitrogen was bubbled through the reaction for 5 minutes. The reaction vessel was capped and warmed to 100 °C, then stirred for 2.5 h and cooled to room temperature. Water and EtOAc were added and the combination was then filtred through a pad of Celite washing with EtOAc. The filtrate was then extracted with EtOAc. The organics were then combined and washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo,* then purified by silica gel chromatography (0-8% EtOAc/hex over 30 minutes) to provide product (0.21 g, 81%).

Step 5: To the nitrile prepared in step 4 (0.21 g, 1.0 mmol) in ethanol (2 mL) was added 2N $LiOH_{(aq)}$ (2.7 mL). The reaction was warmed to 100 °C and stirred for 2 h. The reaction was cooled to room temperature and the ethanol removed *in vacuo.* The pH of the aqueous was adjusted to pH~4 using saturated aqueous citric acid. Solid sodium chloride was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a white solid (0.14 g, 62%).

Step 6: To the aniline prepared in scheme 10 (0.20 g, 0.52 mmol) in THF (0.84 mL) at 0 °C was added the carboxylic acid prepared in step 5 (0.14 g, 0.63 mmol), *N,N*-diisopropylethylamine (0.27 mL, 1.6 mmol), and 50% 1-propanephosphonic acid cyclic anhydride in ethyl acetate (0.42 mL, 0.71 mmol), respectively. The reaction mixture was then stirred for 1h at 0 °C and then another hour at room temperature. Water was added to the reaction and the mixture was stirred vigorously for 20 minutes. The mixture was then extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The residue was purified by silica gel chromatography (0-30% EtOAc/hex over 30 minutes) to provide the amide (0.26 g, 84%). To the amide (0.26 g, 0.44 mmol) in DCM (1 mL) at room temperature was added TFA (0.68 mL, 8.8 mmol). The reaction was stirred for 18 h and then concentrated *in vacuo.* The residue was taken up into DCM and stirred with saturated $NaHCO_3$ (aq). The mixture was extracted with DCM. The combined DCM layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide **Example 122.** LCMS data: (method D): t_R = 2.06 min, *m/e* = 492 (M+H).

Scheme 26



Ex. 123

Step 1: To antimony trifluoride (4.05 g, 23 mmol) and antimony pentachloride (0.22 mL, 1.7 mmol) at 120 °C was added the trichloromethyl ether prepared in step 1 of scheme 25 (2.80 g, 11 mmol). The reaction was warmed to 165 °C under nitrogen and stirred for 14 h and then warmed to 175 °C and stirred for an additional 4h. The reaction was cooled to room temperature. The resulting solid mass was stirred vigorously with saturated $NaHCO_{3\,(aq.)}$ [Gas evolution!] and EtOAc. The mixture was filtered through a plug of Celite washing with EtOAc. The filtrate was extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-10% EtOAc/hex over 30 minutes) (0.90 g, 40%).

Step 2: The trifluoromethylether prepared in step 1 was converted to the bromopyridine according to the procedure in step 3 of scheme 25.

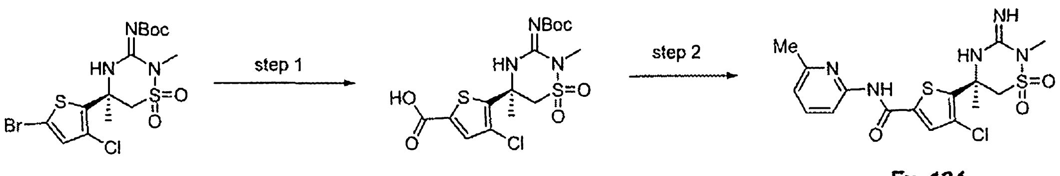
Step 3: The bromopyridine prepared in step 2 was converted to the cyanopyridine according to the procedure in step 4 of scheme 25.

Step 4: The cyanopyridine prepared in step 3 was converted to the pyridylcarboxylic acid according to the procedure in step 5 of scheme 25.

Step 5: The pyridylcarboxylic acid prepared in step 4 was converted to **Ex. 123** according to the procedures in step 6 of scheme 25. LCMS (conditions D): t_R = 2.04 min, *m/e* = 476.0 (M+H).

Scheme 27

2013234424 30 Sep 2013



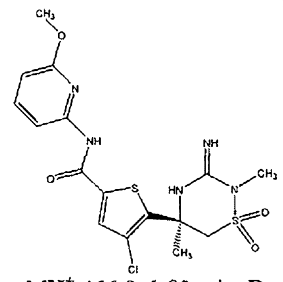
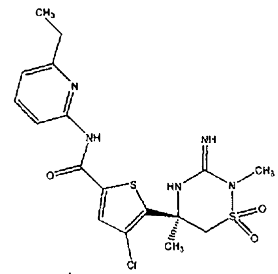
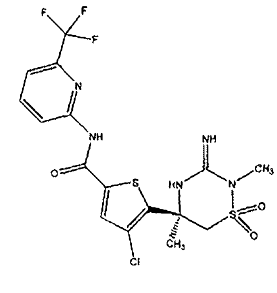
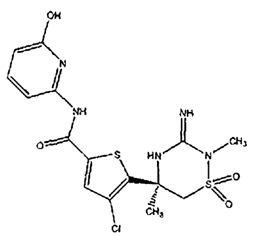
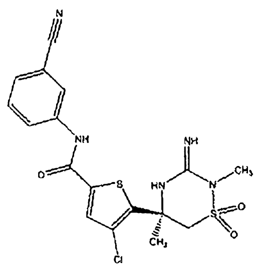
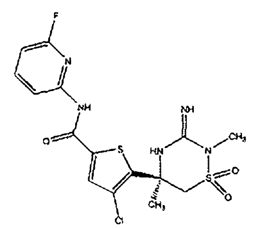
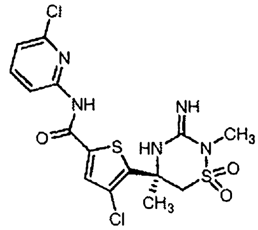
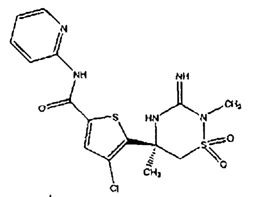
Scheme 13 Ex. 124

Step 1: To the bromothiophene prepared in scheme 13 (1.34 g, 2.83 mmol) in THF (9.2 mL) at 0 °C was added methylmagnesium chloride (3.0 M in THF, 1.18 mL, 3.54 mmol). The reaction was stirred for 30 minutes at 0 °C and then cooled to -78 °C. *n*-Butyllithium (2.5 M in hexanes, 2.55 mL, 6.38 mmol) was added over 10 minutes. The reaction was stirred for 1 hour at -78 ° and then CO_2 gas was bubbled through the reaction. The cold bath was taken away and the reaction allowed to warm to room temperature while continuing to bubble CO_2 gas through the mixture. To the mixture was added 1N HCl $_{(aq.)}$ and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-80% EtOAc/hex over 30 minutes) to provide the carboxylic acid (0.97 g, 78%).

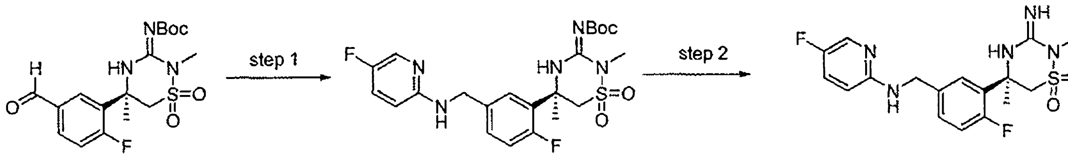
Step 2: To the carboxylic acid prepared in step 1 (0.027 g, 0.06 mmol) in pyridine (0.25 mL) was added 2-amino-6-methylpyridine (0.013 g, 0.12 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.024 g, 0.09 mmol). The reaction was stirred for 18 h at room temperature and then concentrated *in vacuo*. Water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by preparative silica gel TLC (1000 μm SiO_2, 30% EtOAc/hexane) to provide product (13 mg, 40%). To the amide (0.065 g, 0.14 mmol) in DCM (0.4 mL) was added TFA (0.2 mL). The reaction was stirred for 20 h at RT and then concentrated in vacuo to provide **Ex. 124** as the TFA salt. LCMS data: (method D): t_R = 1.59 min, *m/e* = 428.0 (M+H).

Table XIV: The following examples were prepared using procedures similar to those described in Scheme 27 using the appropriate aryl amines.

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)

125  MH+:466.0, 1.82 min, D	**126**  MH+:482.0, 2.21 min, D	**127**  MH+:442.0, 1.70 min, D
128  MH+:430.0, 1.74 min, D	**129**  MH+:438.0, 1.84 min, D	**130**  MH+:432.0, 1.83 min, D
130a  MH+:448.0, 1.89 min, D	**130b**  MH+:414.0, 1.65 min, D	

Scheme 28



Ex. 131

Step 1: To the aldehyde (intermediate from scheme 21 step 1 prior to treatment with $NaBH_4$) (0.10 g, 0.2 mmol) in methanol (1.5 mL) and pyridine (0.5 mL) was added 4 Å mol sieves (100 mg), 2-amino-5-fluoropyridine (0.056 g, 0.5 mmol), and acetic acid (0.02 mL, 0.35 mmol). The reaction was warmed to 50 °C and stirred for 18 h. After cooling to room temperature, saturated sodium bicarbonate (0.5 mL) was added and the mixture was stirred for

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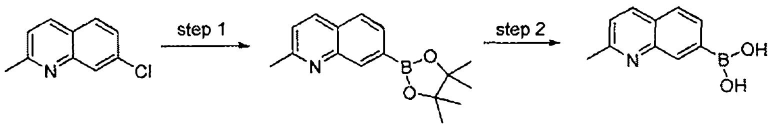
10 minutes. The mixture was then filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-35% EtOAc/hex over 30 minutes) to provide product (0.077 g, 78%).

Step 2: To the material prepared in step 1 (0.077 g, 0.16 mmol) in DCM (0.4 mL) was added TFA (0.24 mL, 3.1 mmol). The reaction was stirred at room temperature for 2 h and then concentrated *in vacuo*. The residue was taken up into DCM and washed with saturated $NaHCO_3$ (aq) water, and brine. The DCM layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was then taken up into DCM and excess 2N HCl/ether was added. The mixture was concentrated to provide **Ex. 131** (57 mg) as the HCl salt. LCMS data: (method D): t_R = 1.56 min, *m/e* = 396.2 (M+H).

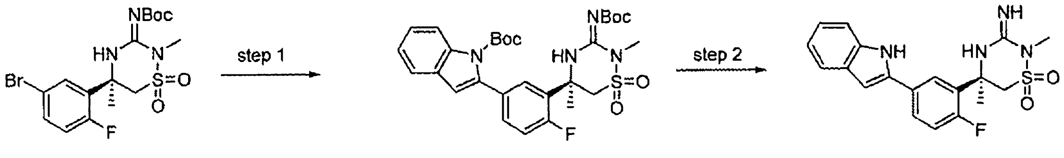
Scheme 29:



Step1: To 7-chloroquinaldine (1.2 g, 6.5 mmol) in THF (80 mL) was added bis(pinacolato)diboron (1.9 g, 7.6 mmol), 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene hydrochloride (0.17 g, 0.4 mmol), and potassium acetate (1.6 g, 16 mmol). Nitrogen was bubbled through the reaction for 10 minutes. Palladium acetate (0.044 g, 0.20 mmol) was added and the reaction was warmed to reflux and stirred for 6 hours. The reaction was filtered through a plug of silica gel washing with EtOAc. The filtrate was concentrated *in vacuo*. The filtrate was purified by silica gel chromatography (0-30% EtOAc/hex over 30 minutes) to provide the boronic ester (0.97 g, 55%).

Step 2: To the boronic ester prepared in step 1 (0.78 g, 2.9 mmol) in THF (6 mL) was added water (24 mL) and sodium metaperiodate (0.93 g, 4.4 mmol). The reaction was stirred for 1 h and then 3M $HCl_{(aq)}$ (19 mL) were added. The mixture was stirred for 45 minutes and then extracted with EtOAc. The aqueous layer was then basified with saturated $NaHCO_{3(aq)}$ and extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the boronic acid (0.34 g, 63%).

Scheme 30:

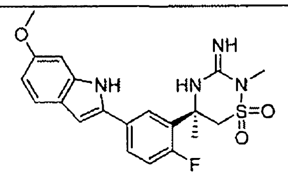
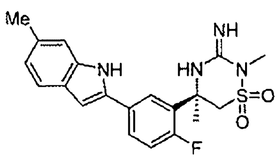
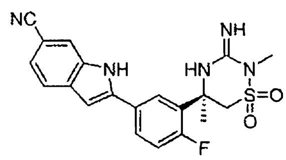


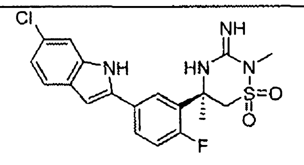
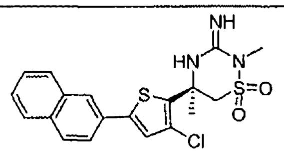
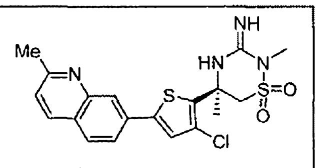
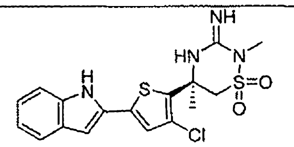
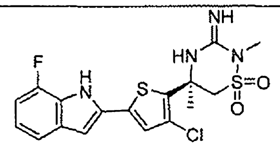
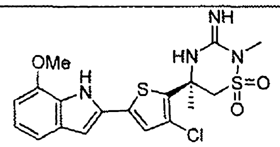
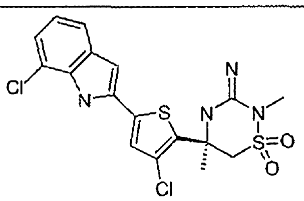
Ex.132

Step 1: To the bromide (Table IIb, entry 14) (0.15 g, 0.33 mmol) in a microwave reaction vial was added *t*-butanol (1.5 mL), 1-(*t*-butoxycarbonyl)-indole-2-boronic acid (0.16 g, 0.60 mmol) and aqueous potassium carbonate (2M, 0.25 mL, 0.50 mmol). Nitrogen was bubbled through the reaction mixture for 10 minutes. $PdCl_2$(dppf) (0.054 g, 0.066 mmol) was added and nitrogen was bubbled through the reaction for 5 minutes. The reaction vessel was capped, warmed to 65 °C, and stirred for 3 h. The reaction was cooled to room temperature and EtOAc was added. The mixture was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-20% EtOAc/hex over 30 minutes) to provide the biaryl product (0.12 g, 60%).

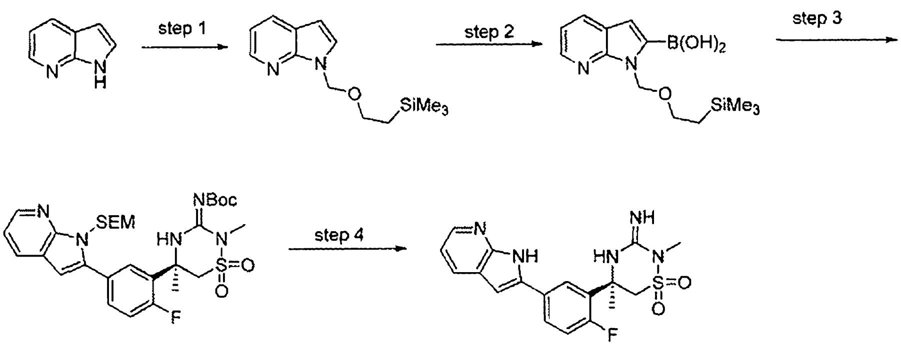
Step 2: To the product prepared in step 1 (0.12 g, 0.20 mmol) in DCM (2 mL) was added TFA (2 mL). The reaction was stirred at room temperature for 1 h and then concentrated *in vacuo* to provide **Ex. 132** as a TFA salt (0.078 g, 78%). LCMS data: (method D): t_R = 1.96 min, *m/e* = 387.0 (M+H). The residue was further purified as needed by reverse phase chromatography [C18 5% (2 column volumes (CV), 5-100% (10 CV), 100 (2 CV); 0.1% formic acid/water//0.1% formic acid/acetonitrile].

Table XV: The following examples were prepared using procedures similar to those described in Scheme 30 using the appropriate aryl bromides and boronic acids.

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)					
133	 MH^+:417.0, 1.93 min, D	**134**	 MH^+:401.0, 2.01 min, D	**135**	 MH^+:412.0, 1.93 min, D

136	 MH+:421.0, 2.03 min, D	**137**	 MH+:420.0, 2.07 min, D	**138**	 MH+:435.0, 1.68 min, D
139	 MH+:409.0, 1.95 min, D	**140**	 MH+:428.0, 1.99 min, D	**141**	 MH+:439.0, 1.96 min, D
141a	 MH+:443.0, 2.13 min, D	**	**	**	**

Scheme 31:



Ex. 142

Step 1: To 7-azaindole (1.5 g, 12.7 mmol) in DMF (30 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.56 g, 14 mmol). The reaction was stirred for 15 minutes at room temperature then cooled to -40 °C (EtOAc/CO_2 cooling bath). (2-(Chloromethoxy)ethyl) trimethylsilane (2.5 mL, 14 mmol) was then added and the reaction allowed to warm to room temperature. The reaction was stirred at room temperature for 18 h. EtOAc was added and the mixture was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

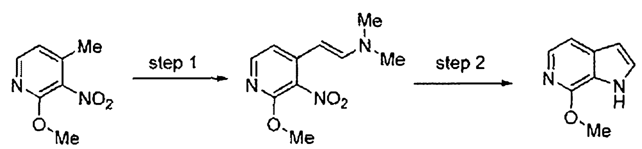
The residue was purified by silica gel chromatography (0-10% EtOAc/hex over 30 minutes) to provide the SEM-protected indole (2.9 g, 91%).

Step 2: To the SEM-protected indole prepared in step 1 (0.99 g, 4.0 mmol) in THF (10 mL) at -40 °C was added *n*-BuLi (2.5 M in hexanes, 1.9 mL, 4.8 mmol). The mixture was stirred at -40 °C for 1 h and then triisopropyl borate (1.2 mL, 5.2 mmol) was added. The mixture was allowed to warm to room temperature while stirring for 18 h. To the reaction mixture was added 1N HCl (aq). The mixture was stirred at room temperature for 30 minutes. The mixture was then adjusted to pH~5 using saturated $NaHCO_3$ (aq) The mixture was extracted with ether. The combined ether extracts were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-50% EtOAc/hex over 30 minutes) to provide the indole boronic acid (0.20 g, 17%).

Step 3: To the bromide (Table IIb, entry 14) (0.21 g, 0.46 mmol) in *t*-butanol (3 mL) a microwave reaction vial was added the boronic acid prepared in step 2 (0.20 g, 0.68 mmol) and 2M K_2CO_3 $_{(aq)}$ (0.34 mL, 0.68 mmol). Nitrogen was bubbled through the reaction for 10 minutes. $PdCl_2$(dppf) (0.075 g, 0.092 mmol) was added and the reaction was sealed and heated to 65 °C. After 3 h, the reaction was cooled to room temperature and EtOAc was added. The mixture was washed with water and brine ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-20% EtOAc/hex over 30 minutes) to provide the coupling product (0.21 g, 74%).

Step 4: To the coupling product prepared in step 3 (0.086 g, 0.14 mmol) was added 4M HCl in ethanol (6 mL). The reaction was warmed to 60 °C and stirred for 20 h. The reaction was concentrated *in vacuo* and then purified by reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:formic acid) to provide **Ex. 142** (0.030 g). LCMS data: (method D): t_R = 1.67 min, *m/e* = 388.0 (M+H).

Scheme 32:



Step 1: To the nitropyridine (5.1 g, 30 mml) in DMF (5 mL) was added 1,1-methoxy-*N,N*-dimethylmethanamine (15 mL, 110 mmol). The reaction was warmed to 130 °C and stirred

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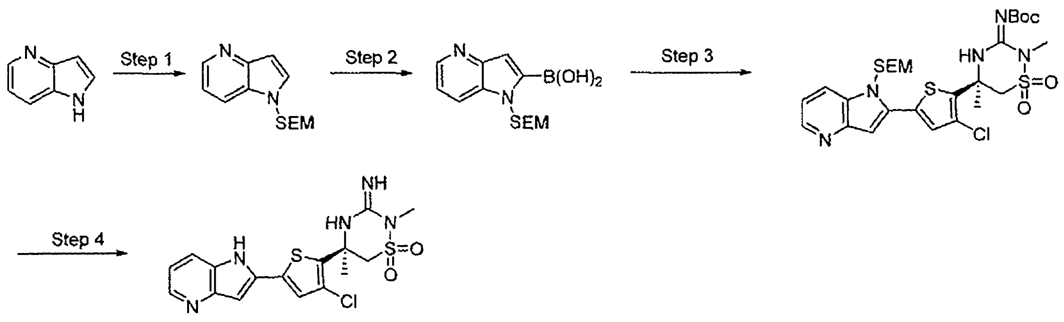
for 16 h. The reaction was cooled to room temperature and then added to a beaker of ice. The resulting solid was isolated by filtration to give product (5.9 g, 88%).

Step 2: To the enamine prepared in step 1 (5.9 g, 26 mmol) in ethanol (275 mL) was added 10% palladium on carbon, Degussa type (1.5 g). The reaction mixture was shaken under a hydrogen atmosphere (15 psi) for 15 minutes. The reaction was filtered through a bed of celite washing with DCM. The filtrate was concentrated *in vacuo* to provide the indole (4.3 g, 61%).

Scheme 33:



Ex. 143

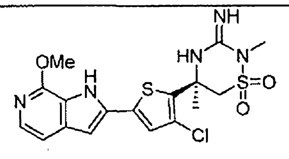
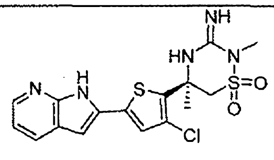
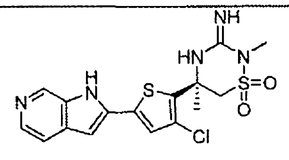
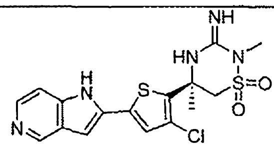
Step 1: The 4-azaindole was protected with the SEM group according to the procedure described in step 1 of Scheme 31.

Step 2: The SEM protected indole prepared in step 1 was converted to the 2-boronic acid according to the procedure described in step 2 of Scheme 31.

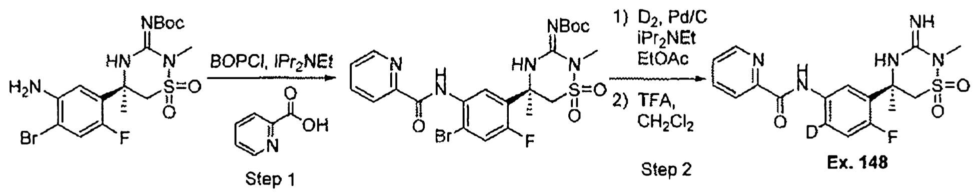
Step 3: To SEM-protected indole 2-boronic acid prepared in step 2 (0.40 g, 1.37 mmol) in a microwave reaction vial in *t*-butanol (3 mL) was added potassium carbonate (2M, 0.6 mL, 1.1 mmol) and the bromothiophene prepared in scheme 13 (0.36 g, 0.76 mmol). Nitrogen was bubbled through the reaction mixture for 10 minutes after which $PdCl_2$(dppf) (0.12 g, 0.15 mmol) was added. The reaction vessel was capped and warmed to 65 °C. The reaction was stirred for 16 h and then cooled to room temperature. EtOAc was added and the mixture was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was taken up into DCM (2 mL) and $(Boc)_2O$ (166 mg) was added. The reaction was stirred at room temperature for 18 h. The reaction was concentrated *in vacuo* to provide a residue that was purified by silica gel chromatography (0-40% EtOAc/hex) to provide a mixture of desired product and bis-boc product (360 mg). The mixture was carried on directly to the next step

Step 4: The biaryl prepared in step 3 (0.28 g, 0.43 mmol) was heated in 4N HCl in ethanol (12 mL) to 65 °C for 12 h. The reaction was concentrated *in vacuo* to provide desired material and the indole *N*-hydroxymethyl intermediate. The mixture was taken up into acetone (2 mL) and ethanol (1 mL) and potassium carbonate was added (0.15 g, 1.1 mmol). The mixture was stirred at room temperature for 1 h and then added to saturated $NH_4Cl_{(aq)}$. The mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by preparative silica gel TLC (10% MeOH/DCM) to provide **Ex. 143** (0.10 g, 57%). LCMS data: (method D): t_R = 1.67 min, *m/e* = 410.0 (M+H). (Alternatively, the residue could be purified by reverse phase chromatography [C18 5% (2 column volumes (CV), 5-100% (10 CV), 100 (2 CV); 0.1% formic acid/water//0.1% formic acid/acetonitrile]).

Table XVI: Using the conditions described in Scheme 33, the following examples were prepared from the appropriate aryl bromides and aryl boronic acids.

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)			
144	 MH^+:440.0, 1.65 min, D	**145**	 MH^+:410.0, 1.78 min, D
146	 MH^+:410.0, 1.70 min, D	**147**	 MH^+:410.0, 1.67 min, D

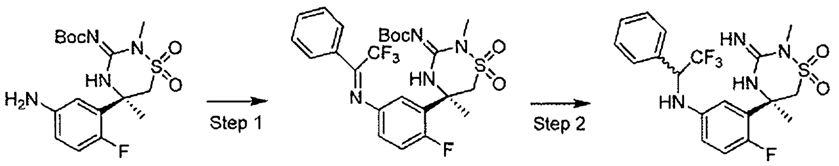
Scheme 34:



Step 1: To a slurry of the aniline from Scheme 10a (95 mg, 0.20 mmol), picolinic acid (30 mg, 0.25 mmol) and BOPCl (78 mg, 0.31 mmol) in CH_2Cl_2 (4 mL) at 0°C was added iPr_2NEt (89 µL, 0.51 mmol). The resultant mixture was warmed to RT and stirred for 16 hours. The mixture was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via preparative TLC (SiO_2: 1:1 hexanes:EtOAc) to afford the amide (47 mg, 40%) as a white solid.

Step 2: Ex. 148 was prepared as its TFA salt from the above material using a procedure similar to that described in Scheme 23. LCMS data: (method D): t_R = 1.75 min, *m/e* = 393.0 (M+H).

Scheme 35:



Step 1: To a RT mixture of aniline (Scheme 10, 0.1 g, 0.26 mmol), 2 mL DCM, diisopropylethylamine (45 µL, 0.26 mmol), and trifluoroacetophenone (0.045 g, 0.26 mmol) was slowly added dropwise titanium tetrachloride (1.0 M in DCM, 0.26 mL, 0.26 mmol). The reaction was stirred for 2 hours. Saturated aqueous sodium bicarbonate was then poured into the reaction, forming a white precipitate, which was then filtered through celite. The celite was washed with DCM and the filtrate was extracted with DCM. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-30% EtOAc/hexanes over 20 minutes) to provide the imine compound (0.051 g, 36%).

Step 2: To the imine prepared in Step 1 (0.051 g, 0.09 mmol) stirring in 2 mL MeOH was added sodium borohydride (0.007 g, 0.18 mmol). The reaction was stirred at room temperature for 1 hour, then concentrated to dryness *in vacuo*. The reaction was purified by preparative RP HPLC (10-100% acetonitrile with 0.1% formic acid/water with 0.1% formic acid over 22 minutes) to provide the amine product. This material was treated with 2 mL 20% TFA/DCM for 1 hour, and then concentrated *in vacuo* to provide **Example 149** (1:1 mixture of

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diastereomers) as a trifluoroacetate salt (39 mg, 75%). LCMS data: (method D): t_R = 1.97 min, *m/e* = 445.0 (M+H).

Table XVII: The following examples were made according to the methods described in Scheme 35:

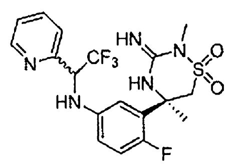
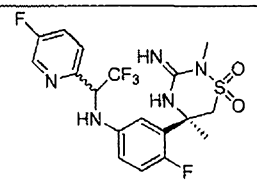
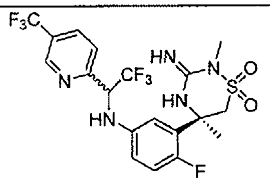
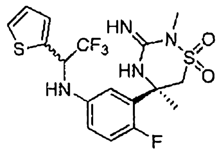
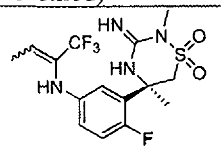
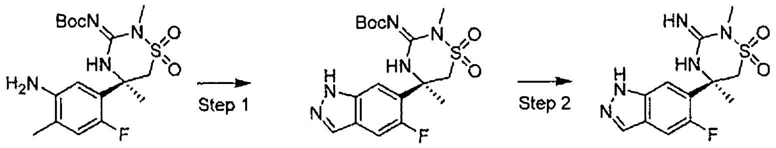
Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)			
150	 MH^+:446.0, 1.87 min, D	**151**	 MH^+:464.0, 1.93 min, D
152	 MH^+:514.0, 1.99 min, D	**153**	 MH^+:451.0, 1.93 min, D

Table XVIII: The following Example was made as a mixture of diastereomers using the following sequence: (1) Scheme 35, Step 1, (2) Scheme 11b, Step 2:

Example (LCMS data: observed MH^+, HPLC retention time and LCMS method)	
154	 MH^+:395.0, 1.89 min, D

Scheme 36:

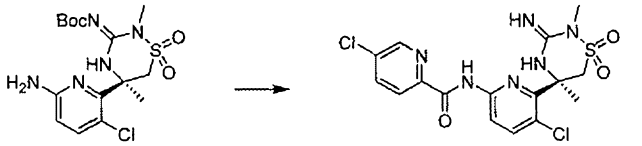


Example 155

Step 1: To the aniline (Table IV, entry 5 0.2 g, 0.5 mmol) stirring at room temperature in glacial acetic acid (5 mL) was added dropwise a solution of sodium nitrite (0.035 g, 0.5 mmol) in water (0.25 mL). The reaction was stirred at room temperature 6 hrs, then concentrated to dryness *in vacuo*. The residue was purified by silica gel chromatography (0-100% EtOAc/hexanes over 30 minutes) to provide the indazole compound as a solid (0.060 g, 29%).

Step 2: The material from step 1 (0.005g, 0.012 mmol) was treated according to Scheme 11b, step 2 to afford **Example 155** as the TFA salt (0.005 g, 97%). LCMS data: (method D): t_R = 1.63 min, *m/e* = 312.0 (M+H).

Scheme 37:



Example 156

To the aminopyridine compound (Table IIIb, 0.068 g, 0.17 mmol) stirring in 1.68 mL 4:1 DMF:diisopropylethylamine at room temperature was added 5-chloropicolinoyl chloride (Scheme 11p) and 1 crystal of DMAP. The reaction was heated to 50°C and stirred for 48 hours. The reaction was cooled to room temperature and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-60% EtOAc/hexanes over 20 minutes, then 60-100% EtOAc/hexanes 20-30 minutes) to provide an amide product (0.014 g, 15%). This material was treated according to Scheme 11b, step 2 to provide **Example 156** (0.014 g, 97%) as a trifluoroacetate salt. LCMS data: (method D): t_R = 1.91 min, *m/e* = 443.0 (M+H).

Table XIX: The following examples were made according to the methods described in Scheme 37 using acid chlorides from Table IVj:

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)

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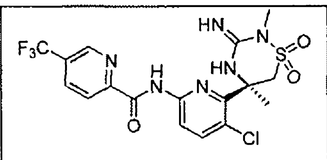
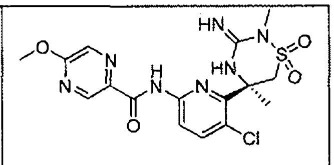
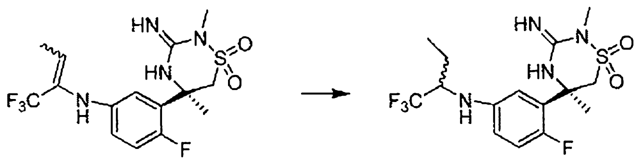
157	 MH+:477.0, 1.93 min, D	**158**	 MH+:440.0, 1.84 min, D

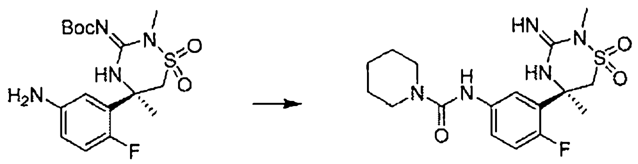
Scheme 38:



Example 159

To **Example 154** (0.020 g, 0.04 mmol) stirring in 2 mL EtOH was added 10% palladium on carbon (0.010 g). This solution was subjected to a hydrogen atmosphere (balloon) and stirred 16 hours. The reaction was filtered through celite and washed with MeOH. The filtrate was concentrated to dryness *in vacuo* and purified by preparative RP HPLC (10-100% acetonitrile with 0.1% formic acid/water with 0.1% formic acid over 22 minutes) to provide **Example 159** as a mixture of diastereomers as a formate salt (0.013 g, 65%). LCMS data: (method D): t_R = 1.92 min, *m/e* = 397.0 (M+H).

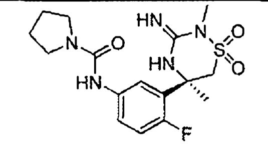
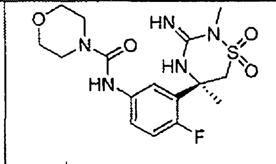
Scheme 39:



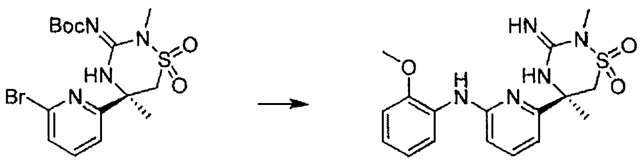
Example 160

Step 1: To the aniline (Scheme 10, 0.1 g, 0.26 mmol) stirring in 3 mL DCM was added triethylamine (54 μL, 0.39 mmol) and 1-piperidinecarbonyl chloride (34 μL, 0.27 mmol), and the mixture was allowed to stir for 3 days at room temperature. The reaction was poured into water and extracted with DCM. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-80% EtOAc/hexanes over 20 minutes) to provide a urea product (0.093 g, 72%). This compound was then treated according to Scheme 11b, Step 2 to provide **Example 160** (0.094 g, 98%) as a trifluoroacetate salt. LCMS data: (method D): t_R = 1.75 min, *m/e* = 398.2 (M+H).

Table XX: The following examples were made according to the methods described in Scheme 39 using the appropriate carbonl chloride:

Example (LCMS data: observed MH$^+$, HPLC retention time and LCMS method)			
161	 MH^+: 384.2, 1.61 min, D	**161a**	 MH^+: 400.0, 1.47 min, D

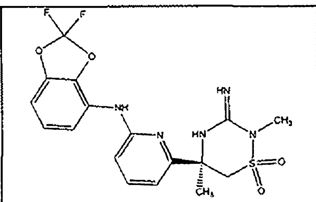
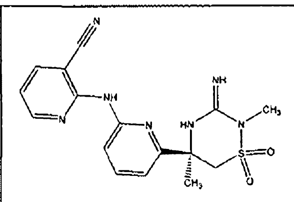
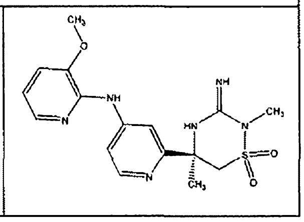
Scheme 40:

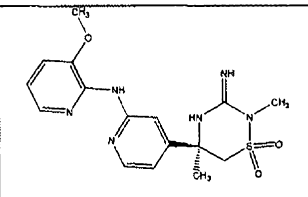
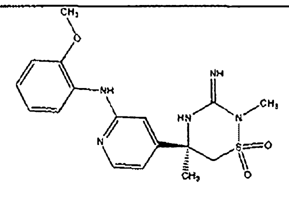


Ex. 162

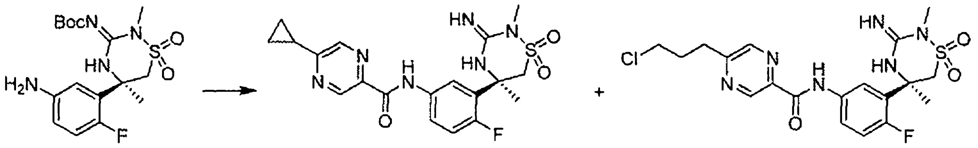
The bromopyridine compound (Scheme 7a , step 6) 0.07 g, 0.16 mmol) along with *O*-anisidine (22 μL, 0.19 mmol), tris(dibenzylideneacetone)dipalladium (0.003 g, 0.003 mmol), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.004 g, 0.006 mmol), and sodium *t*-butoxide (0.022 g, 0.22 mmol) were stirred in a flame-dried, sealed microwave vial flushed with nitrogen in 2 mL anhydrous toluene at 80°C for 3.5 hours. The reaction mixture was cooled to room temperature, poured into water, and extracted with DCM. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-60% EtOAc/hexanes over 20 minutes) to provide biarylamine product (0.007 g, 9%). This material was treated according to Scheme 11b, Step 2 to provide **Example 162** as a trifluoroacetate salt (0.007 g, 97%). LCMS data: (method D): t_R = 1.80 min, *m/e* = 376.2 (M+H).

Table XXI: The following Examples were made according to the methods in Scheme 40:

Examples (LCMS data: observed MH$^+$, HPLC retention time and LCMS method)					
163		**164**		**165**	

	MH^+:426.0, 2.05 min, D		MH^+:372.0, 1.83 min, D		MH^+:377.0, 1.65 min, D
166	 MH^+:377.0, 1.18 min, D	**167**	 MH^+:376.0, 1.38 min, D		**

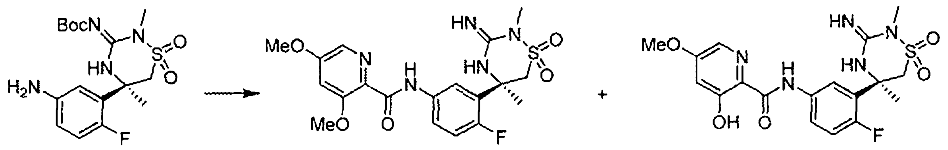
Scheme 41:



Example 168 Example 169

The aniline shown (Scheme 10) was treated according to Scheme 11b using 5-cyclopropylpyrazine-2-carboxylic acid (Table IVg, entry 4) to afford, after separation, both **Example 169** [LCMS data: (method D): t_R = 1.80 min, *m/e* = 433.0 (M+H)] and **Example 168** [LCMS data: (method D): t_R = 1.83 min, *m/e* = 469.0 (M+H)] both as TFA salts.

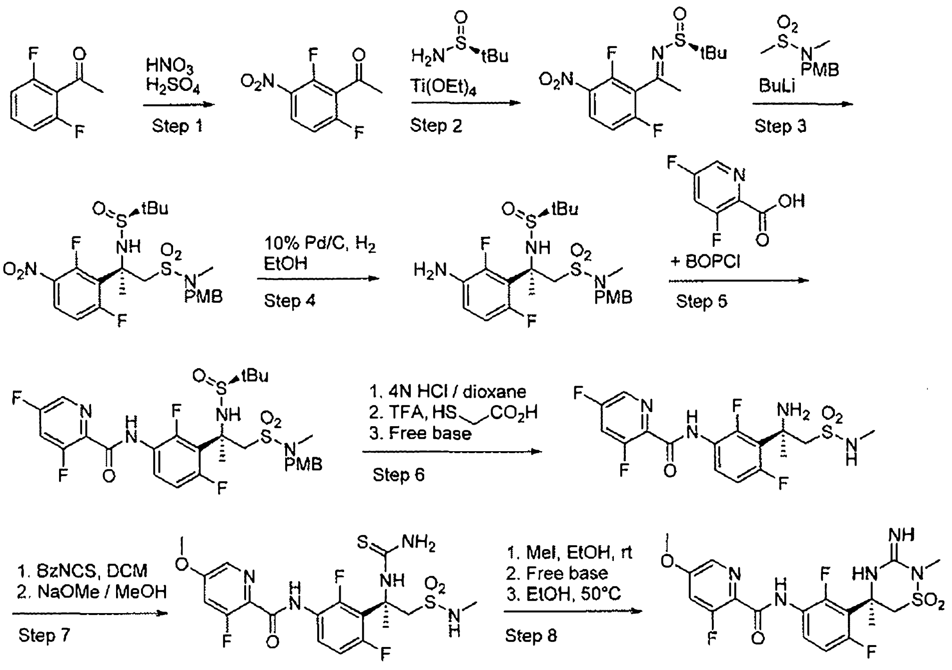
Scheme 42:



Example 170 Example 171

The aniline shown (Scheme 10) was treated according to Scheme 11b using 3,5-dimethoxypyridine-2-carboxylic acid (Scheme 11q) to afford, after separation, both **Example 170** [LCMS data: (method D): t_R = 1.73 min, *m/e* = 452.0 (M+H)] and **Example 171** [LCMS data: (method D): t_R = 1.85 min, *m/e* = 438.0 (M+H)] both as TFA salts.

Scheme 43:



Ex.172

Step 1: To a -40 °C mixture of concentrated H_2SO_4 (100 mL) and fuming HNO_3 (100 mL) was added 1-(2,6-difluorophenyl)ethanone (20 g, 128 mmol) dropwise. The resulting mixture was stirred at -40 °C for 2h then poured slowly onto ice. That mixture was diluted with DCM and the phases were separated. The aqueous layer was neutralized with sat. aq. $NaHCO_3$ and then extracted with DCM. All organic portions were combined, dried over $MgSO_4$, filtered, and concentrated to give 1-(2,6-difluoro-3-nitrophenyl)ethanone (26.3 g, 131 mmol, > theoretical) that was used without further purification.

Step 2: The nitrophenyl ketone from the previous step was treated according to Scheme 1a, Step 1 [substituting (S)-2-methyl-2-propanesulfinamide for (R)-2-methyl-2-propanesulfinamide] to give a ketimine product (17.1 g, 44% based on 1-(2,6-difluorophenyl)ethanone from Step 1).

Step 3: The ketimine from step 2 (17.1 g, 56.2 mmol) was treated according to Scheme 1a, Step 3 to give desired syn addition product (6 g, 20%) as well as a mixture of syn and anti diastereomers (6 g, 3:1, 20%).

Step 4: To a solution of the syn addition product from Step 3 (2.71 g, 5.1 mmol) in 25 mL of ethanol was added 10% Pd/C (298 mg). The mixture was placed under H_2 balloon atmosphere overnight. After filtration through Celite, the filtrate was concentrated. The crude residue was purified by flash silica column (60%-100% EtOAc/hexanes) to give the aniline product (1.75 g, 68% yield).

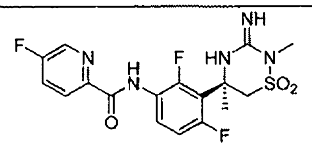
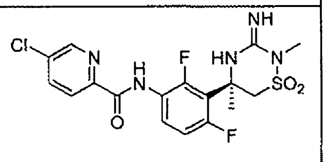
Step 5: A mixture of the aniline from Step 4 (453 mg, 0.9 mmol), 3,5-difluoropicolinic acid (215 mg, 1.4 mmol), and BOPCl (527 mg, 2.07 mmol) in 4 mL of pyridine was stirred overnight. After it was quenched with 1N HCl (aq), the mixture was extracted with ethyl acetate. The organic portions were combined, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash silica column (40% EtOAc/hexane) to give an amide product (431 mg, 74% yield).

Step 6: To a solution of the above material (431 mg, 0.67 mmol) in 3 mL of DCM and 1 mL of methanol was added 4N HCl in dioxane (1 mL, 4.0 mmol). After the mixture was stirred for 1 h, it was concentrated. This sample was treated with a mixture of TFA (4 mL) and thioglycolic acid (0.46 mL, 6.7 mmol). After the mixture was stirred for 4 h, it was concentrated. The crude residue was neutralized by carefully adding saturated sodium bicarbonate solution. The resulting mixture was extracted with ethyl acetate, the organic portions were combined, dried over magnesium sulfate, and concentrated to an amine product that was used in the subsequent step without further purification.

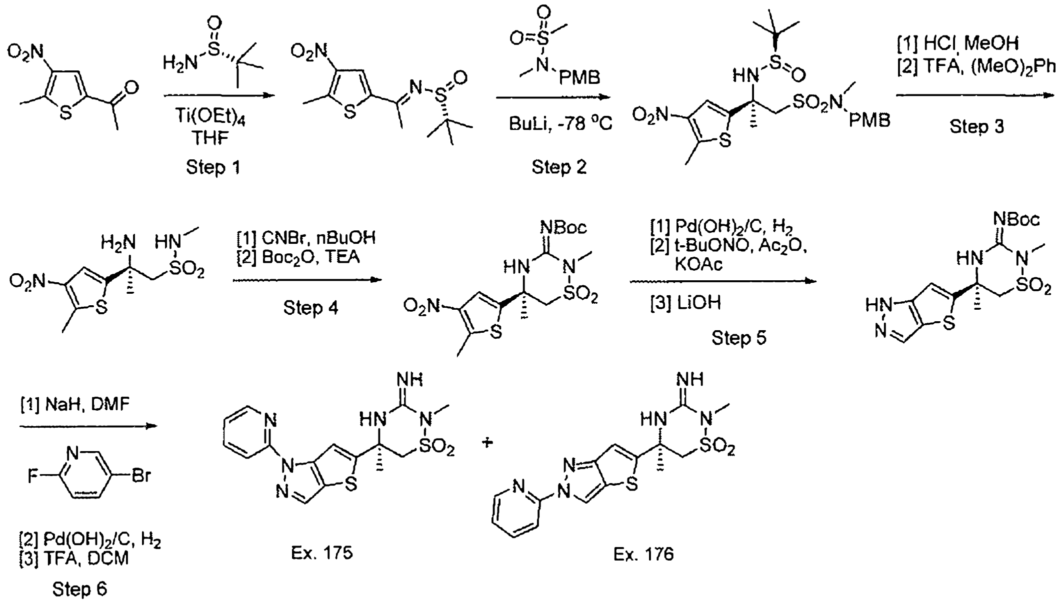
Step 7: To the material from step 6 (assumed to be 0.67 mmol) in 5 mL of DCM was added benzoyl isothiocyanate (0.12 mL, 0.87 mmol). The mixture was stirred overnight at RT. After it was concentrated, the residue was dissolved in 5 mL of methanol, and sodium methoxide (25% in methanol, 0.37 mL) was added. The mixture was stirred for 2 h at RT. It was quenched with 2 drops of acetic acid. After the mixture was concentrated, the crude was diluted with saturated sodium carbonate, and extracted with DCM. The combined organic portions were dried over magnesium sulfate and concentrated to give an isothiourea product that was used in the subsequent step without purification.

Step 8: To a solution of the material from step 7 (assumed to be 0.67 mmol) in 5 mL of ethanol was added methyl iodide (0.05 mL, 0.8 mmol). The mixture was stirred overnight at room temperature and then diluted with saturated sodium bicarbonate. After the mixture was extracted with ethyl acetate, the organic layers were combined, dried over magnesium sulfate, and concentrated. The crude residue was dissolved in 5 mL of ethanol, and the mixture was heated at 50°C for 2 h. The mixture was then diluted with saturated sodium bicarbonate, and extracted with ethyl acetate. The organic portions were combined, dried over magnesium sulfate, and concentrated. The crude residue was purified by reverse phase HPLC (C18 radial compression, 10% to 100% MeCN/water with 0.1% TFA) to give **Example 172** as a TFA salt (40.3 mg, 14% from the product of Step 5). LCMS (conditions A): t_R = 2.43 min, *m/e* = 458.3 (M+H).

Table XXII: The following examples were made from 1-(2,6-difluorophenyl)ethanone using methods similar to those described in Scheme 43, substituting the appropriate acid in Step 5:

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)			
173	 MH^+:428.2, 2.46 min, A	**174**	 MH^+:442.2, 3.17 min, A

Scheme 44:



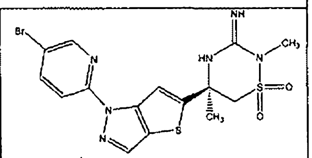
Steps 1-4: 1-(5-Methyl-4-nitrothiophen-2-yl)ethanone, obtained by nitration from 1-(5-methylthiophen-2-yl)ethanone according to the literature procedure (E. Campaigne, J. L. Diedrich, *J. Am. Chem. Soc.* **1951**, *73*, 5240-5243), was converted into the product of step 4 using similar procedures in the following sequence: (i) Scheme 1a, steps 1-4, (ii) Scheme 3b.

Step 5: To a solution of the product of step 4 (570 mg, 1.37 mmol) in MeOH (25 mL) was added 10% $Pd(OH)_2/C$ (250 mg), and the reaction was stirred in a Parr-shaker under an atmosphere of H_2 (50 psi) for 18 h. The reaction was filtered over a pad of celite, the filter residue rinsed with MeOH and the combined organic layers concentrated under reduced pressure to give a residue (423 mg, 80%). To a solution of this residue (423 mg, 1.08 mmol) in toluene (3 mL) was added KOAc (85 mg, 0.86 mmol), acetic anhydride (0.205 mL, 2.16 mmol) and *tert*-butylnitrite (0.145 mL, 1.2 mmol). The reaction was stirred at 90 °C for 4.5 h, then cooled to RT and diluted with EtOAc. After filtration through celite, the filtrate was concentrated under reduced pressure to give a residue that was subjected to silica gel chromatography (gradient elution 100:0 to 70:30 hexanes:EtOAc). The resulting mixture of acetylated and deacetylated materials (298 mg) was dissolved in THF (5 mL) and treated with aqueous 1 M LiOH (2 mL) for 30 min at RT. The reaction was diluted with EtOAc, the layers separated and the aqueous layer extracted with EtOAc (1 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum to give the product of step 5 (282 mg, 65%).

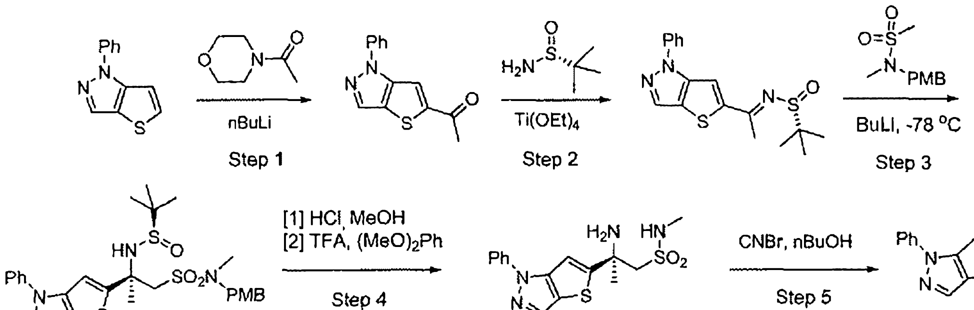
Step 6: Sodium hydride (60% in mineral oil, 20 mg, 0.5 mmol) was added to a solution of the product from step 5 (78 mg, 0.195 mmol) in DMF (2 mL) at RT. After 5 min, 2-fluoro-5-bromopyridine (54 mg, 0.306 mmol) was added and the reaction stirred for 19 h at RT, then quenched with water and EtOAc. The organic layer was washed with saturated aqueous $NaHCO_{3\ (aq.)}$, brine, and then dried over $MgSO_4$, and concentrated under vacuum. To a solution of this residue in MeOH was added 10% $Pd(OH)_2/C$ (110 mg), and the reaction was stirred under a balloon-atmosphere of H_2 for 72 h. The catalyst was removed by filtration over celite, and the filtrate concentrated under reduced pressure to give a mixture of regioisomeric intermediates that were separated by silica gel chromatography (gradient elution with hexanes:EtOAc). Each regioisomer was deprotected according to the procedure described in Scheme 11b, Step 2, then subjected to reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:TFA) to provide **Example 175** and **Example 176** as their

TFA salts. LCMS for **Ex. 175** (conditions D): t_R = 1.80 min, *m/e* = 377.0 (M+H); LCMS for **Ex. 176** (conditions D): t_R = 1.78 min, *m/e* = 377.0 (M+H).

Table XXIII: The following examples were prepared using a procedure similar to that described in Scheme 44 omitting the hydrogenation portion of step 6.

Example	
177	 MH$^+$:455.0, 1.92 min, D

Scheme 45:



Ex. 178

Step 1: To a -78°C solution of 1-phenyl-1H-thieno[3,2-c]pyrazole (1.94 g, 9.68 mmol), obtained from 3-bromothiophene-2-carbaldehyde according to the literature procedure (Lebedev et al., *J. Org. Chem.* **2005**, *70*, 596-602), was added nBuLi (4.25 mL of a 2.5 M solution in hexanes, 10.65 mmol) over 5 min. After 30 min at -78°C, N-acetylmorpholine (2.3 mL, 20 mmol) was added and the reaction was stirred for 60 min at -78°C, then stirred for 6 h while slowly warming to RT. The reaction was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was washed with sat. aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (gradient elution 100:0 to 85:15 hexanes:EtOAc) to give 1-(1-phenyl-1H-thieno[3,2-c]pyrazol-5-yl)ethanone (682 mg, 2.81 mmol, 29%) along with recovered starting material (823 mg, 4.13 mmol, 43%).

Steps 2-5: These steps were performed using similar procedures to the following sequence: (i) Scheme 1a, steps 1-4, (ii) Scheme 3b, omitting the coversion to the *t*-butyl carbamate. The

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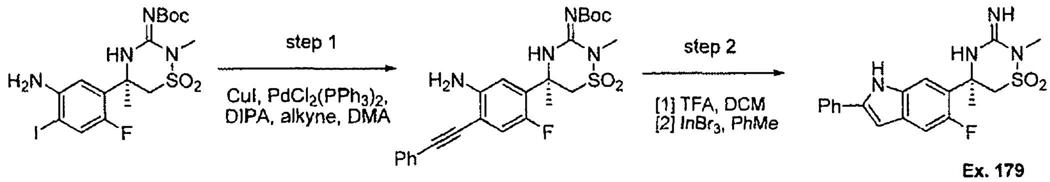
final intermediate was subjected to reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:TFA) to provide **Ex. 178** as its TFA salt. LCMS for **Ex. 178** (conditions D): t_R = 1.82 min, *m/e* = 376.0 (M+H).

Scheme 46:



Ex. 179

Step 1: CuI (7.6 mg, 0.04 mmol) was added to a solution of iodoaniline (200 mg, 0.39 mmol, Scheme 10a), diisopropylamine (0.169 mL, 1.2 mmol), $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol) and phenyl acetylene (0.132 mL, 1.2 mmol) in dimethylacetamide (2 mL), and the reaction was stirred at 40°C for 6 h. The reaction was diluted with sat. aqueous $NaHCO_3$ solution and EtOAc, then filtered reaction over celite. After rinsing the residue with EtOAc, the aqueous layer was extracted with EtOAc (3 x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give a residue that was subsequently subjected to silica gel chromatography (10→20 % EtOAc/hexanes) to provide the anilino acetylene intermediate (181 mg, 95%).

Step 2: Trifluoroacetic acid (0.2 mL) was added to a solution of the product from step 1 (181 mg, 0.37 mmol) in DCM (1 mL) at RT. After 2 h, the reaction was concentrated under vacuum. To part of the residue (50 mg, 0.13 mmol) in toluene (1 mL) was added $InBr_3$ (46 mg, 0.13 mmol.), and the reaction was heated to 115°C for 2 h. After removing volatiles under reduced pressure, the residue was suspended in MeOH, filtered through a PTFE-filter and the filtrate subjected to reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:TFA) to provide **Ex. 179** as its TFA salt (11.7 mg, 30%). LCMS for **Ex. 179** (conditions D): t_R = 1.98 min, *m/e* = 387.2 (M+H).

Scheme 47:

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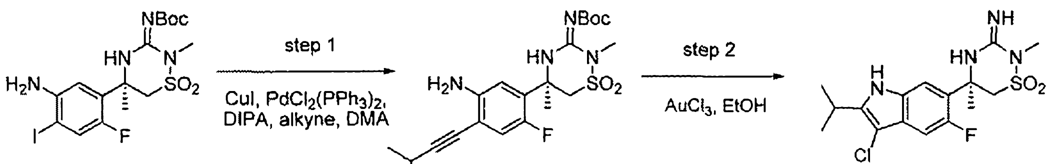
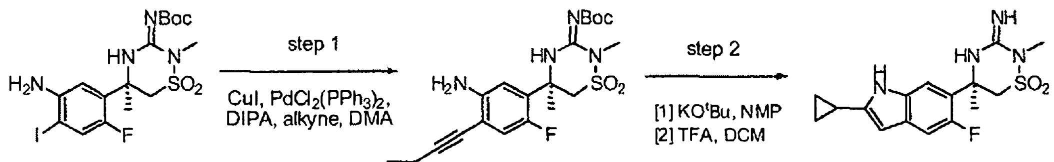


Ex. 180

Step 1: The anilino acetylene intermediate was prepared in the same manner as in Scheme 46, Step 1 except that isoproylacetylene was used instead of phenylacetylene.

Step 2: To the anilino acetylene intermediate from Step 1 (100 mg, 0.22 mmol) in EtOH (1 mL) was added $AuCl_3$ (133 mg, 0.44 mmol), and the reaction was heated to 70°C for 3 h. After removing volatiles under reduced pressure, the residue was suspended in MeOH, filtered through a PTFE-filter and the filtrate subjected to reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:TFA) to provide **Example 180** as its TFA salt (17.2 mg, 20%). LCMS for **Example 180** (conditions D): t_R = 2.04 min, *m/e* = 387.0 (M+H).

Scheme 48:



Ex. 181

Step 1: The anilino acetylene intermediate was prepared in the same manner as in Scheme 46, Step 1 except that cycloproylacetylene was used instead of phenylacetylene.

Step 2: To the anilino acetylene intermediate from Step 1 (54 mg, 0.11 mmol) in NMP (1 mL) was added potassium *tert*-butoxide (37 mg, 0.33 mmol), and the reaction was stirred for 18 h at RT. The mixture was then diluted with water and EtOAc, the organic layer was dried over Na_2SO_4, filtered, and concentrated to give a residue that was subsequently subjected to silica gel chromatography (10→25 % EtOAc/hexanes) to provide the Boc-protected indole intermediate (35 mg, 70%). This intermediate was deprotected according to the procedure described in Scheme 11b, Step 2, then subjected to reverse phase chromatography (C_{18}:

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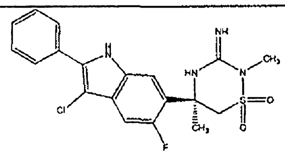
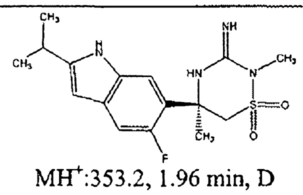
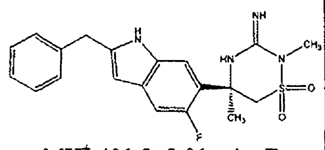
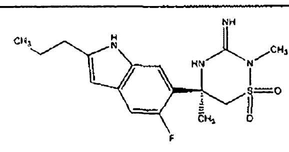
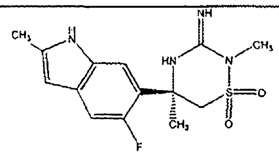
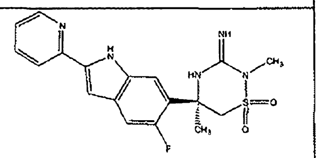
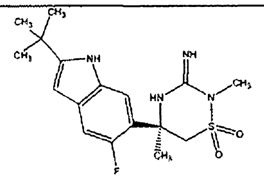
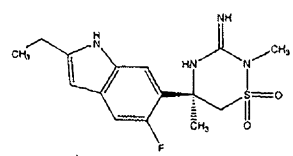
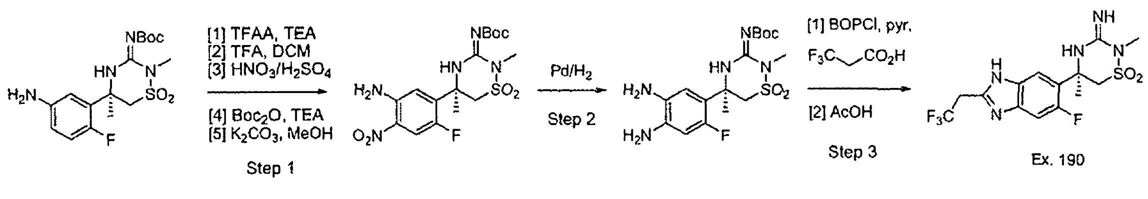
gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:TFA) to provide **Ex. 181** as its TFA salt. LCMS for **Ex. 181** (conditions D): t_R = 1.91 min, *m/e* = 351.2 (M+H).

Table XXIV: The following examples were prepared using a procedure similar to that described in Schemes 46, 47 and 48.

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)					
182	 MH^+:421.2, 2.07 min, D	**183**	 MH^+:353.2, 1.96 min, D	**184**	 MH^+:401.2, 2.01 min, D
185	 MH^+:353.0, 1.98 min, D	**186**	 MH^+:325.0, 1.85 min, D	**187**	 MH^+:388.0, 1.74 min, D
188	 MH^+:367.0, 2.02 min, D	**189**	 MH^+:339.0, 1.87 min, D		

Scheme 49:



Step 1: Trifluoroacetic anhydride (2.34 mL, 16.85 mmol) was added dropwise to a solution of aniline (5.5 g, 14.24 mmol, Scheme 10) and triethylamine (2.39 mL, 17.1 mmol) in DCM (30 mL) at 0°C. After stirring at RT for 2h, the reaction was quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give a solid (6.0 g), which was dissolved in DCM (10 mL) and

stirred with TFA (2 mL) for 1 h at RT. The reaction was concentrated under reduced pressure, and the residue dissolved in concentrated H_2SO_4 (9 mL). After cooling to 0°C, a mixture of fuming HNO_3/conc. H_2SO_4 (1.26 mL / 3 mL) was slowly added via addition funnel. After 40 min, the reaction was carefully quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc. The aqueous layer was extracted with EtOAc (3 x), and the combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was dissolved in DCM (100 mL), and triethylamine (7.93 mL, 56.56 mmol) and di-*tert*-butylcarbonate (3.09 g, 28.28 mmol) were added. After stirring for 18 h at RT, the reaction was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and the resulting residue was subjected to silica gel chromatography (gradient elution 80:20 to 75:25 hexanes:EtOAc) to give a mixture of acetylated and deacetylated material. To a solution of this mixture in MeOH (100 mL) at RT was added a solution of K_2CO_3 (5 g, 36 mmol) in water (20 mL), and the reaction stirred for 2h at RT. The reaction was quenched with 1 M HCl (aq) and diluted with EtOAc. The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure to give product (3.3 g, 54%).

Step 2: To a solution of the product from step 1 (600 mg, 1.39 mmol) in EtOAc/EtOH (10 mL / 10 mL) was added 5% Pd/C (300 mg) and the resulting mixture agitated in a Parr Shaker for 4 h under a 45-psi atmosphere of H_2. The catalyst was filtered off over celite, the residue rinsed with EtOAc, and the organic layer was concentrated under reduced pressure. The resulting residue was subjected to silica gel chromatography (gradient elution 95:5 to 90:10 hexanes:EtOAc) to give product (377 mg, 68%).

Step 3: To a solution of the product from step 2 (150 mg, 0.37 mmol) in pyridine (3 mL) was added 3,3,3-trifluoropropionic acid (0.032 mL, 0.37 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (188 mg, 0.74 mmol). After stirring for 18 h at RT, the volatiles were removed under vacuum, and the residue was subjected to silica gel chromatography (gradient elution 60:40 to 30:70 hexanes:EtOAc) to give a mixture of amides (102 mg, 54%). This mixture was dissolved in glacial AcOH (2 mL) and heated to 130°C for 1 h. The volatiles were removed under reduced pressure, and the resulting residue purified by reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1

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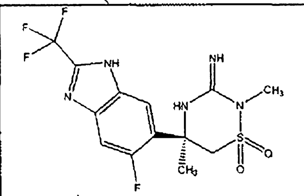
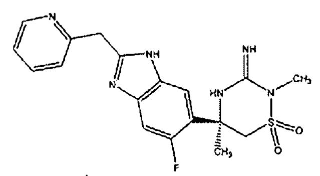
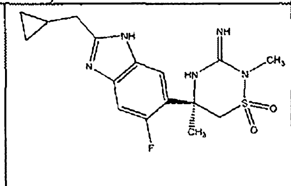
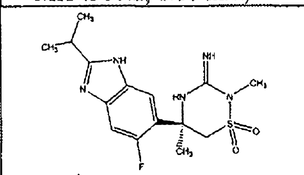
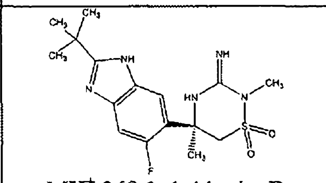
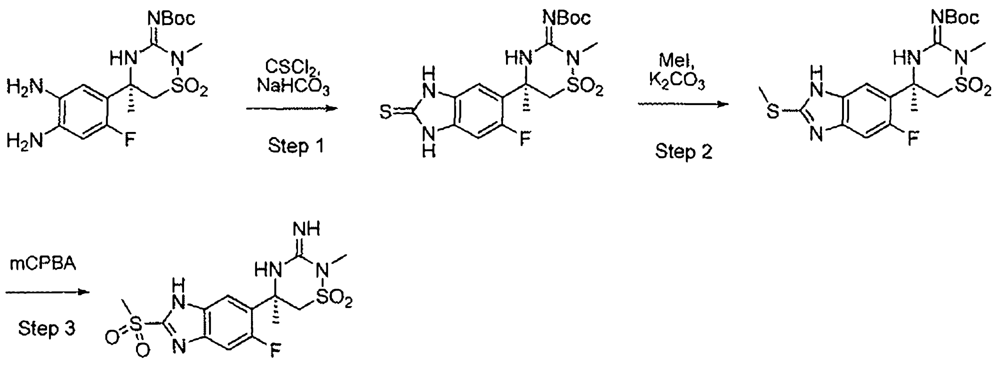
water:MeCN:TFA) to provide **Ex. 190** as its TFA salt. LCMS for **Ex. 190** (conditions D): t_R = 1.29 min, *m/e* = 394.2 (M+H).

Table XXV: The following examples were prepared using a procedure similar to that described in Scheme 49.

Examples (LCMS data: observed MH^+, HPLC retention time and LCMS method)					
191	 MH^+:380.2, 1.10 min, D	**192**	 MH^+:403.2, 1.18 min, D	**193**	 MH^+:366.2, 1.18 min, D
194	 MH^+:354.0, 0.97 min, D	**195**	 MH^+:368.0, 1.44 min, D		

Scheme 50:



Ex. 196

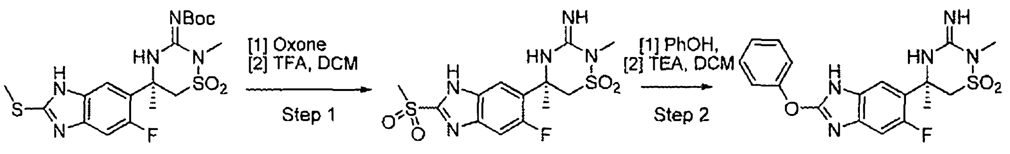
Step 1: Thiophosgene (0.320 mL, 4.21 mmol) was slowly added to a biphasic mixture of saturated aqueous $NaHCO_3$ and a solution of dianiline (1.566 g, 3.90 mmol, Scheme 49, Step 2) in DCM (15 mL). After 1 h at RT, the phases were separated and the aqueous layer extracted with DCM. The combined organic layers were washed with saturated aqueous

$NaHCO_3$, brine, then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the thiourea (1.604 g, 93%).

Step 2: Potassium carbonate (750 mg, 5.43 mmol) was added to a solution of the thiourea from Step 1 (1.604 g, 3.62 mmol) in DMF (18 mL) at RT. After 10 min, a solution of methyl iodide (0.23 mL, 3.68 mmol) in DMF (2 mL) was added over 10 min, and the reaction was stirred for 90 min. The reaction was quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc, and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure (1.725 g). The residue was subjected to silica gel chromatography (gradient elution 100:0 to 60:40 hexanes:EtOAc) to give the thiomethylurea (846 mg, 51%).

Step 3: Meta-chloroperoxybenzoic acid (72%, 150 mg, 0.63 mmol) was added at RT to a solution of the thiomethylurea from step 2 (100 mg, 0.21 mmol) in DCM (5 mL). After 1 h, the mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ (2 x), brine, and dried over $MgSO_4$ and concentrated under reduced pressure to give a residue (150 mg) that was further subjected to reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:TFA) to provide **Ex. 196** as its TFA salt. LCMS for **Ex. 196** (conditions D): t_R = 1.41 min, *m/e* = 390.0 (M+H).

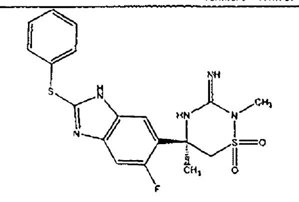
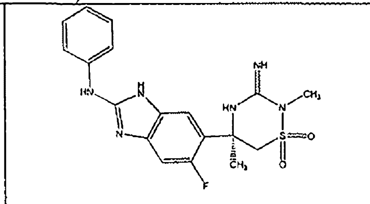
Scheme 51:



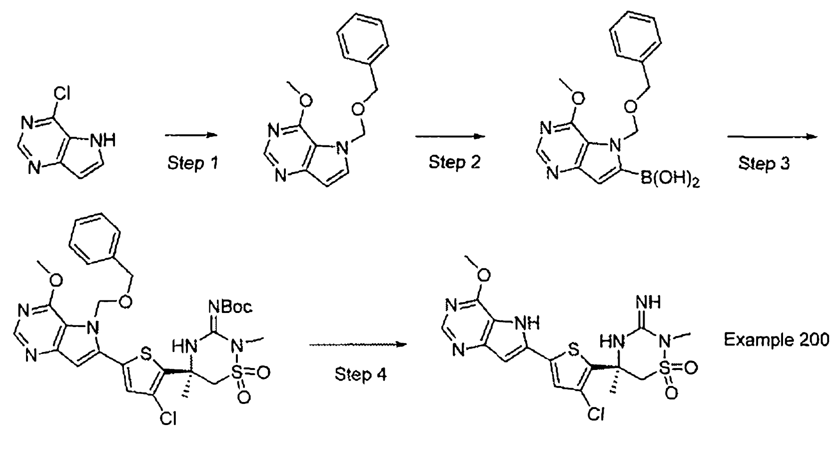
Step 1: A solution of oxone (potassium peroxymonosulfate, 3.2 g, 5.20 mmol) in water (10 mL) was added at RT to a solution of the thiomethylurea from Scheme 50, step 2 (755 mg, 1.65 mmol) in MeOH (10 mL). After 1 h, the mixture was filtered over celite, the filter cake rinsed with EtOAc, and the filtrate diluted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure to give the intermediate (681 mg) in 84% yield.

Step 2: The product of Step 1 (93 mg, 0.19 mmol) was deprotected using a method similar to that described in Scheme 11b step 2. After deprotection, the resulting residue was concentrated under vacuum, and triethylamine (0.132 mL, 0.95 mmol) and phenol (90 mg, 0.95 mmol) were added. The mixture was heated at 120°C for 22 h, then cooled to RT. The residue was subjected to reverse phase chromatography (C18: gradient elution, 90:10:0.1 to 0:100:0.1 water:MeCN:TFA) to provide **Ex. 197** as its TFA salt. LCMS for **Ex. 197** (conditions D): t_R = 1.78 min, *m/e* = 404.2 (M+H).

Table XXVI: The following examples were prepared using a procedure similar to that described in Scheme 51, replacing phenol in Step 2 with thiophenol or aniline, respectively.

Examples (LCMS data listed with each compound: observed MH^+, HPLC retention time and LCMS method)			
198	 MH^+:420.0, 1.76 min, D	**199**	 MH^+:403.2, 1.64 min, D

Scheme 52:



Step 1: To a suspension of 4-chloro-5H-pyrrolo[3,2-d]pyrimidine (1.53 g, 10.0 mmol) in 30 mL of THF was added NaH (560 mg, 14.0 mmol, 60% in mineral oil) by portion under N_2. After the mixture was cooled to 0 °C, benzyl chloromethyl ether (1.71 mL, 13.0 mmol) was added. Then the mixture was stirred at RT for 1 h (monitored by TLC 40% EtOAc/Hex). 8 mL of anhydrous MeOH was added into the reaction mixture followed by NaH (400 mg, 10.0 mmol, 60% mineral oil) by portion. The resulting mixture was stirred at RT overnight. After being quenched with sat. NH_4Cl, the mixture was extracted with EtOAc (3x). The organic

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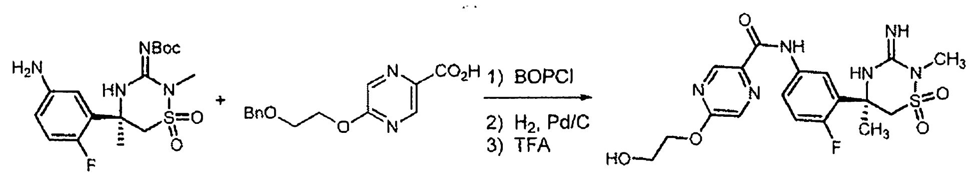
layer was washed with sat.$NaHCO_3$ (aq), brine, then dried ($MgSO_4$) and concentrated. Silica gel chromatography (elution with 0-30% EtOAc/Hex) afforded product 5-(benzyloxymethyl)-4-methoxy-5H-pyrrolo[3,2-d]pyrimidine (2.36 g).

Step 2 and 3: 5-(Benzyloxymethyl)-4-methoxy-5H-pyrrolo[3,2-d]pyrimidine was treated according to Scheme 31, Steps 2 and 3 to afford a biaryl product.

Step 4: To a solution of the material from step 3 (26 mg, 0.039 mmol) in 8 mL of DCM was added a suspension of $AlCl_3$ (52 mg, 0.39 mmol) in 4 mL of DCM. After the mixture was stirred at RT for 1.5 h, 3 mL of water was added. The reaction mixture was basified with $NaHCO_3$ and extracted with DCM (3x). The organic layer was washed with brine and dried (Na_2SO_4), and concentrated. The crude residue was purified by preparative TLC (10% 2N NH_3 MeOH in DCM) to provide **Example 200** (10 mg). LCMS (conditions E): t_R = 0.60 min, *m/e* = 441.0 (M+H).

Scheme 53:



Ex. 201

Step 1: The aniline from Scheme 10 and the acid (Entry 3, Table IVb) were coupled using a procedure similar to that described in Scheme 11b step 1.

Step 2: To a pressure vessel containing a solution of the amide from step 1 (181 mg, 0.28 mmol) in EtOH (15 mL) was added 10% Pd/C (50% water-Degussa Type). The vessel was sealed, evacuated and backfilled with N_2 (3x). The vessel was then evacuated and backfilled with H_2 (3x). The vessel was pressurized with H_2 to 50 psi and shaken at RT for 6 hours. The mixture was purged with N_2, filtered through Celite and concentrated. The crude product was purified via flash chromatography (SiO_2: gradient elution 100:0 to 1:1 hex.: EtOAc) to afford the hydroxy compound (24 mg, 15%).

Step 3: **Example 201** was prepared from the product of step 2 (24 mg) using a procedure similar to that described in Scheme 11b step 2. The crude product was purified via reverse phase flash chromatography (C_{18}; gradient elution 95:5:0.1 to 0:100:0.1 H_2O:MeCN:formic acid) to afford **Example 201** (11 mg, 51%) as the formate salt.

LC/MS Conditions

Method A:

Column: Gemini C-18, 50 x 4.6 mm, 5 micron, obtained from Phenomenex.

Mobile phase: A: 0.05% Trifluoroacetic acid in water

B: 0.05% Trifluoroacetic acid in acetonitrile

Gradient: 90:10 to 5:95 (A:B) over 5 min.

Flow rate: 1.0 mL/min

UV detection: 254 nm

ESI-MS: Electro Spray Ionization Liquid chromatography-mass spectrometry (ESI-LC/MS) was performed on a PE SCIEX API-150EX, single quadrupole mass spectrometer.

Method B:

Column: Waters SunFire C-18 4.6mm x 50 mm

Mobile phase: A: 0.05% Trifluoroacetic acid in water

B: 0.05% Trifluoroacetic acid in acetonitrile

Gradient: 90:10 (A:B) for 1 min, 90:10 to 0:100 (A:B) over 4 min, 0:100 (A:B) for 2 min.

Flow rate: 1.0 mL/min

UV detection: 254 nm

Mass spectrometer: Finnigan LCQ Duo electrospray.

Method C:

Column: Agilent Zorbax SB-C18 (3.0 x 50 mm) 1.8 uM

Mobile phase: A: 0.05% Trifluoroacetic acid in water

B: 0.05% Trifluoroacetic acid in acetonitrile

Gradient: 90:10 (A:B) for 0.3 min, 90:10 to 5:95 (A:B) over 5.1 min, 5:95 (A:B) for 1.2 min.

Flow rate: 1.0 mL/min

UV detection: 254 and 220 nm

Mass spectrometer: Agilent 6140 quadrupole.

Method D:

Column: Agilent Zorbax SB-C18 (3.0 x 50 mm) 1.8 uM

Mobile phase: A: 0.05% Trifluoroacetic acid in water

B: 0.05% Trifluoroacetic acid in acetonitrile

Gradient: 90:10 (A:B) for 0.3 min, 90:10 to 5:95 (A:B) over 1.2 min, 5:95 (A:B) for 1.2 min.

Flow rate: 1.0 mL/min

UV detection: 254 and 220 nm

Mass spectrometer: Agilent 6140 quadrupole.

Method E:

Column: Agilent Zorbax SB-C18 (3.0 x 50 mm) 1.8 uM

Mobile phase: A: 0.05% Trifluoroacetic acid in water

B: 0.05% Trifluoroacetic acid in acetonitrile

Gradient: 90:10 (A:B) for 0.1 min, 90:10 to 5:95 (A:B) over 1.0 min, 5:95 (A:B) for 0.36 min.

Flow rate: 2.0 mL/min

UV detection: 254 and 220 nm

Mass spectrometer: Agilent 6140 quadrupole.

Method F:

Column: Agilent Zorbax SB-C18 (3.0 x 50 mm) 1.8 uM

Mobile phase: A: 0.05% Formic acid in water

B: 0.05% Formic acid in acetonitrile

Gradient: 90:10 to 5:95 (A:B) over 1.5 min, 5:95 (A:B) for 1.2 min.

Flow rate: 1.0 mL/min

UV detection: 254 and 220 nm

Mass spectrometer: Agilent 6140 quadrupole.

ASSAYS

The protocol that was used to determine the recited values is described as follows.

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 was used to determine IC_{50} values for inhibitors of the soluble human BACE1 catalytic domain. This assay monitored 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 contained an N-terminal QSY7 moiety that served as a quencher of the C-terminal Europium fluorophore (620 nm Em). In the absence of enzyme activity, 620 nm fluorescence was 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 was manifested as a suppression of 620 nm fluorescence.

Varying concentrations of inhibitors at 3x the final desired concentration in a volume of 10ul were 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 were 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 were incubated at 30° C for 1.5 hours. The 620nm fluorescence was then read on a Rubystar HTRF plate reader (BMG Labtechnologies) using a 50 μs delay followed by a 400 millisecond acquisition time window. Inhibitor IC_{50} values were derived from non-linear regression analysis of concentration response curves. K_i values were 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.

All of the example compounds of the invention were tested (except for Examples 8, 9, 10, 14b, 14c, 14d, 14e, and 14f) in this BACE-1 assay and exhibited K_i values of less than about 7.5 μM and greater than about 0.5 nM in this assay. All of the example compounds except for examples 19, 40x, 98, 101, and 189 exhibited K_i values of less than about 5 μM in this assay. Some of the example compounds exhibited K_i values of less than about 4 μM in this assay; others less than about 3 μM in this assay; others less than about 2 μM in this assay;

others less than about 1 μM in this assay; others less than about 500 nM in this assay; others less than about 300 nM in this assay; others less than about 200 nM in this assay; others less than about 100 nM in this assay; others less than about 50 nM in this assay; others less than about 10 nM in this assay; others less than about 5 nM in this assay. The compound of Example 45 exhibited a Ki value of about 26 nM in this assay. The compound of Example 47 exhibited a Ki value of about 6.5 nM in this assay.

BACE-2 Assay

Inhibitor IC_{50s} at purified human autoBACE-2 were 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 were 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 was 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 was present at 5% final concentration in the assay. Following laser excitation of sample wells at 320 nm, the fluorescence signal at 620 nm was collected for 400 ms following a 50 μs delay on a RUBYstar HTRF plate reader (BMG Labtechnologies). Raw RFU data was normalized to maximum (1.0 nM BACE/DMSO) and minimum (no enzyme/DMSO) RFU values. IC_{50s} were 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} were obtained when using raw RFU data. The K_i values were calculated from the IC_{50} using the Cheng-Prusoff equation.

All of the example compounds of the invention were tested in this BACE-2 assay except for the following examples: 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 14b, 14c, 14d, 14e, 14f, 15, 16, 17, 19, 40a, 40b, 40ea, 40h, 40o, 40p, 40q, 40u, 40w, 40x, 40y, 40aa, 40au, 40cc, 40co, 40cp, 40cy, 40dj, 40gy, 40gz, 40ha, 40hb, 40hc, 40ih, 41, 43, 45, 49, 60, 61, 67, 68, 69, 70, 71, 73, 74, 75, 77, 85, 86, 88, 89, 90, 91, 96, 97, 98, 99, 100, 101, 102, 103, 105, 108, 109, 109, 115, 116, 117, 122, 123, 125, 130b, 137, 138, 143, 145, 161b, 176, 179, 182, 189, 192, 194, 195, 199. Of the example compounds of the invention that were tested in this BACE-2 assay, all exhibited K_i values of less than about 900 nM and greater than about 0.04 nM in this assay. All of the example compounds that were tested in this assay, except for examples 40ex, 40do, 160, 161a, 164, and 197 exhibited K_i values of less than about 500 nM in this assay. Some of the example compounds exhibited K_i values of less than about 200 nM in this assay; others less than about 100 nM in this assay; others less than about 50 nM in this assay; others less than about 25 nM in this assay; others less than about 10 nM in this assay; others less than about 5 nM in this assay; others less than about 1 nM in this assay; others less than about 0.5 nM in this assay. The compound of Example 47 exhibited a Ki value of about 1 nM in this assay.

The novel iminothiadiazine dioxide compounds of the invention have surprisingly been found to exhibit properties which are expected to render them advantageous as BACE inhibitors and/or for the various methods of used herein.

Cortical $A\beta_{40}$

The iminothiadiazine dioxide compounds of the invention have been found, surprisingly and advantageously, to exhibit improved efficacy in lowering $A\beta_{40}$ production in the cerebral cortex than their iminopyrimidone analogs. The following procedures were used. Results are shown in the table below.

Rat Tissue Collection

Male CD rats (~100 g; Crl:CD(SD); Charles River Laboratories, Kingston, NY) were group housed and acclimated to the vivarium for 5-7 days prior to use in a study. Compounds were formulated in 20% hydroxypropyl-β-cyclodextrin and administered orally with a dosing volume of 5 ml/kg for rats. Three h after drug administration, rats were euthanized with excess CO_2. The brain was removed from the skull and immediately frozen on dry ice. All tissues were stored at -70°C until Aβ quantification.

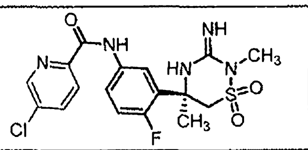
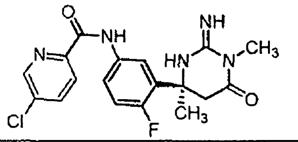
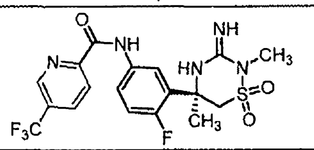
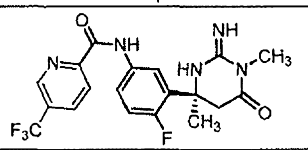
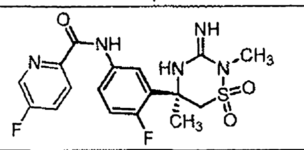
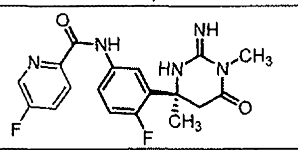
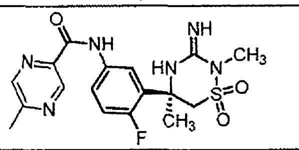
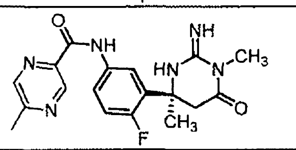
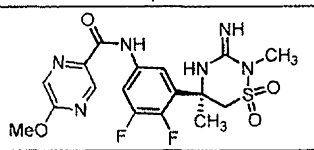
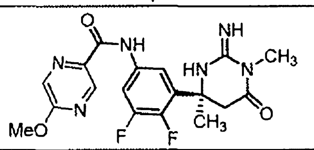
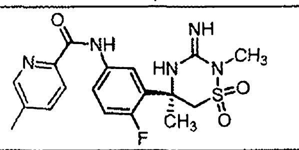
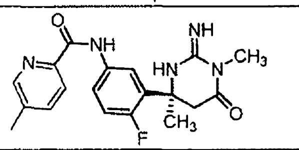
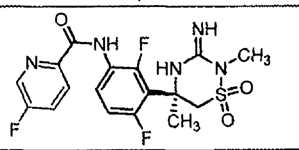
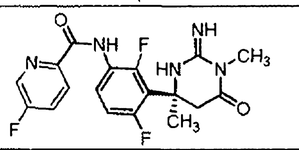
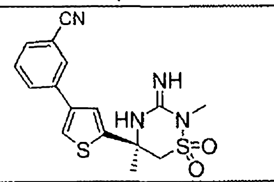
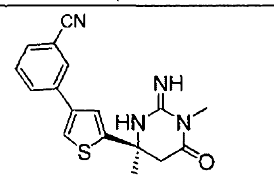
Determination of $A\beta_{40}$ Levels in Rat Cortex by ELISA

The measurement of endogenous rat Aβ1-40 (Aβ40) in cortex relied on the 585 antibody (Ab585, BioSource), catalogue no. NONO585), which specifically recognizes the N-terminal sequence of rodent Aβ40, and the monoclonal antibody, G2-10, which specifically recognizes the free C-terminus of Aβ40. Ab585 was labeled with biotin (b-Ab585) by first dialyzing the antibody sample extensively versus PBS (pH 7.8) to remove impurities, followed by dilution to between 1 and 2 mg/mL protein concentration. EZ-Link Sulfo-NHS-LC-Biotin (Pierce) was dissolved in PBS (pH 7.8) at a concentration of 1 mg/mL immediately prior to use. Ab585 was labeled with EZ-Link Sulfo-NHS-LC-biotin using a 10:1 biotin:antibody ratio by incubation at room temperature for 1 hour. The labeling reaction was quenched by addition of 1.0 M glycine to a final concentration of 0.1 M followed by 10 minute incubation at room temperature. Glycine was removed by extensive dialysis versus PBS.

The use of the Luminex based immunoassay for measurement of rat cortical Aβ40 required that the G2-10 antibody be labeled with Bio-Plex COOH Bead 25 (Bio-Rad laboratories catalogue no. 171506025). The antibody was coupled to the beads using the Bio-Plex Amine Coupling Kit (Bio-Rad) as per the manufacturer's recommendations.

Rat cortex Aβ40 levels were measured from guanidine HCl extracts of individual rat cortices using a Luminex-based immunodetection assay. Rat brains were thawed briefly at 37° C and both mid- and hindbrain regions were removed. The remaining material, consisting primarily of cortex (~800 mg) was carried through the guanidine extraction procedure. Cortices were added to a 2 ml BioPur tube (Eppendorf) along with a 6.35 mm chrome-coated steel ball and 1.0 ml of sucrose homogenization buffer (20 mM HEPES [pH 7.5], 50 mM KCl, 50 mM sucrose, 2 mM EDTA, 2 mM EGTA supplemented with complete protease inhibitors [Roche, EDTA-free]). Samples were then homogenized by agitation for 1.5 min at 30 cylces/sec in a MM300 tissue mixer (Retsch®). The resulting cortical homogenate was extracted with guanidine-HCl by mixing 67 μl of homogenate with 133 μl of 5 M Guanidine HCl, 50 mM Tris HCl (pH 8.0). To maximize the efficiency of Aβ extraction, samples were vortexed and then sonicated for 2 minutes in an ice bath using an Ultrasonics XL cup horn sonicator at a power setting of 8 (Heat Systems, Inc.). Insoluble material was removed by ultracentrifugation using a using a TLA-55 rotor in a TL-100 benchtop centrifuge (Beckman) at 100,000xg for 30 minutes. The resulting supernatant was then either diluted 1:10 in 5 M guanidine HCl, 0.05 M Tris HCl (pH 8.0) for protein analysis (BCA protein assay, Pierce Biochemicals) or assayed neat for Aβ40 levels. The Luminex rodent Aβ40 assay was performed as follows. First, 96 well filter binding plates (Millipore, catalogue # MSBVN12) were wetted with 100 μl of 1x LAβ40 buffer (0.05 M HEPES [pH 7.5], 0.2% BSA, 0.2% Tween-20, 0.15 M NaCl) by vacuum filtration on a Millipore 96-well manifold. The plate bottom was sealed and 100 μl of 1x LAβ40 buffer was added to each well followed by addition of 50 μl each of G2-10:COOH beads (1000 beads/well) and 50 μl b-Ab585 at 0.5 μg/ml in 1 x LAβ40 buffer. Guanidine HCl was added to synthetic rodent Aβ40 standards in order to control for the effect of guanidine in brain extracts on the assay performance. Ten microliters of cortical extract, rodent Aβ40 standards or cortical extract from amyloid precursor protein knockout mice (to define background immunoreactivity) was added to each well. Plates were covered and incubated overnight at 4°C. Following the incubation, wells were cleared by vacuum and washed twice with 100 μl of 1x LAβ40 buffer on a Millipore manifold. Phycoerythrin-conjugated streptavidin (PE-strepavidin, BioRad) for detection of bound b-Ab585 was diluted 100-fold in 1x LAβ40 buffer and 50 μl was added to each well and incubated for 1 hour at room temperature with shaking. Unbound PE-streptavidin was removed by three 100 μl washes with cytokine assay buffer (BioRad). Washed beads were resuspended in 125 μl of cytokine assay buffer by shaking on a microplate shaker. Plates were read on a BioPlex suspension array system (BioRad) with target region beads set to 40 beads/region and the upper end of the DD gate set to 10,000. Raw fluorescence data was analyzed using nonlinear regression analysis and absolute Aβ40 levels were extrapolated from the standard curve using GraphPad Prism 4.0.2. Absolute amounts of $A\beta_{1-40}$ are expressed as picograms per micrograms protein. Percent change values for each compound were calculated by normalization of the average absolute cortical Aβ1-40 level in each compound treated cohort to the average absolute cortical Aβ1-40 levels in the vehicle cohort. Comparative results are shown in the table below. "NT" means not tested.

Change in Cortical $A\beta_{40}$ in Rats 3 h After a 10 mg/kg Oral Dose of Compound					
Iminothiadiazine Dioxide				**Iminopyrimidinone**	
Ex. #	**Structure**	BACE-1 Ki (nM) / BACE-2 Ki (nM)	**Change in rat cortex $A\beta_{40}$**	**Structure**	**Change in rat cortex $A\beta_{40}$**

Change in Cortical Aβ$_{40}$ in Rats 3 h After a 10 mg/kg Oral Dose of Compound					
Iminothiadiazine Dioxide				Iminopyrimidinone	
Ex. #	Structure	BACE-1 Ki (nM) / BACE-2 Ki (nM)	Change in rat cortex Aβ$_{40}$	Structure	Change in rat cortex Aβ$_{40}$
34		0.949 / 0.22	-51%		-19%
26		1.261 / 2.46	-33%		0%
25		1.753 / 0.37	-49%		-11%
36		10 / 4.85	-25%		NT
40di		1.05 / 2.15	-38%		+5%
35		3.0 / 0.45	NT		NT
173		4.88 / 0.47	-27%		-3%
45		25.6 / NT	NT		-5%

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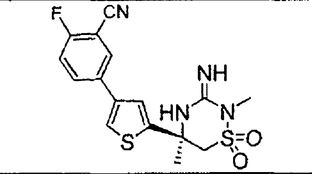
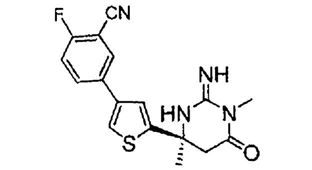
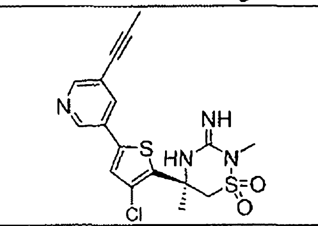
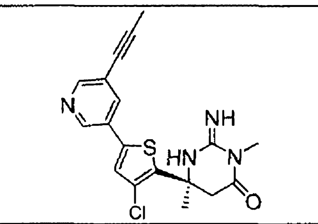
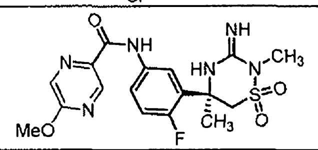
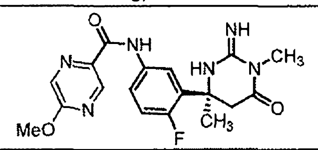
Change in Cortical $A\beta_{40}$ in Rats 3 h After a 10 mg/kg Oral Dose of Compound					
Iminothiadiazine Dioxide				Iminopyrimidinone	
Ex. #	Structure	BACE-1 Ki (nM) ----- BACE-2 Ki (nM)	Change in rat cortex $A\beta_{40}$	Structure	Change in rat cortex $A\beta_{40}$
46		46 ------ 8.23	NT		NT
52		2.387 ------ 0.37	-53%		-54%
40ai		1.64 ------ 1.99	-51%		

Caco-2 Bi-Directional Permeability

It has been found that compounds of the invention exhibit unexpectedly reduced susceptibility to efflux by P-glycoprotein (P-gp) versus compounds having an iminopyrimidinone moiety that are otherwise structurally identical. P-gp is found, among other locations, at the blood-brain barrier, and reduced susceptibility to efflux by this protein is a desirable characteristic of centrally acting compounds (A. Schinkel *Advanced Drug Delivery Reviews* **1999**, *36*, 179-194). The following procedures were used. Results are shown in the table below.

Caco-2 Bi-directional Permeability

The bi-directional permeability with efflux potential of selected compounds of the invention vs. otherwise structurally identical iminopyrimidinones (collectively referred to as test compounds, shown in the table below) were assessed using Caco-2 cell line. The Caco-2 cells were maintained in DMEM (Dulbecco's Modified Eagle Medium) containing 10% fetal bovine serum, 1% non-essential amino acids, 2 mM L-glutamine, and 1% penicillin-streptomycin in an incubator at ~37°C in an atmosphere of 5% CO_2 and about 90%

relative humidity. The cell culture medium was changed three times weekly. Caco-2 cell monolayers were grown on polyethylene terephthalate filters using 24-well BD Falcon™ Cell Culture Insert Plates (0.33 cm^2 insert area, 1 μm pore size; BD BioSciences, Bedford, MA). The culture medium of the plate was changed every other day until used for the transport experiment (21-28 days post seeding).

The transport buffer (TM) was Hank's balanced salt solution (HBSS) with 10 mM HEPES and 25 mM glucose (pH 7.4) for dosing and TM with 4% bovine serum albumin for receiver (pH 7.4). The bi-directional permeability of the test compounds were tested at concentrations of 1, 10 and 100 μM was measured in triplicate with 2-hr incubation. The cell monolayer integrity was monitored with pre- and post-experimental trans-epithelial electrical resistance and post-experimental Lucifer Yellow (LY) permeability with 1 hr incubation. Test article samples were analyzed using LC-MS/MS and the concentration of LY was measured using a Perkin Elmer HTS 7000 Plus Bio Assay Reader (Waltham, MA) with an excitation and emission wavelength of 485 nm and 538 nm, respectively.

The apparent permeability, recovery and efflux ratio values were calculated using the following equations:

$$P_{app}\,(nm/s) = \frac{dM/dt}{S * C_0} = \frac{dC_R/dt * V_R}{S * C_0} * 10^7$$

$$\text{Efflux Ratio} = \frac{P_{app\_BLtoAP}}{P_{app\_APtoBL}}$$

$$\text{Total Recovery}\,(\%) = \frac{C_{D,\,final}}{C_0} \times 100 + \frac{\text{Receiver Accumulated Amount}}{C_0 * V_D} \times 100$$

where,

dC_R/dt: The slope of the accumulative concentration in the receiver compartment versus time incubation ($\mu M \cdot s^{-1}$)

C_{0hr}: Donor concentration (μM) immediately after dosing

$C_{D,\,final}$: Donor concentration (μM) at the end of incubation

S: Membrane surface area (cm^2)

V_D: Volume of donor compartment (mL)

V_R: Volume of receiver compartment (mL)

P_{app_BLtoAP}: Permeability from basolateral (BL) to apical (AP) transport

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P_{app_APtoBL}: Permeability from AP to BL transport

Evaluation of P-gp efflux inhibition using Caco-2 bi-directional permeability assay

A preliminary study to assess the compounds in the table below as potential P-gp substrates were performed using the Caco-2 bi-directional transport assay. Digoxin was used as a probe P-gp substrate. The ^{3}H-digoxin dosing solution was prepared by diluting a digoxin DMSO stock with TM and/or the inhibitor solutions and titrating with ^{3}H-digoxin (final digoxin concentration was 5 μM with 0.5 μCi/mL radioactivity). Two concentrations of test compounds (5 and 50 μM) were prepared by diluting a DMSO stock solution with TM (pH 7.4). The Caco-2 bi-directional permeability of ^{3}H-digoxin with or without test compound as inhibitor was measured as described in the Caco-2 bi-directional permeability section. The total radioactivity for each sample was counted using a Packard 2250CA Tri-Carb Liquid Scintillation Analyzer.

The percentage of digoxin efflux inhibition was calculated using the following equation:

$$\%\_\text{Inhibition} = \left(1 - \frac{P^{\text{inhibitor}}_{\text{app\_BLtoAP}} - P^{\text{inhibitor}}_{\text{app\_APtoBL}}}{P_{\text{app\_BLtoAP}} - P_{\text{app\_APtoBL}}}\right) * 100$$

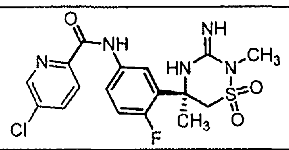
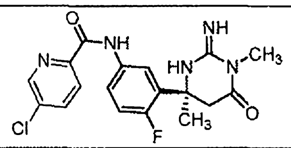
where,

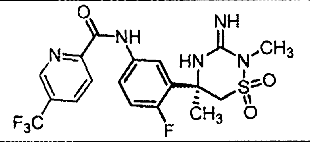
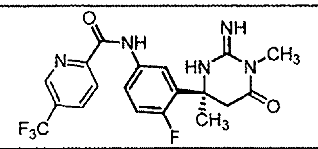
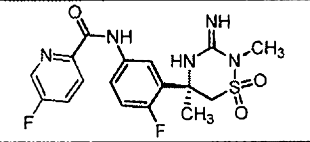
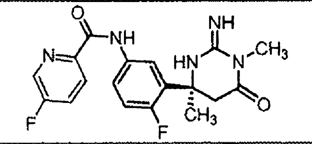
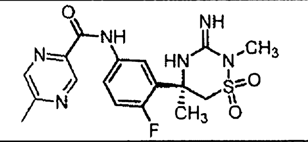
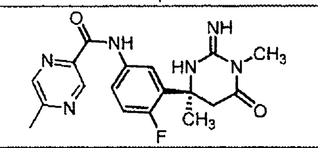
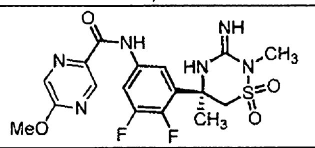
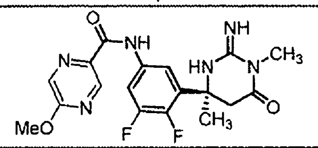
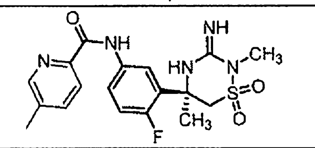
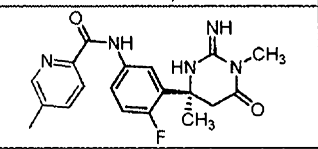
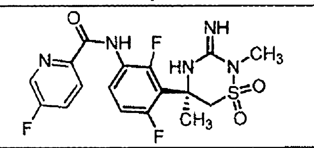
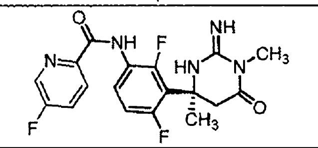
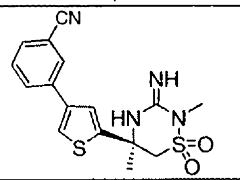
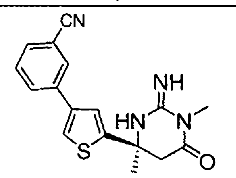
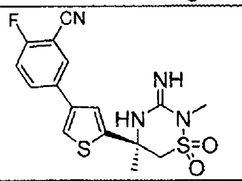
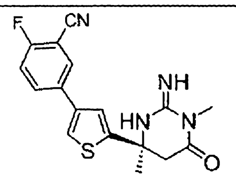
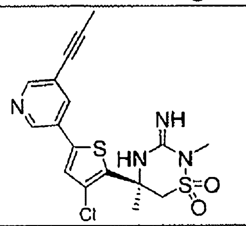
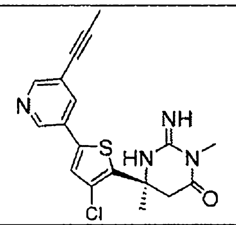
P_{app_BLtoAP}: Digoxin permeability from BL to AP transport

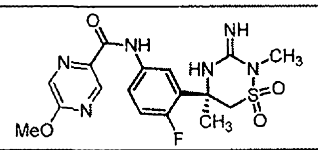
P_{app_APtoBL}: Digoxin permeability from AP to BL transport

$P^{inhibitor}_{app\_BLtoAP}$: Digoxin permeability with inhibitor from BL to AP transport :

Digoxin permeability with inhibitor from AP to BL transport

Permeability (AP→BL) and efflux ratio in Caco-2 cells *(AP = apical, BL = basolateral)*						
Iminothiadiazine Dioxide				**Iminopyrimidinone**		
Ex. #	**Structure**	**Caco-2 AP→BL (nm/s)**	**Caco-2 Efflux ratio**	**Cmpd. #**	**Caco-2 AP→BL (nm/s)**	**Caco-2 Efflux ratio**
34		118	3.1		0	NA

26		89	2.9		17	11.3
25		128	2.4		22	10.6
36		54	3.3		11	12.9
40di		136	2.0		65	3.2
35		151	2.1		0	NA
173		126	2.2		25	6.1
45		226	1.4		174	2.6
46		189	1.9		136	2.6
52		278	1.6		153	2.4

40ai		133	1.8	NA		

Solution Stability

The iminothiadiazine dioxide compounds of the invention have been found, surprisingly and advantageously, to exhibit improved solution stability (e.g., by resistence to hydrolysis) compared with structurally similar iminopyrimidinones. The following comparative procedures were used. Results are reported as Examples A and B below.

A 1.05 mg/mL stock solution (5 mL) of **Ex. 45** in MeOH was prepared. From the stock solution was taken out 1.25 mL and diluted to 25 mL with the addition of 23.75 mL of 10 mM phosphate buffer (pH 7.4)/MeOH (70/30 v/v). This new solution was split into three. One solution was incubated at 4°C, another incubated at 25°C and the third incubated at 40°C. Each solution was analyzed by LC/MS after day 1, day 2 and day 6 and compared to a standard calibration curve for **Ex. 45.**

Example A: Stability Studies Comparing Example 45 With Compound Z:

In the following study, the solution stability of the compound of Example 45 was measured and compared to that of Compound Z. The compound of Example 45 is an iminothiadiazine dioxide compound of the invention. Compound Z is the corresponding iminopyrimidinone compound. The structures of the compound of Example 45 and of Compound Z are shown below. Studies were performed in aqueous pH 7.4 buffer containing methanol at 4 °C, 25°C and 40°C. At 4°C, the compound of Example 45 showed 0.93% degredation after 6 days while Compound Z showed 18.3% degredation after 1 day. At 25°C, the compound of Example 45 showed 7.4 % degredation after 6 days while Compound Z showed 53.87% degredation. At 40°C, the compound of Example 45 showed 30.71% degredation after 6 days while Compound Z showed 79.93% degredation after 1 day.

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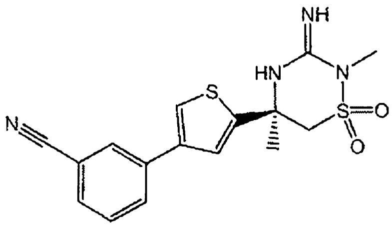
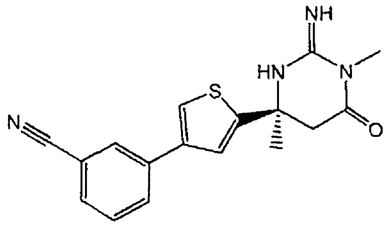


Example 45



Compound Z
(US20060111370)

Solution Stability for Ex. 45 in pH 7.4					
Condition	4°C				
Batch Number	7				
Time, days	Initial	1	2	6	
Assay (Area %)	99.82	99.69	99.04	98.89	
Condition	25°C				
Assay (Area %)	99.82	98.45	96.07	92.43	
Condition	40°C				
Assay (Area %)	99.82	96.32	89.70	69.11	-
a: Results by area normalization ND = Not Detected. (-) stands for > 20 % degradation					

Solution Stability for Compound Z in pH 7.4					
Condition	4°C				
Batch Number	7				
Time, days	Initial	1	2	6	
Assay (Area %)	88.15	69.84	-	-	-

Condition	**25°C**				
Assay (Area %)	88.15	34.28	-	-	-
Condition	**40°C**				
Assay (Area %)	88.15	8.22	-	-	-
a: Approximate RRT for related compounds. Results by area normalization ND = Not Detected. (-) stands for > 20 % degradation					

Stock solutions of the tested compounds were prepared by dissolving about 3 mg of each compound in 3 mL of acetonitrile. Standards for test compounds were prepared by diluting 1 mL of the stock solution with an additional 4 mL of acetonitrile. These standards were stored at 4°C. Samples were prepared by diluting 1 mL of the stock solution with 4 mL of 50 mM pH 7.4 phosphate buffer. These samples were stored at 25°C in the absence of light. Standards and samples were analyzed by LC/MS initially and at day 1, day 4, and day 6.

HPLC conditions:
Mobile phase A: 10 mM pH 5 ammonium acetate buffer : methanol (90 : 10)
Mobile phase B: 10 mM pH 5 ammonium acetate buffer : methanol (10 : 90)
Column: Zorbax SB-Phenyl 4.6 x 50 mm, 1.8 µm
Column temperature: 40°C
Flow: 0.8 mL/min.
Gradient:

Time (min.)	% B
0	40
9	100
11	100

Detectors: UV at 220 nm and 236 nm
MS, ES ionization, positive mode, for identification only at final time point.

The terms reported in the tables below have the following meanings:

Area % is the integration of peak from HPLC as reported by Waters Empower II software.

RRT is the relative retention time of new product compared to the standard of the test compound.

Formula for RRT is:

$$\frac{\text{Retention time of new product}}{\text{Retention time of standard}}$$

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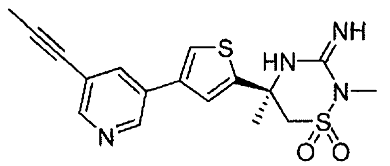
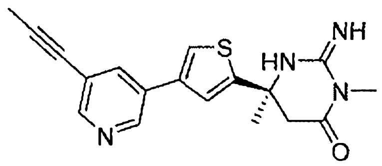
M + 1 is the mass observed including protonation (+ 1 mass unit).
ND stands for no peak detected by the UV detector.
* stands for no ion detected by the mass spectrometer.

Example B: Stability Studies Comparing Example 47 With Compound Y:

In the following study, the solution stability of the compound of Example 47 was measured and compared to that of Compound Y. The compound of Example 47 is an iminothiadiazine dioxide compound of the invention. Compound Y is the corresponding iminopyrimidinone compound. The structures of the compound of Example 47 and of Compound Y are shown below. Studies were performed in pH 7.4 buffer at 25°C. Under these conditions, the compound of Example 47 showed *0*% hydrolysis product after 6 days while Compound Z showed 12.45% hydrolysis product.



Example 47



Compound Y
(US 20070287692)

Example 20: Free base MW = 374.09

	Peak Description	RRT	M + 1	Area %, Initial	Area %, Day 1	Area %, Day 4	Area %, Day 6
Standard	Example 47	1.00	375.10	98.53	98.55	98.52	98.52
	Unknown	1.49	*	1.47	1.45	1.48	1.48
Sample at pH 7.4	Example 47	1.00	375.10	98.55	98.56	98.53	98.53
	Unknown	1.49	*	1.45	1.44	1.47	1.47

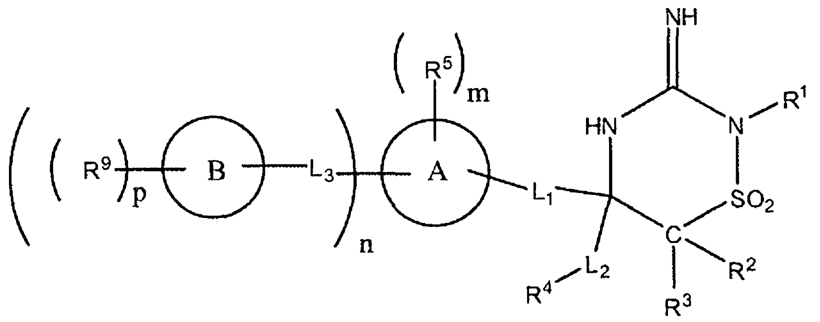
Compound Y: Free Base MW = 338.12

	Peak Description	RRT	M + 1	Area %, Initial	Area %, Day 1	Area %, Day 4	Area %, Day 6
Standard	Compound Y	1.00	339.15	100.0	100.0	100.0	100.0
Sample at pH 7.4	Compound Y	1.00	339.10	99.36	96.89	93.02	87.55
	Hydrolysis product	0.76	357.10	0.64	3.11	6.98	12.45

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

CLAIMS:

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



(I)

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-, $-NHS(O)_2-$, $-S(O)_2NH-$, -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;

R^1 is selected from the group consisting of: H, alkyl, heteroalkyl, heterohaloalkyl, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl, heterocycloalkylalkyl-, aryl, arylalkyl-, heteroaryl, and heteroarylalkyl-,

wherein each of said alkyl, heteroalkyl, heterohaloalkyl, cycloalkyl, cycloalkylalkyl-, heterocycloalkyl, heterocycloalkylalkyl-, aryl, arylalkyl-, heteroaryl, and heteroarylalkyl- of R^1 is unsubstituted or substituted with one or more independently selected R^{10} groups;

R^2 is selected from the group consisting of H, halo, alkyl, haloalkyl, and heteroalkyl,

wherein each of said alkyl and said haloalkyl of R^2 is unsubstituted or substituted with one or more independently selected R^{10} groups;

R^3 is selected from the group consisting of H, halo, alkyl, haloalkyl, and heteroalkyl,

wherein each of said alkyl and said haloalkyl of R^2 is unsubstituted or substituted with one or more independently selected R^{10} groups;

R^4 is selected from the group consisting of alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl,

wherein each of said alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl of R^4 is unsubstituted or substituted with one or more independently selected R^{10} groups;

ring A is selected from the group consisting of monocyclic aryl, monocyclic heteroaryl, monocyclic cycloalkyl, monocyclic cycloalkenyl, monocyclic heterocycloalkyl, monocyclic heterocycloalkenyl, and a multicyclic group;

each ring B (when present) is independently selected from the group consisting of monocyclic aryl, monocyclic heteroaryl, monocyclic cycloalkyl, monocyclic cycloalkenyl, monocyclic heterocycloalkyl, monocyclic heterocycloalkenyl, and a multicyclic group;

each R^5 (when present) is independently selected from the group consisting of halo, -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, haloalkoxy, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl,

wherein each said alkyl, haloalkyl, haloalkoxy, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl of R^5 (when present) is optionally

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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, $-SF_5$, $-OSF_5$, $-NO_2$, $-N(R^8)_2$, $-OR^7$, $-C(O)N(R^8)_2$, 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,

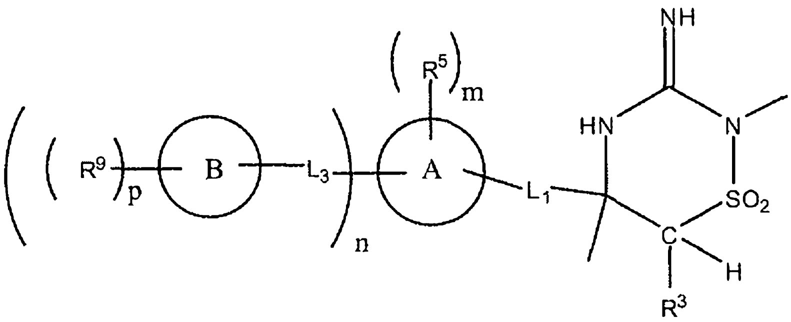
wherein each said alkyl, haloalkyl, haloalkoxy, heteroalkyl, alkenyl, alkynyl, and cycloalkyl of R^{10} (when present) is optionally independently unsubstituted or further substituted with one or more independently selected groups selected from the group consisting of lower alkyl, lower alkenyl, lower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

2. A compound of claim 1, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, wherein:
R^1 is selected from the group consisting of H, lower alkyl, and cyclopropyl.

3. A compound of claim 1, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, wherein:
R^2 is H.

4. A compound of claim 1, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, wherein:
R^3 is selected from the group consisting H, alkyl, haloalkyl, and heteroalkyl.

5. A compound of claim 1, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, said compound having a structural Formula (II):



(II).

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

ring A is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, benzothienyl, benzimidazolyl, indazolyl, indolyl, and thienopyrazolyl;

m is 0 or more;

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each R^5 group (when present) is independently selected from the group consisting of halogen, -CN, -SF_5, -$N(R^8)_2$, -OR^7, -SR^7, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, and cycloalkyl;

n is 1;

-L_3- represents a bond or a divalent moiety selected from the group consisting of –NHC(O)- and –C(O)NH-;

ring B is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, pyrrolopyridyl, and pyrrolopyrimidinyl;

p is 0 or more; and

each R^9 group (when present) is independently selected from the group consisting of halogen, -CN, -SF_5, -$N(R^8)_2$, -OR^7, -SR^7, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, phenyl, benzyl, and cycloalkyl.

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

n is 0;

m is 1 or more;

-L_1- represents a bond, –CH_2-, or –CH_2CH_2-;

ring A is selected from the group consisting of phenyl, pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, imidazolyl, pyrazolyl, quinazolinyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzothienyl, naphthyl, quinolyl, isoquinolyl, indazolyl, indolyl, and thienopyrazolyl; and

each R^5 group (when present) is independently selected from the group consisting of halogen, -CN, -SF_5, -$N(R^8)_2$, -OR^7, -SR^7, lower alkyl, lower haloalkyl, lower heteroalkyl, lower alkynyl, and cycloalkyl.

8. A compound, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, said compound being selected from the group consisting of:

Ex #	Structure

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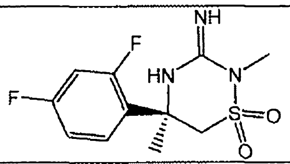
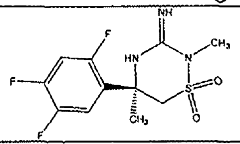
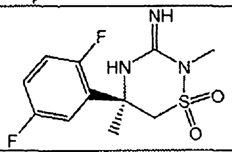
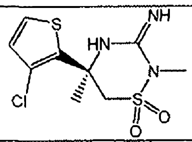
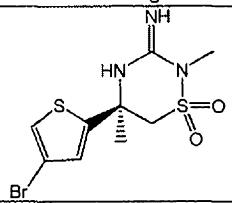
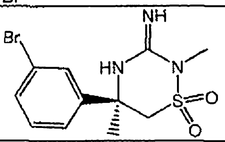
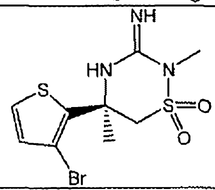
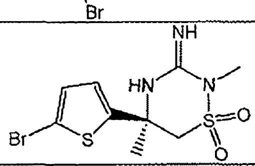
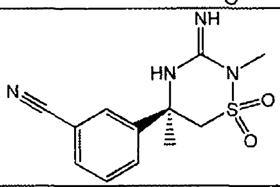
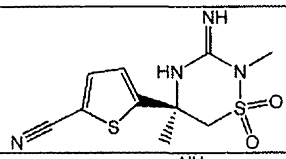
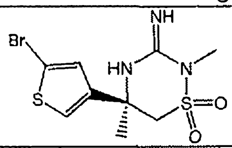
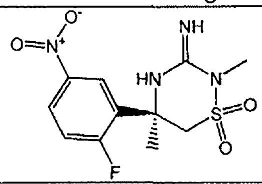
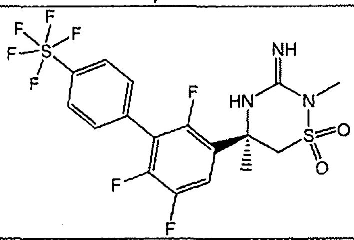
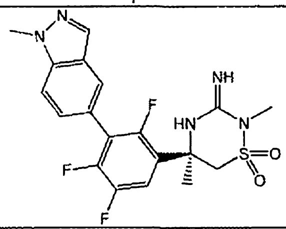
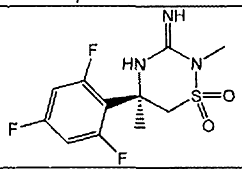
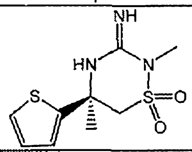
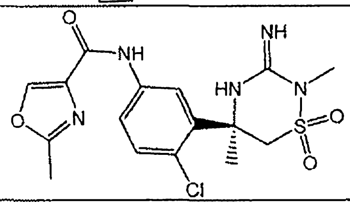
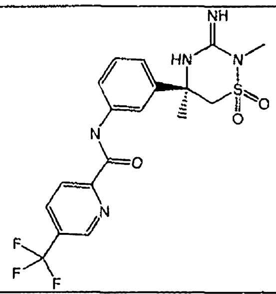
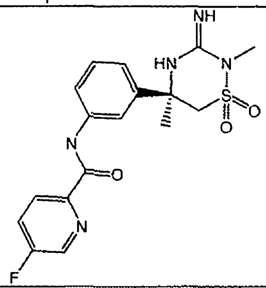
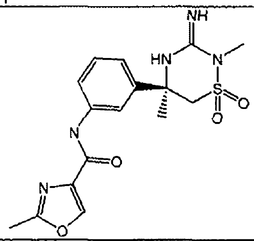
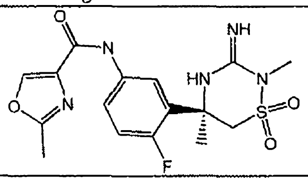
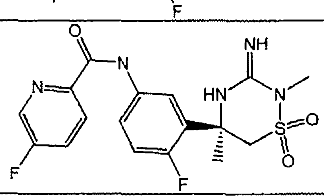
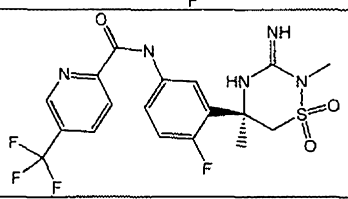
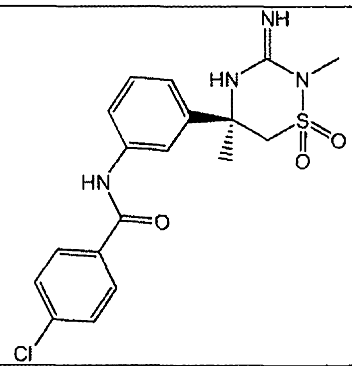
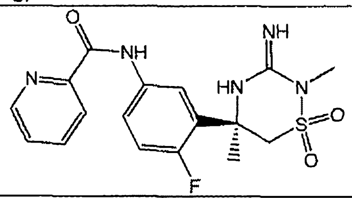
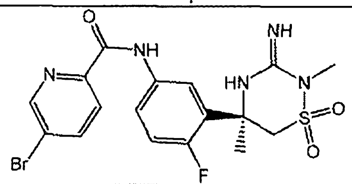
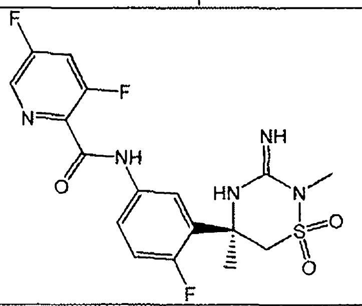
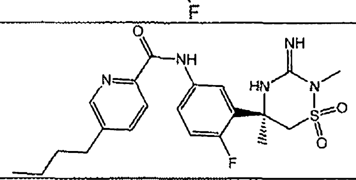
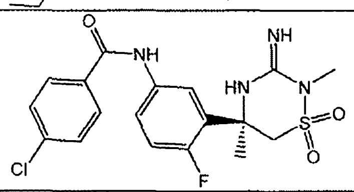
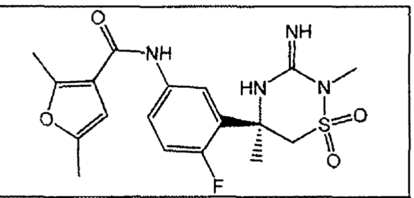
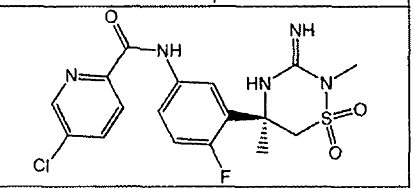
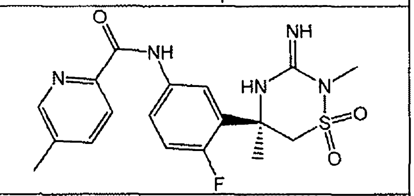
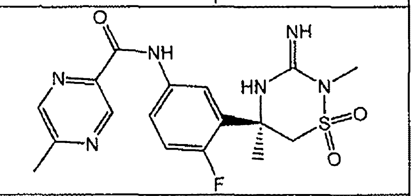
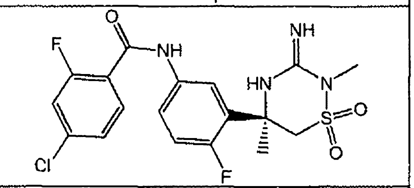
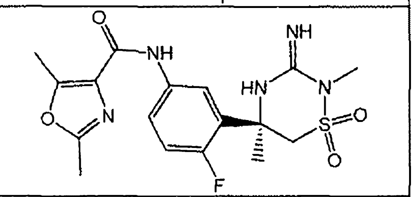
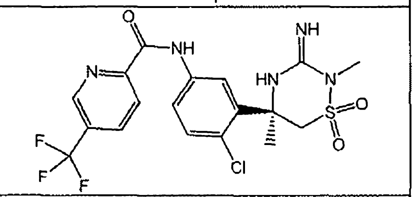
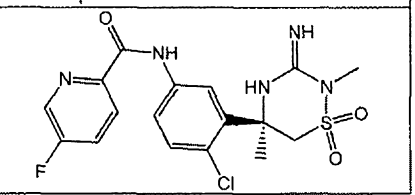
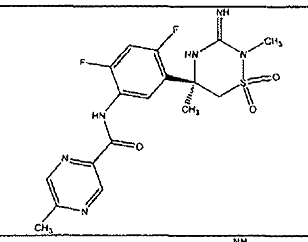
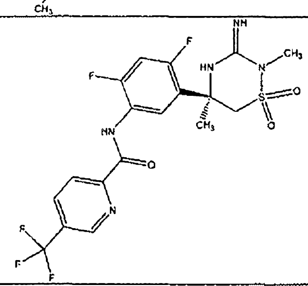
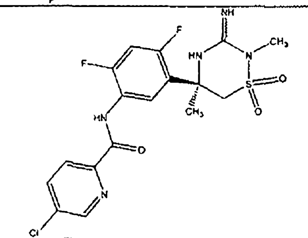
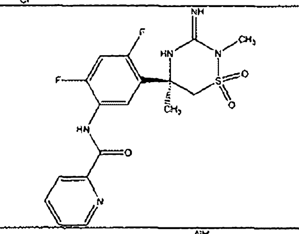
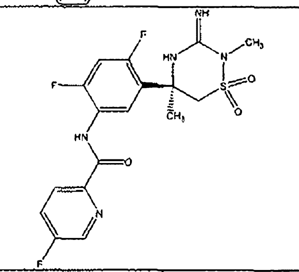
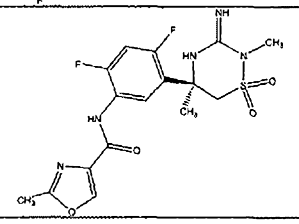
1	
2	
3	
4	
5	
6	
7	
11	
12	

13	
14	
15	
16	
17	
18	
19	
20	

21	
22	
23	
24	
25	
26	

27	
28	
29	
30	
31	
32	

33	
34	
35	
36	
37	
38	
39	
40	
40a	
40b	
40c	
40d	
40e	
40f	

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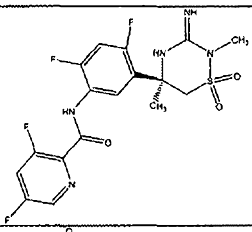
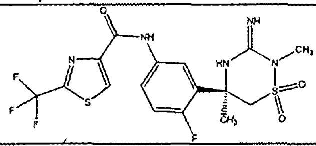
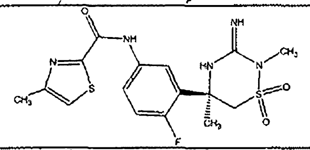
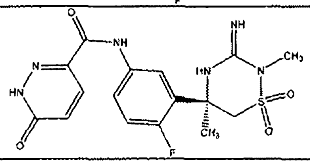
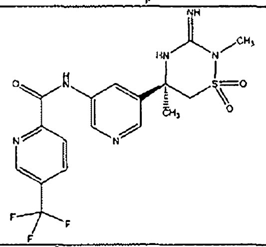
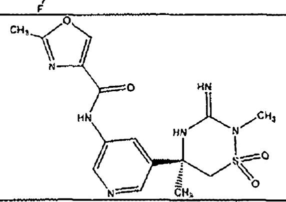
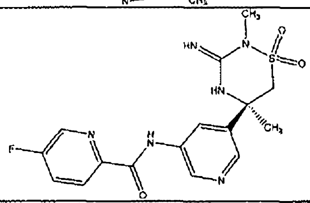
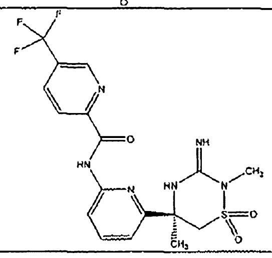
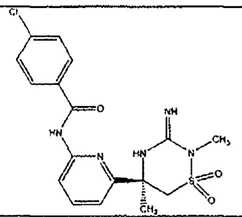
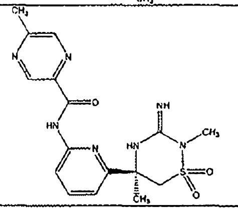
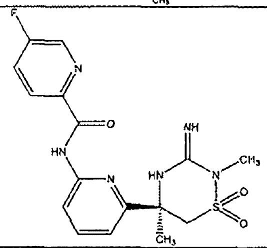
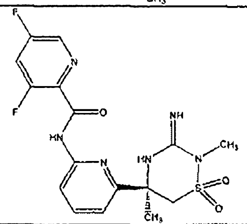
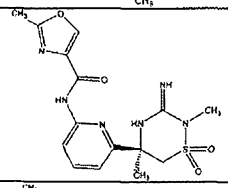
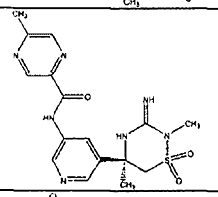
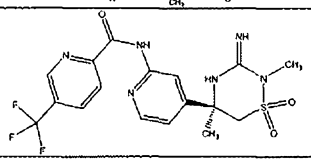
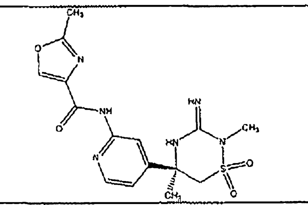
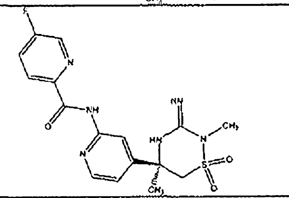
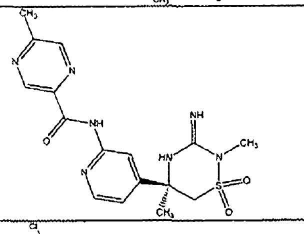
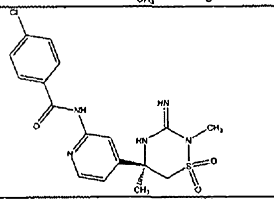
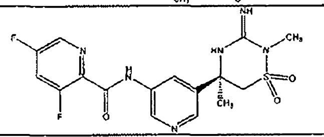
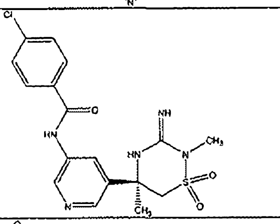
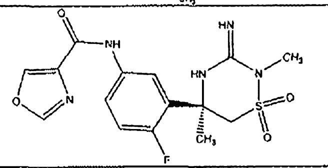
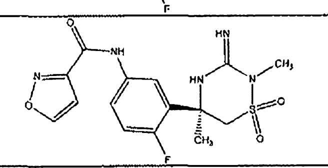
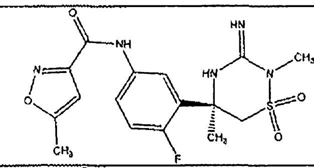
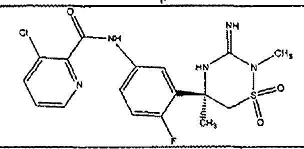
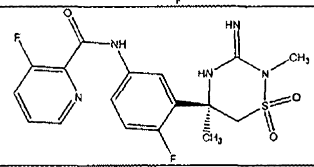
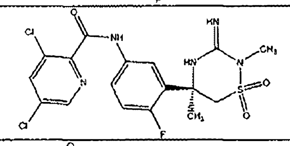
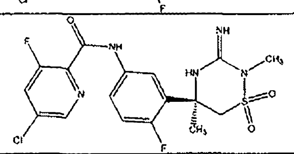
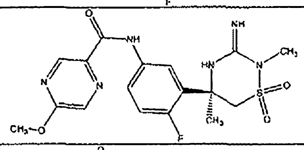
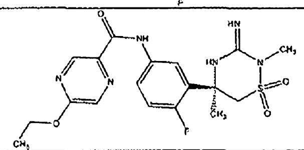
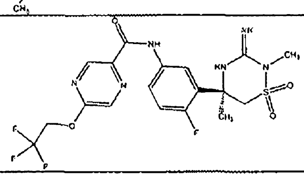
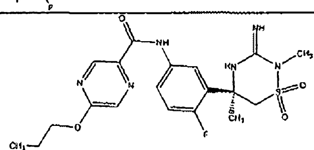
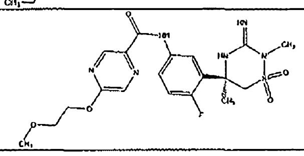
40g	
40h	
40i	
40j	
40k	
40l	
40m	
40n	

40o	
40p	
40q	
40r	
40s	
40t	
40u	

40v	
40w	
40x	
40y	
40z	
40aa	
40ab	
40ac	
40ad	
40ae	
40af	
40ag	
40ah	
40ai	
40aj	
40ak	
40al	
40am	

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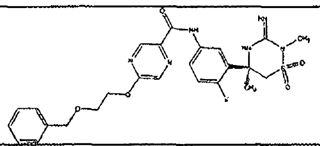
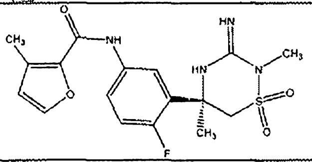
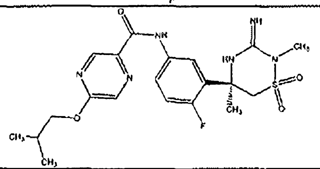
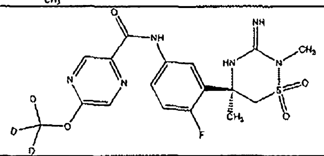
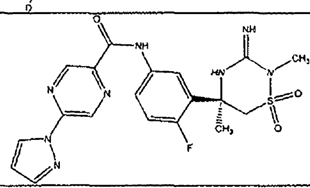
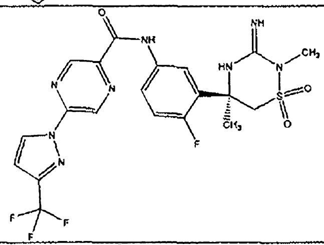
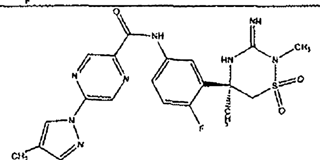
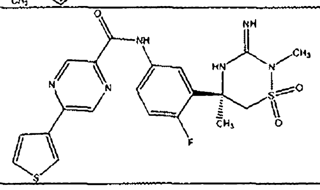
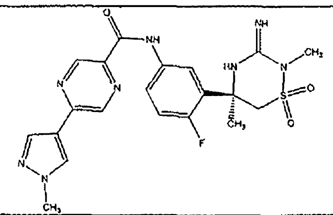
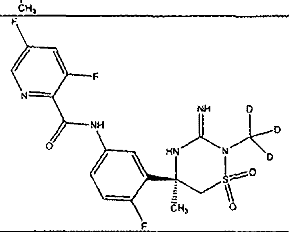
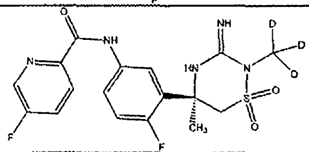
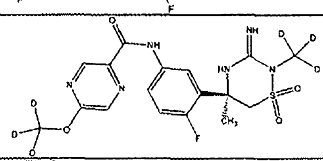
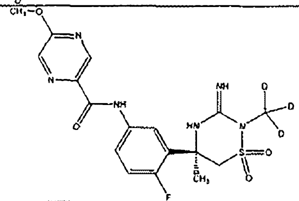
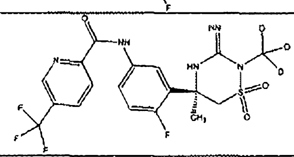
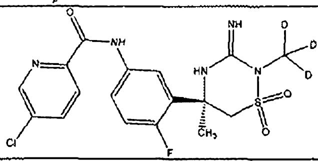
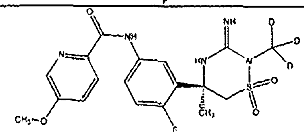
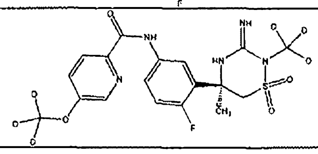
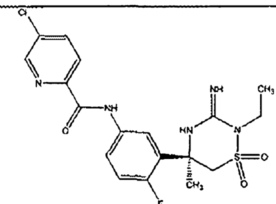
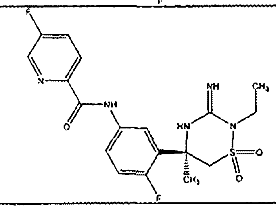
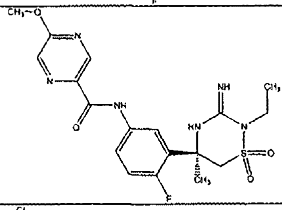
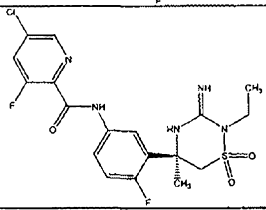
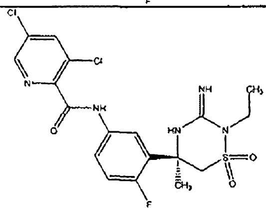
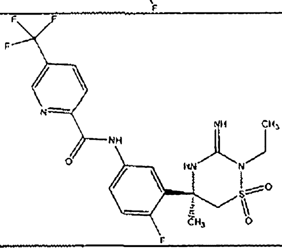
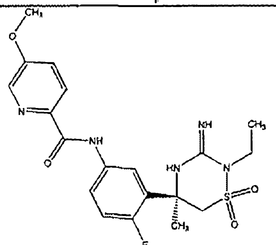
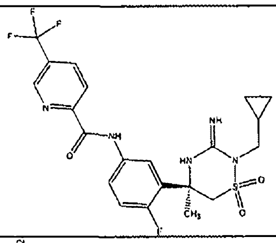
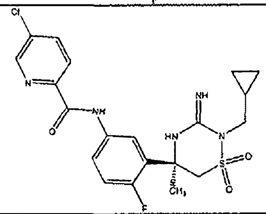
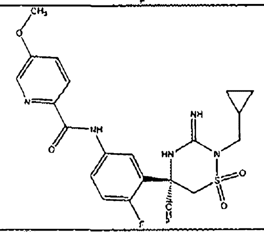
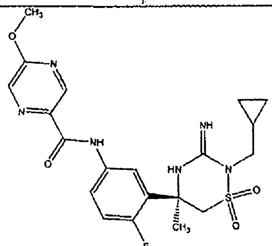
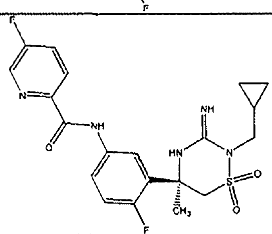
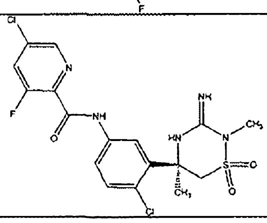
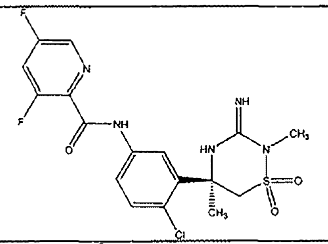
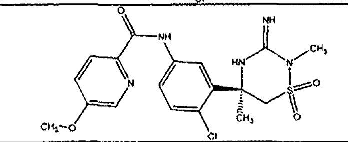
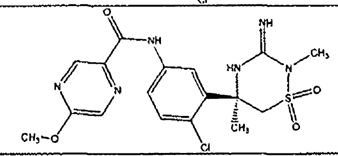
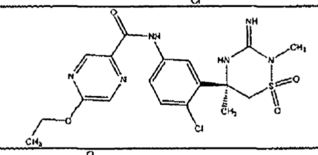
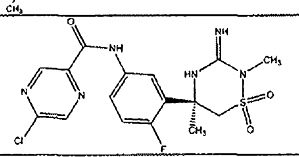
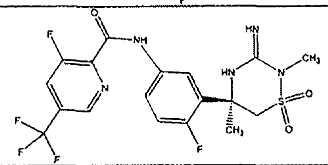
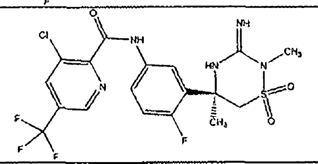
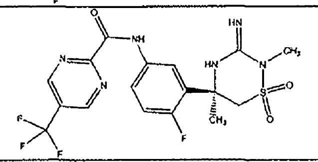
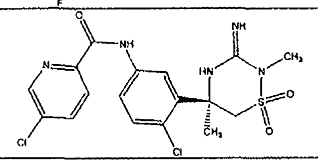
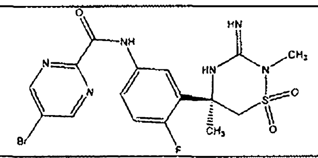
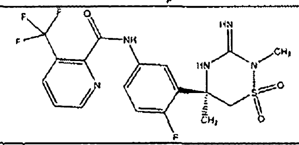
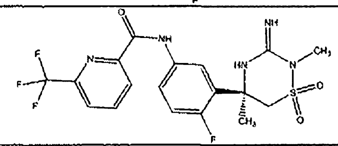
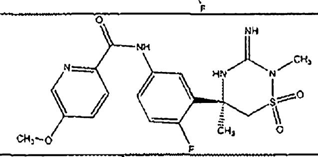
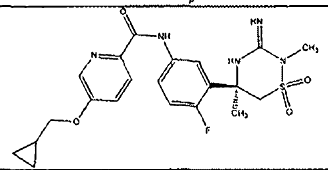
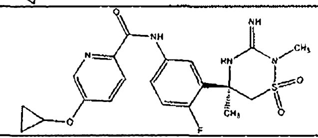
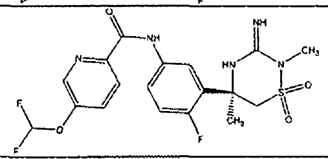
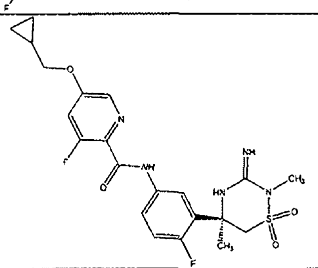
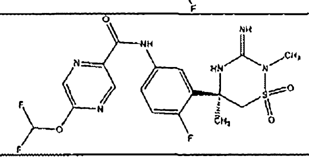
40an	
40ao	
40ap	
40aq	
40ar	
40as	
40at	
40au	
40av	
40aw	
40ax	
40ay	
40az	
40ba	
40bb	
40bc	
40bd	

40be	
40bf	
40bg	
40bh	
40bi	
40bj	
40bk	

40bl	
40bm	
40bn	
40bo	
40bp	
40bq	

40br	
40bs	
40bt	
40bu	
40bv	
40bw	
40bx	
40by	
40bz	

40ca	
40cb	
40cc	
40cd	
40ce	
40cf	
40cg	
40ch	
40ci	

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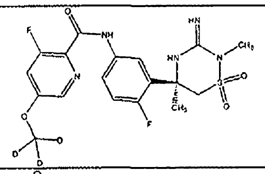
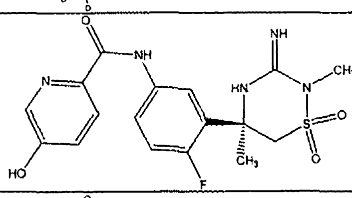
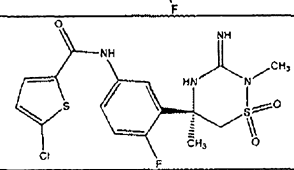
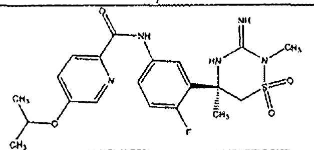
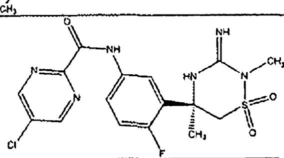
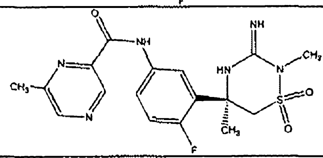
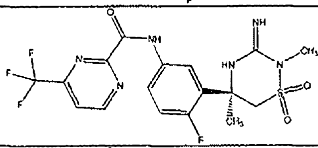
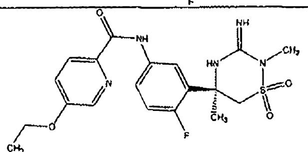
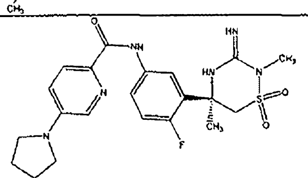
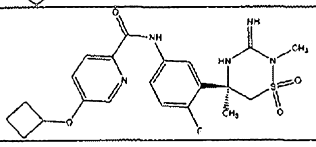
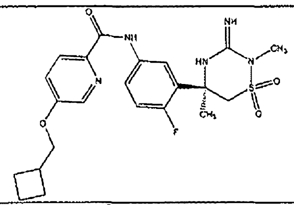
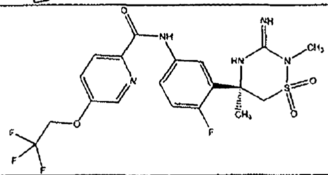
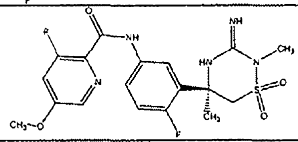
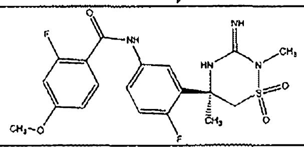
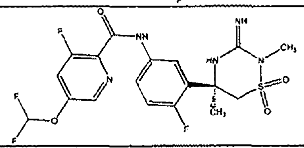
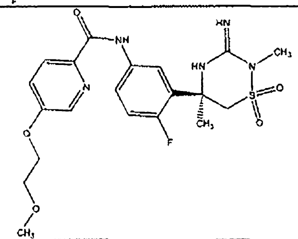
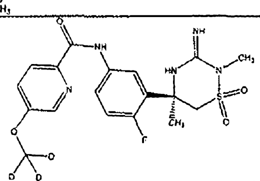
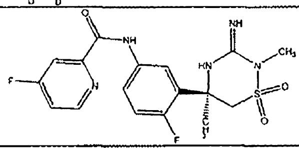
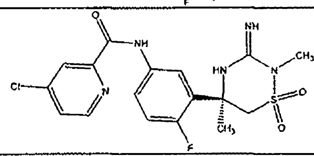
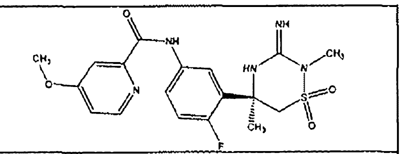
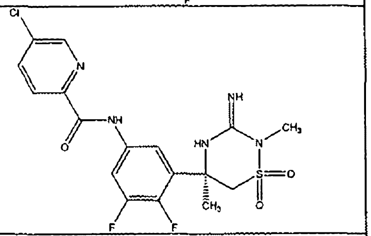
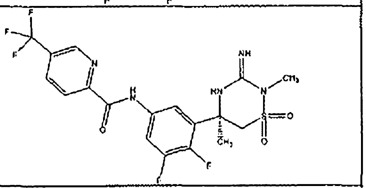
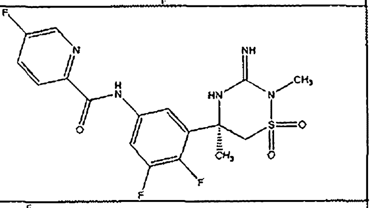
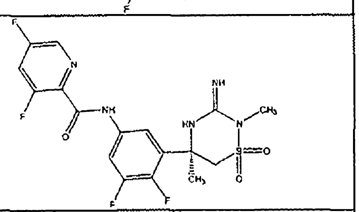
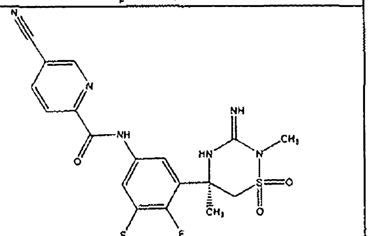
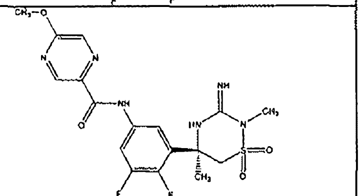
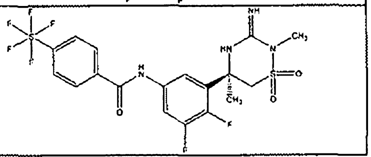
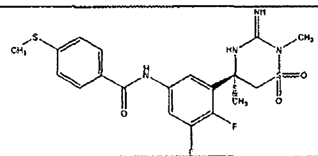
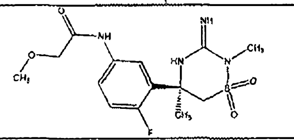
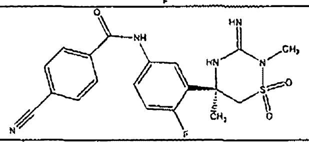
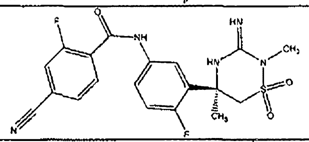
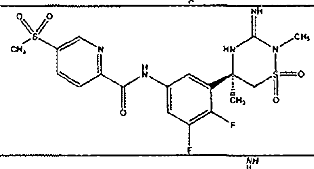
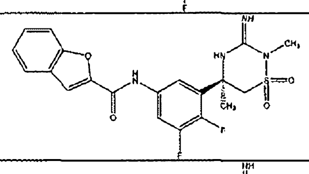
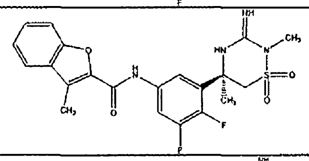
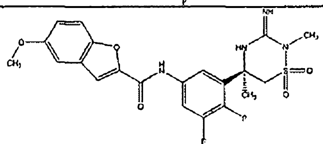
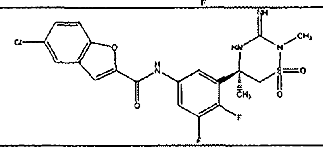
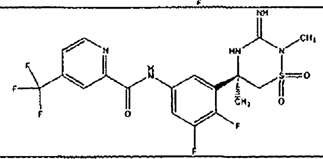
40cj	
40ck	
40cl	
40cm	
40cn	
40co	
40cp	
40cq	
40cr	
40cs	
40ct	
40cu	
40cv	
40cw	
40cx	
40cy	
40cz	
40da	
40db	

40dc	
40dd	
40de	
40df	
40dg	
40dh	
40di	
40dj	

40dk	
40dl	
40dm	
40dn	
40do	
40dp	
40dq	
40dr	
40ds	
40dt	

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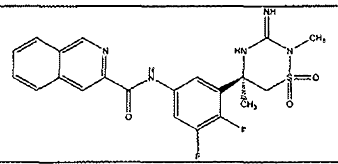
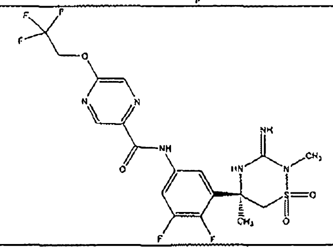
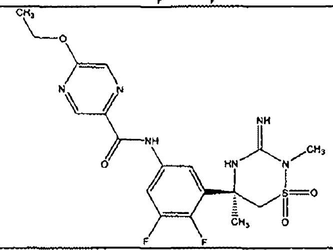
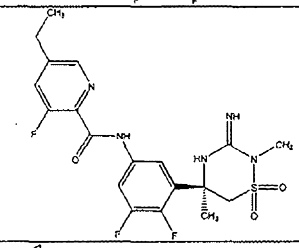
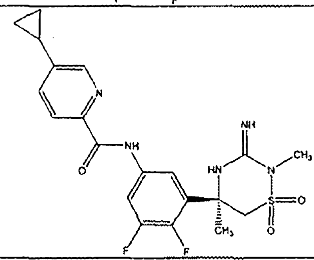
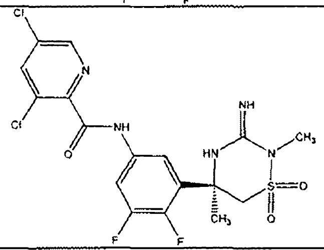
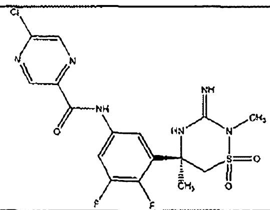
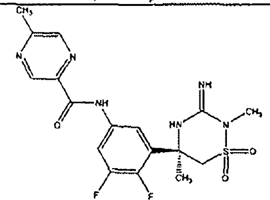
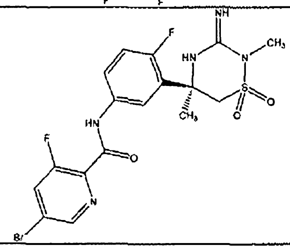
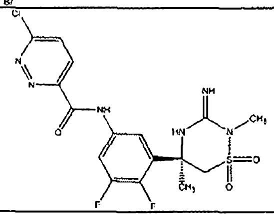
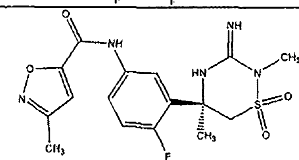
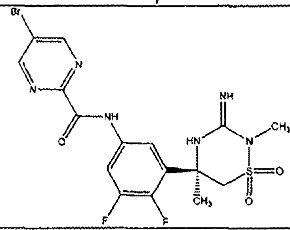
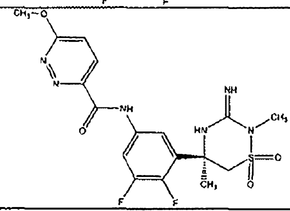
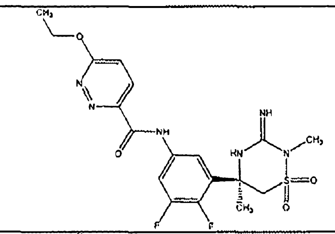
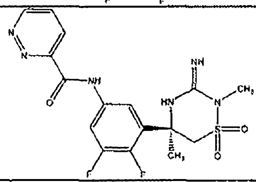
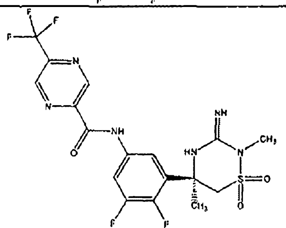
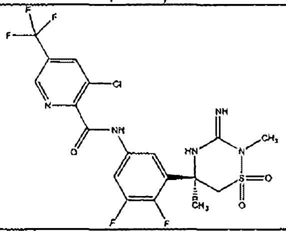
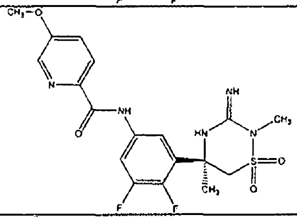
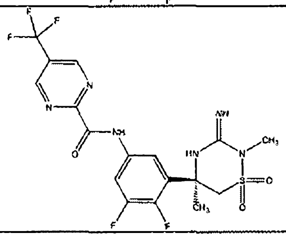
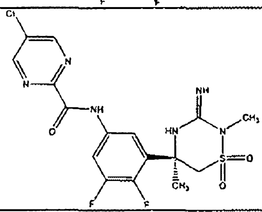
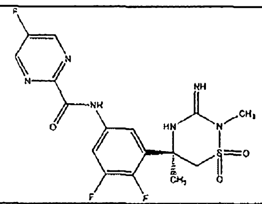
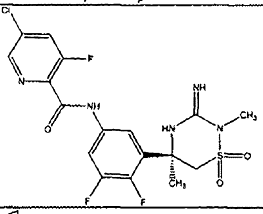
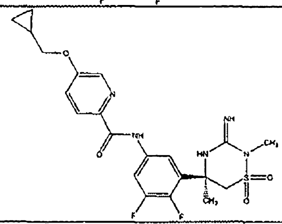
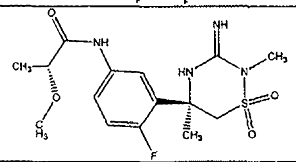
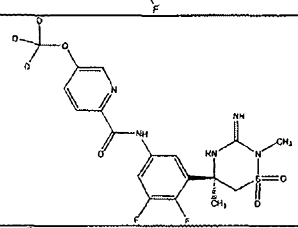
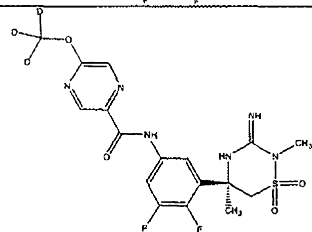
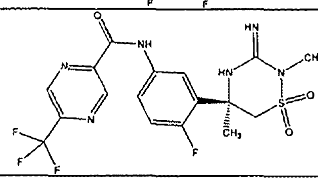
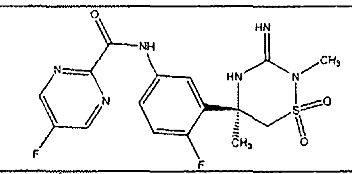
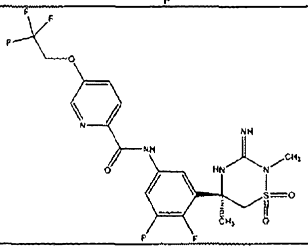
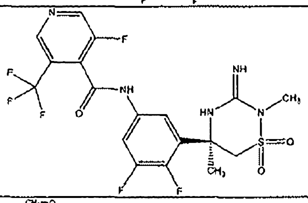
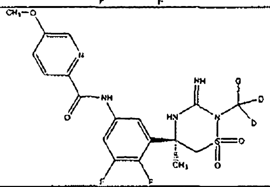
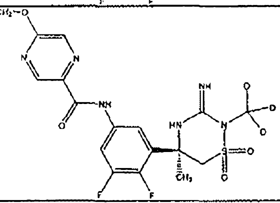
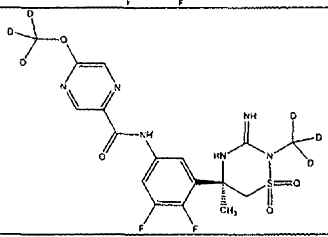
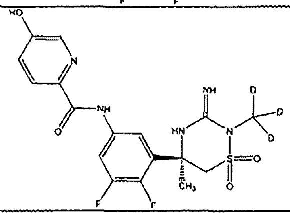
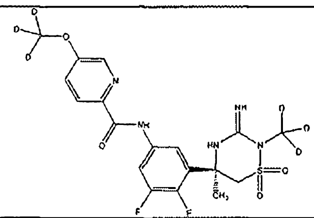
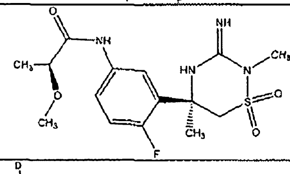
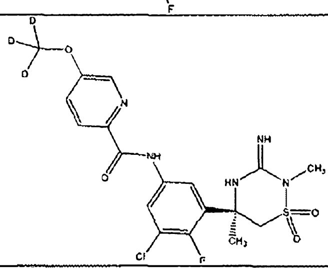
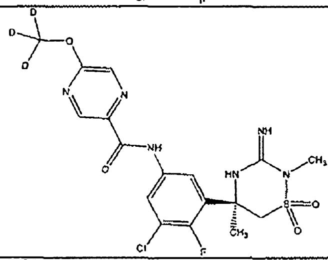
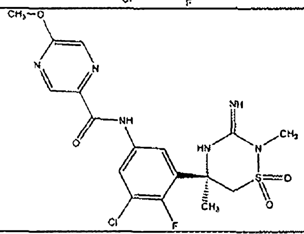
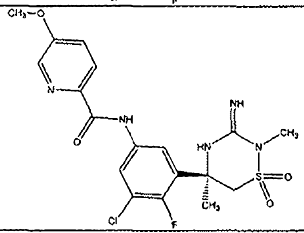
40du	
40dv	
40dw	
40dx	
40dy	
40dz	

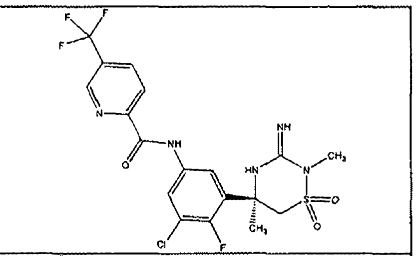
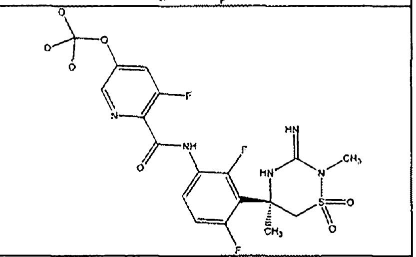
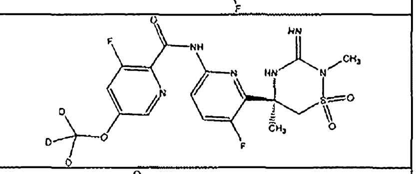
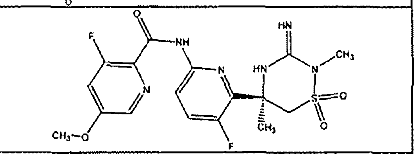
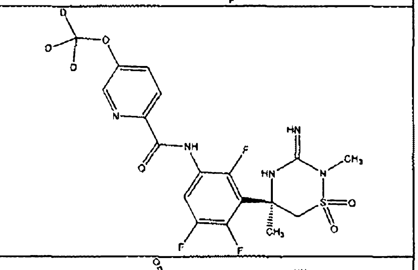
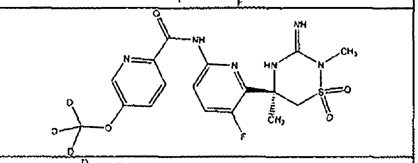
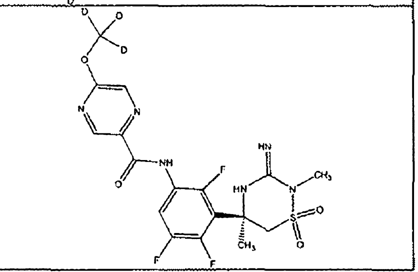
40ea	
40eb	
40ec	
40ed	
40ee	
40ef	
40eg	

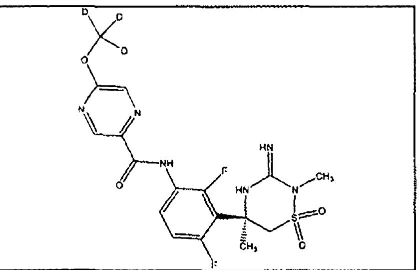
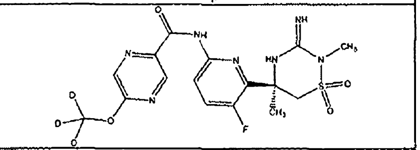
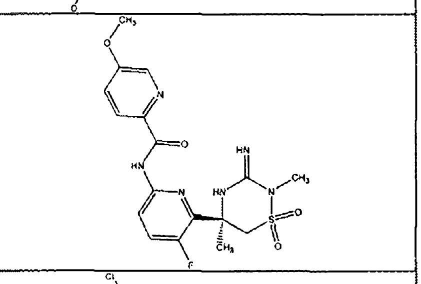
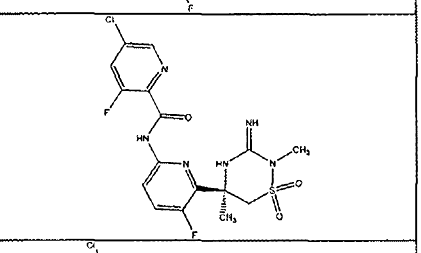
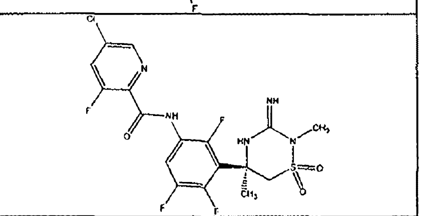
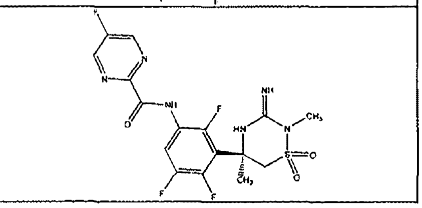
40eh	
40ei	
40ej	
40ek	
40el	
40em	
40en	

40eo	
40ep	
40eq	
40er	
40es	
40et	
40eu	

40ev	
40ew	
40ex	
40ez	
40fa	
40fb	
40fc	

40fd	
40fe	
40ff	
40fg	
40fh	
40fi	

40fj	
40fk	
40fl	
40fm	
40fn	
40fo	
40fp	

40fq	
40fr	
40fs	
40ft	
40fu	
40fv	

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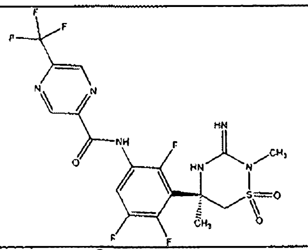
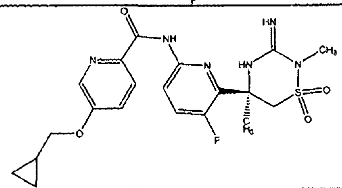
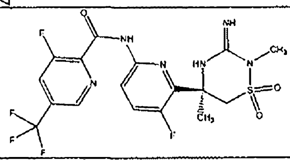
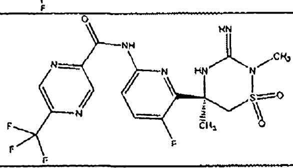
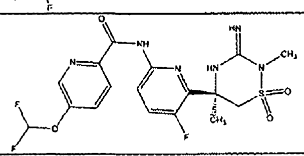
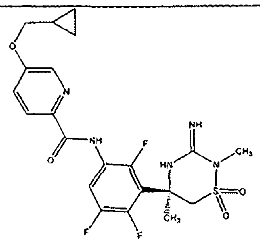
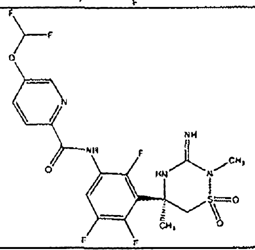
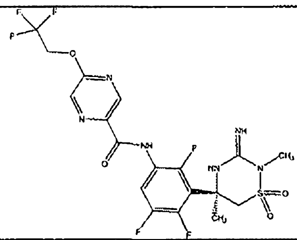
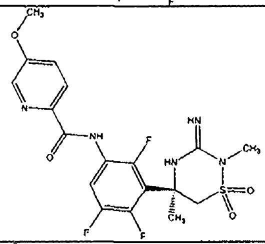
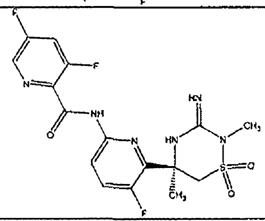
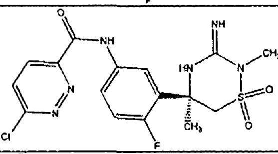
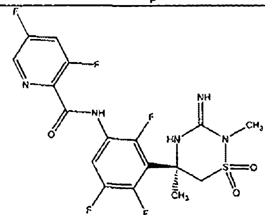
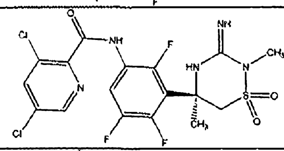
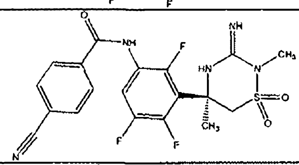
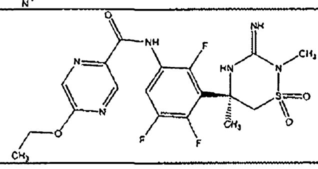
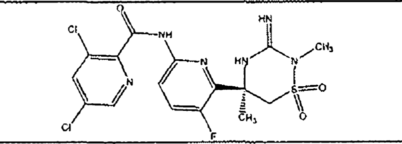
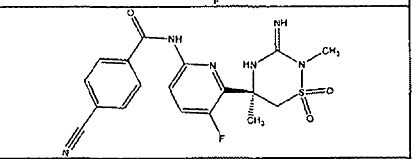
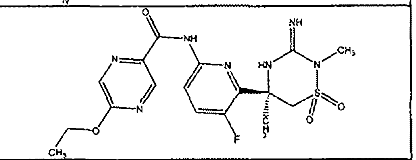
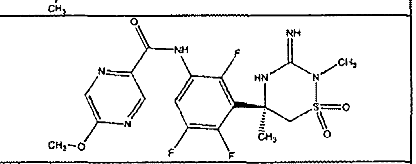
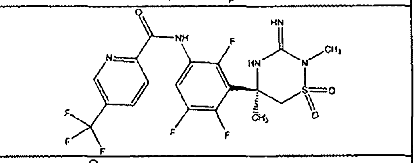
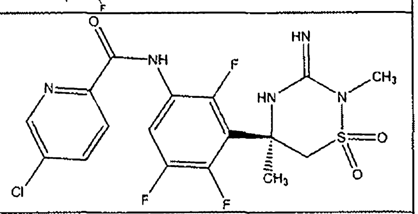
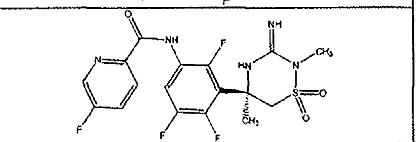
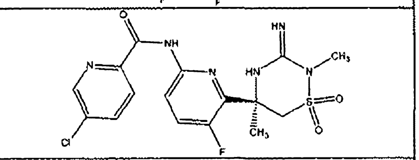
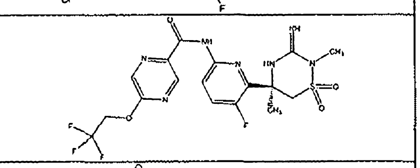
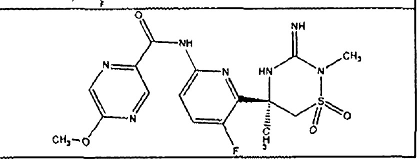
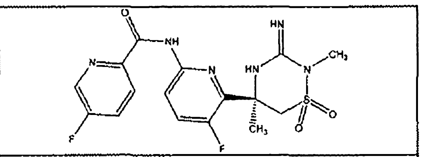
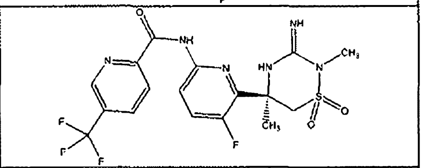
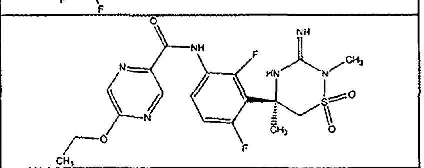
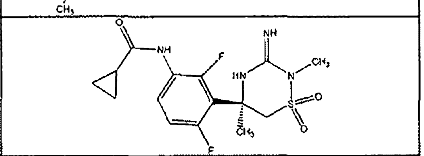
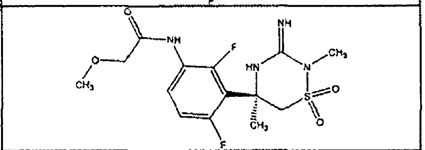
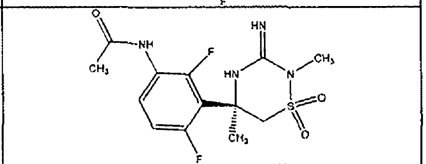
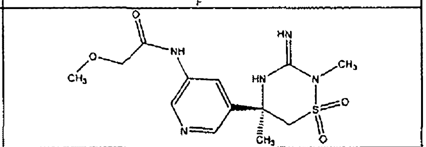
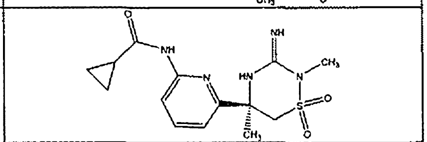
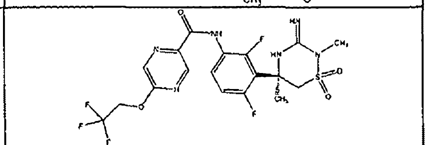
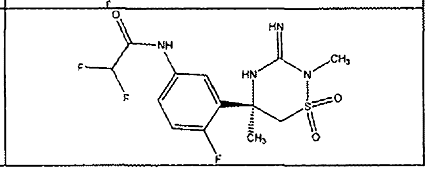
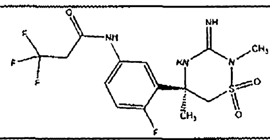
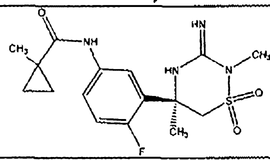
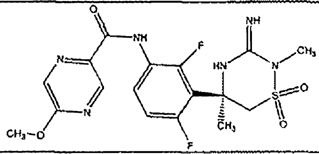
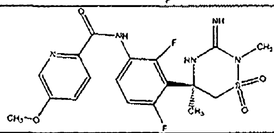
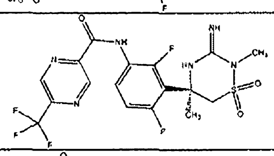
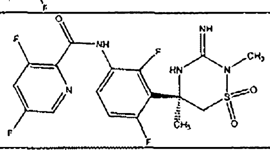
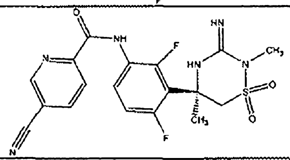
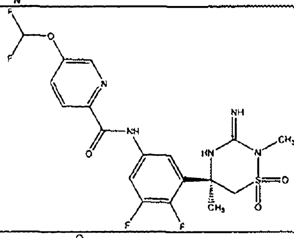
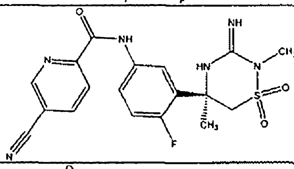
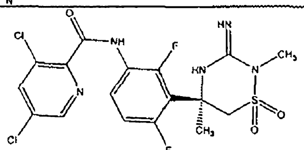
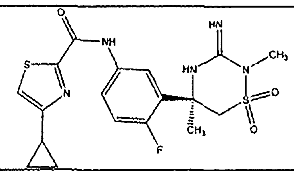
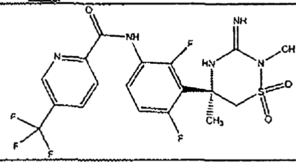
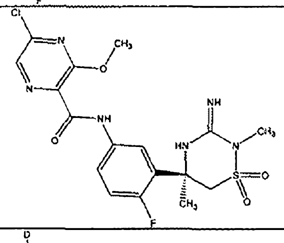
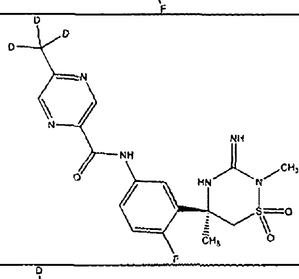
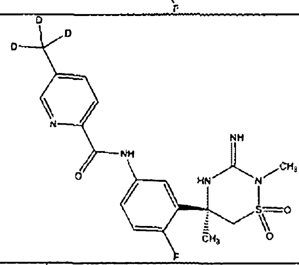
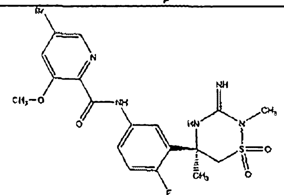
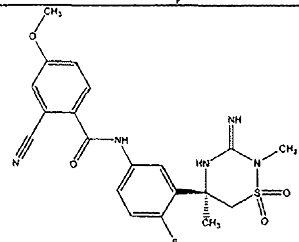
40fw	
40fx	
40fy	
40fz	
40ga	
40gb	
40gc	

40gd	
40ge	
40gf	
40gg	
40gh	
40gi	
40gj	
40gk	

40gl	
40gm	
40gn	
40go	
40gp	
40gq	
40gr	
40gs	
40gt	
40gu	

40gv	
40gw	
40gx	
40gy	
40gz	
40ha	
40hb	
40hc	
40hd	
40he	

40hf	
40hg	
40hi	
40hj	
40hk	
40hl	
40hm	
40hn	
40ho	
40hp	

40hq	
40hr	
40hs	
40ht	
40hu	
40hv	
40hw	

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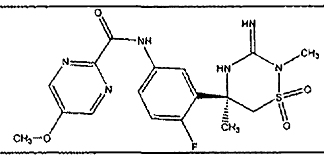
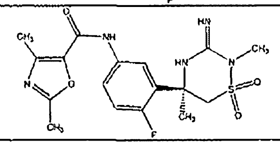
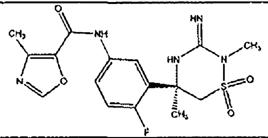
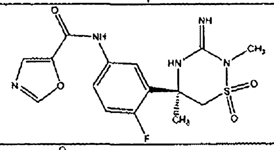
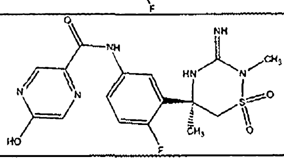
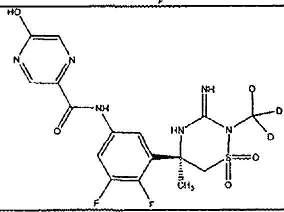
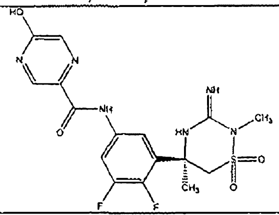
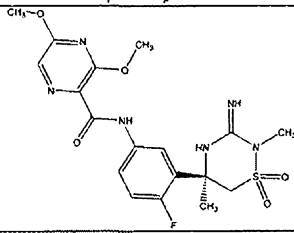
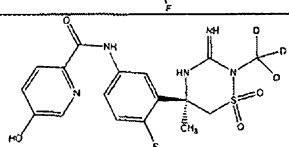
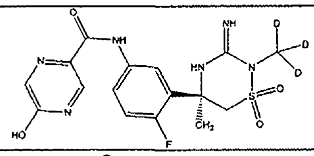
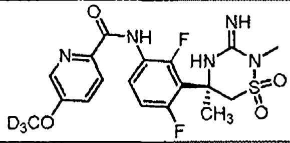
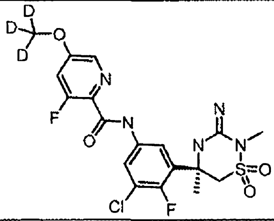
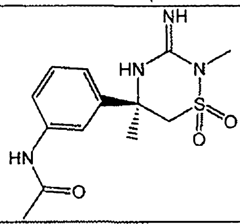
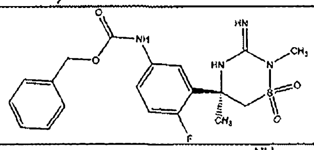
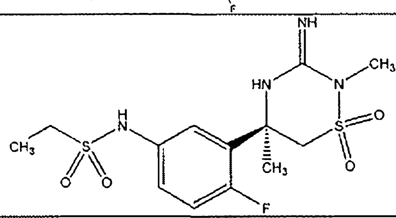
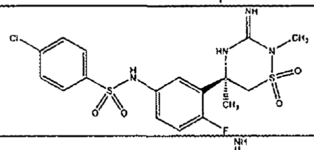
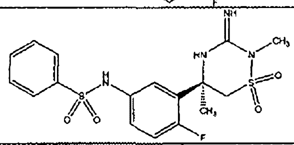
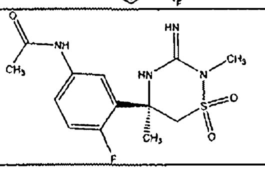
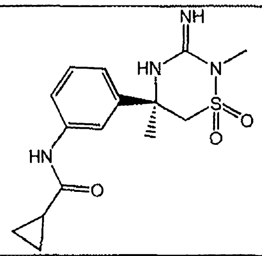
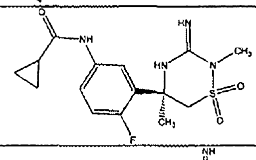
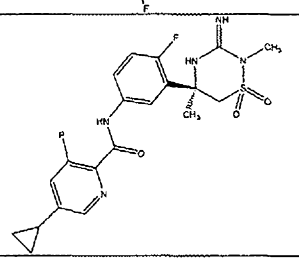
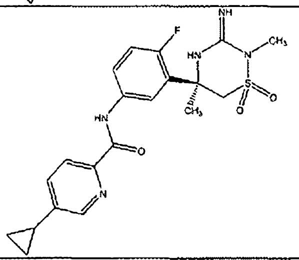
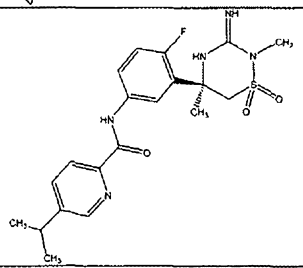
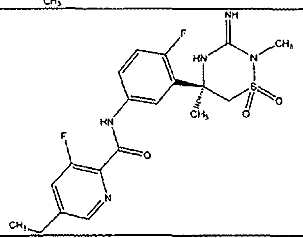
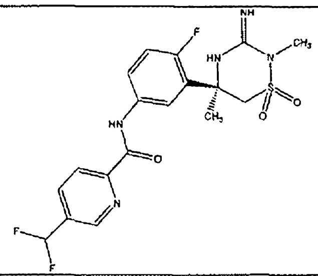
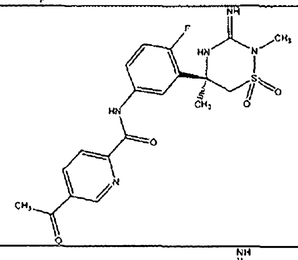
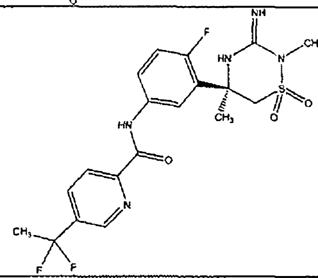
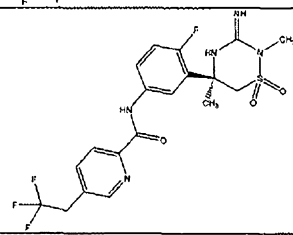
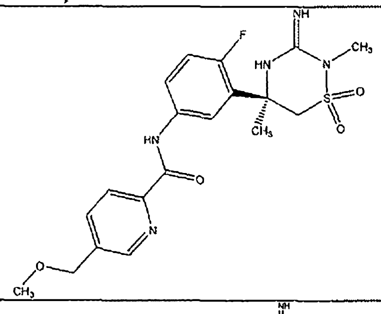
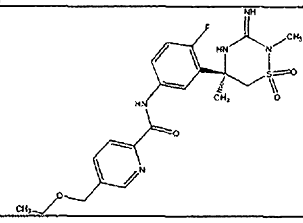
40hx	
40hy	
40hz	
40ia	
40ib	
40ic	
40id	
40ie	
40if	

40ih	
40ii	
40ij	
41	
41b	
41c	
41d	
41e	
41f	

42	
42a	
42b	
42c	
42d	
42e	
42f	
42g	
42h	
42i	
42j	
42k	

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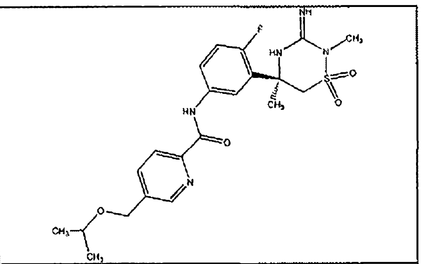
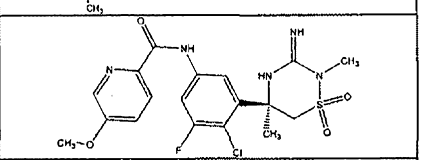
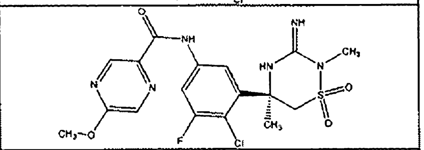
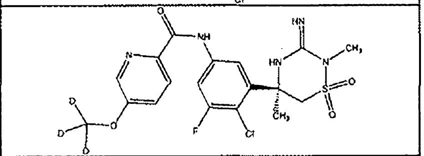
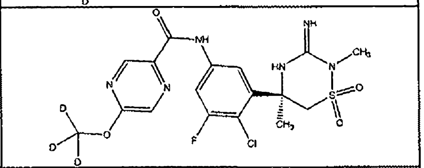
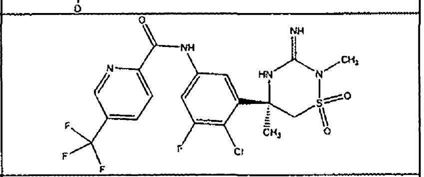
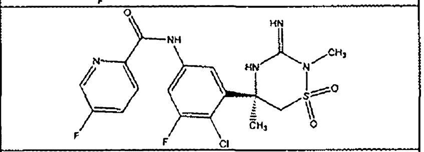
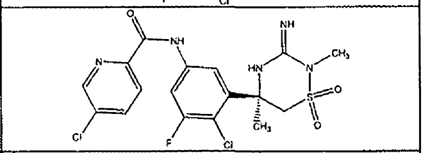
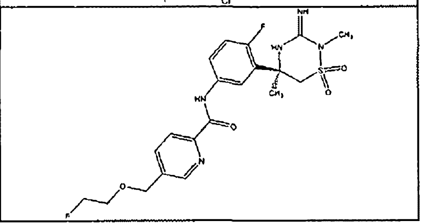
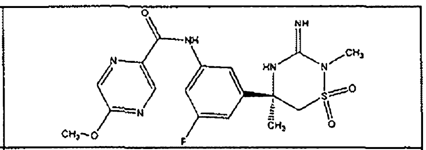
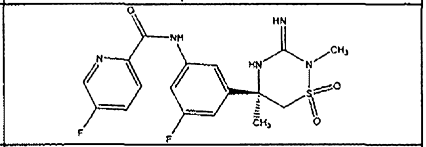
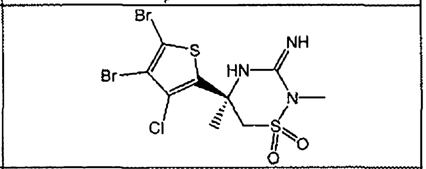
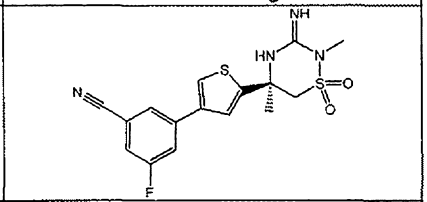
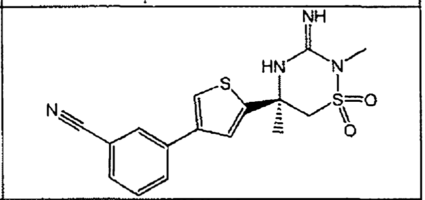
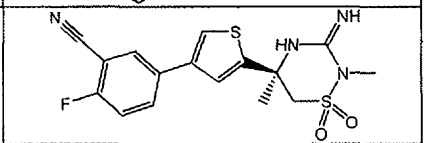
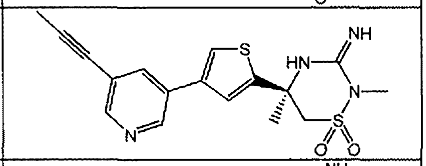
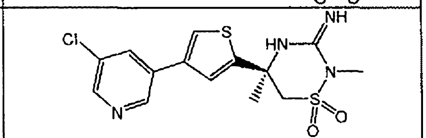
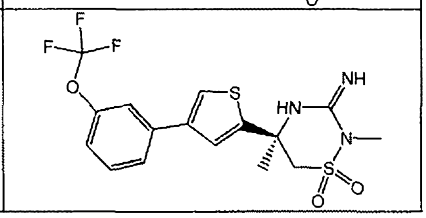
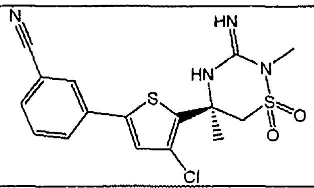
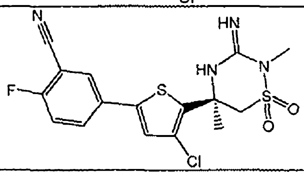
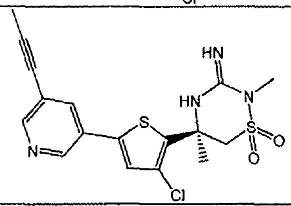
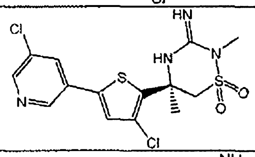
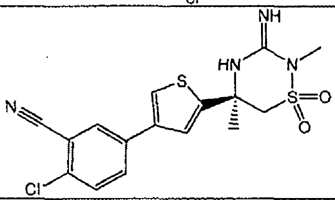
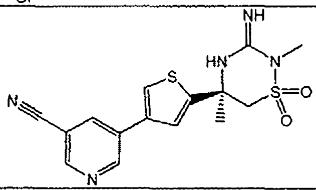
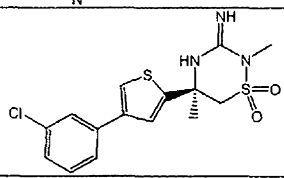
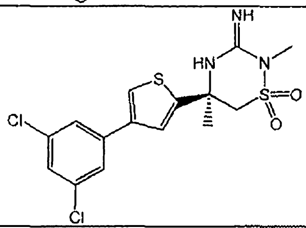
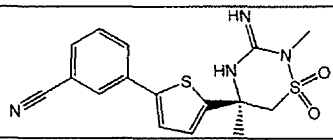
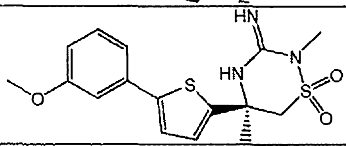
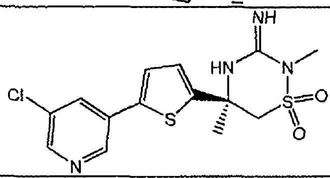
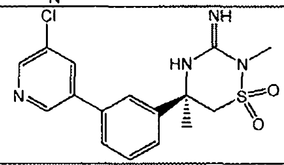
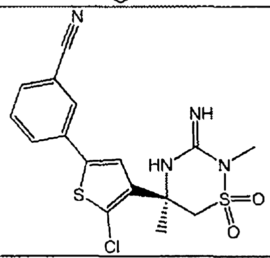
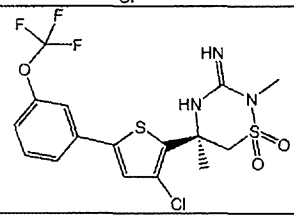
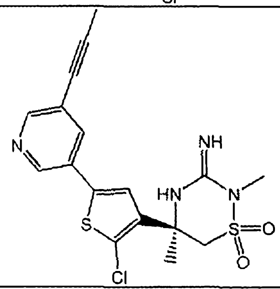
42l	
42m	
42n	
42o	
42p	
42q	
42r	
42s	
42t	

42u	
42v	
43	
44	
45	
46	
47	
48	
49	

50	
51	
52	
53	
54	
55	
56	
57	

58	
59	
60	
61	
62	
63	
64	

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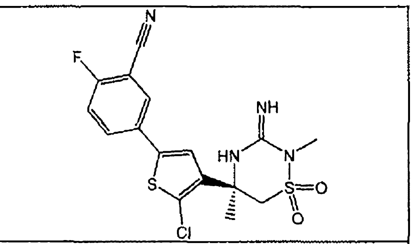
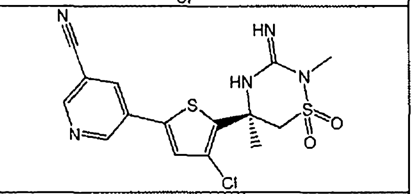
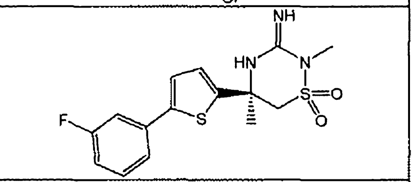
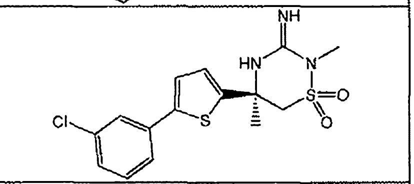
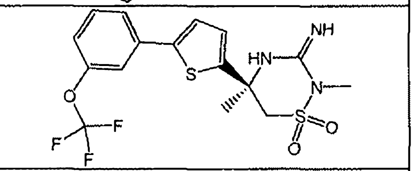
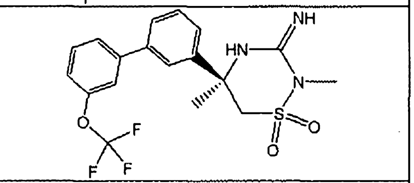
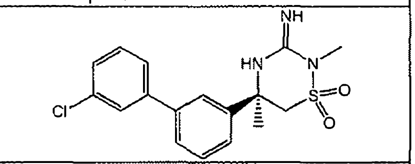
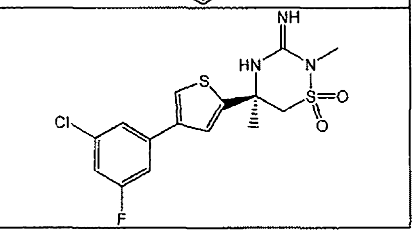
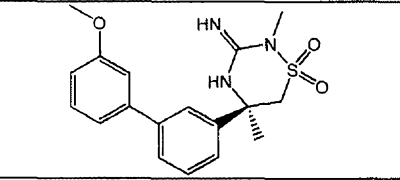
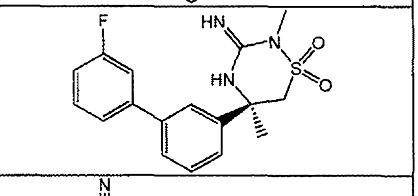
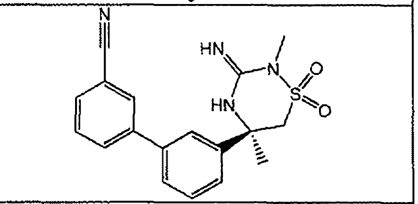
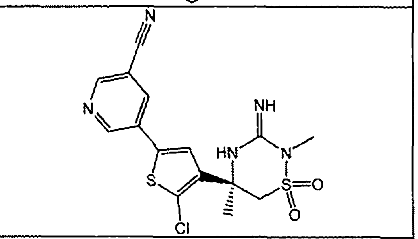
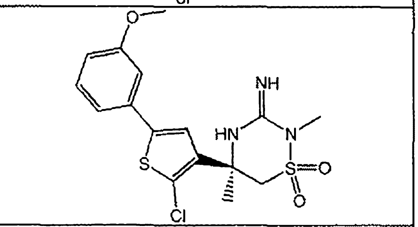
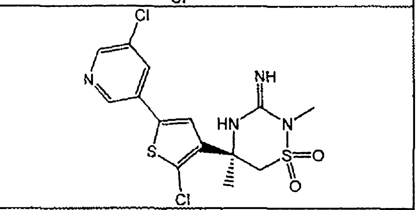
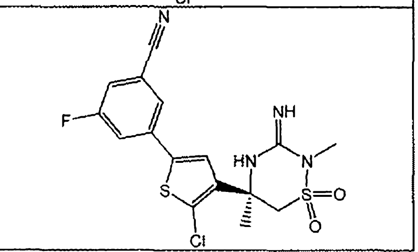
65	
66	
67	
68	
69	
70	
71	
72	
73	
74	
75	
76	
77	
78	
79	

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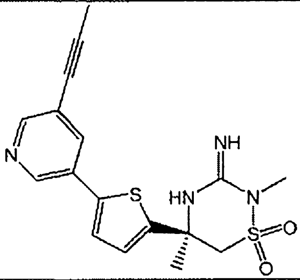
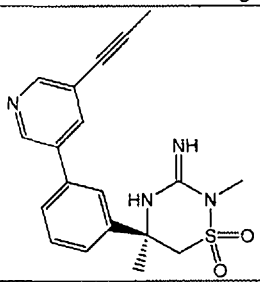
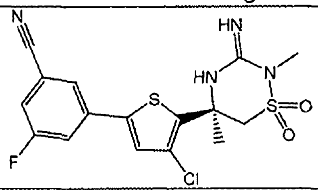
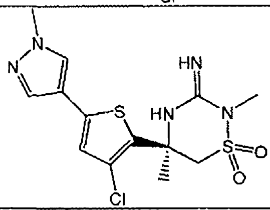
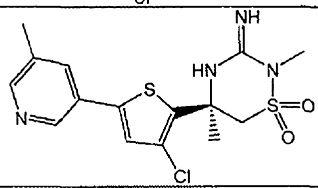
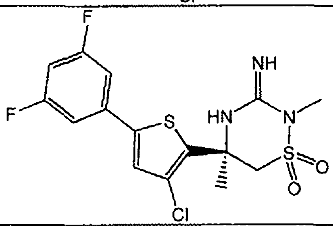
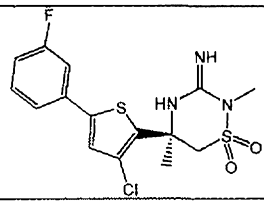
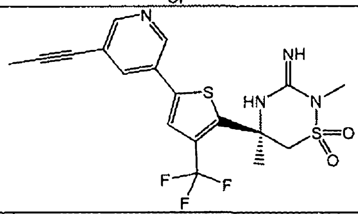
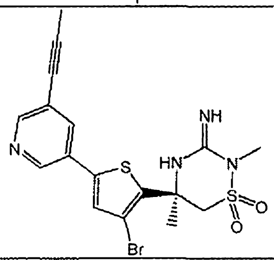
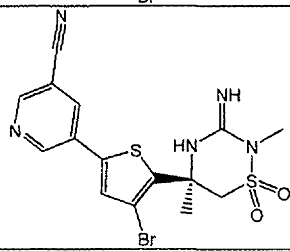
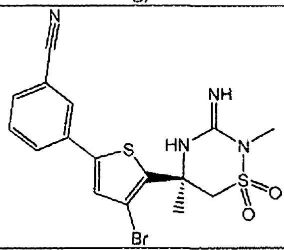
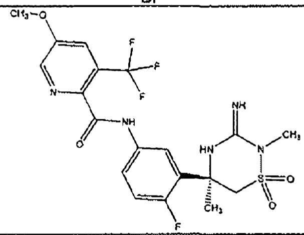
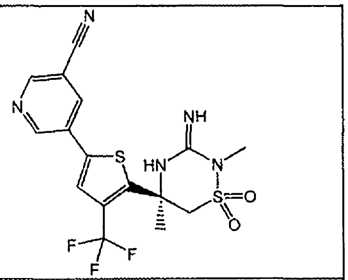
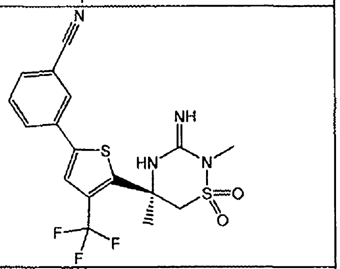
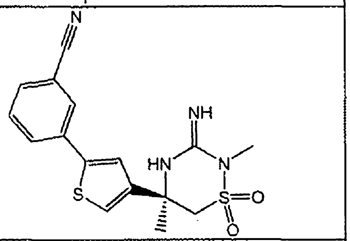
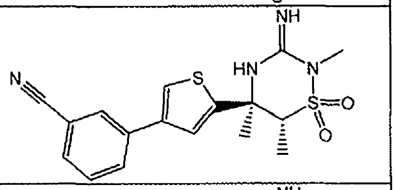
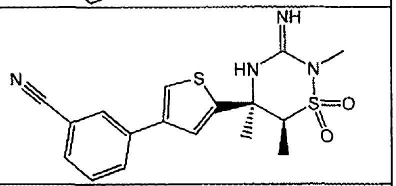
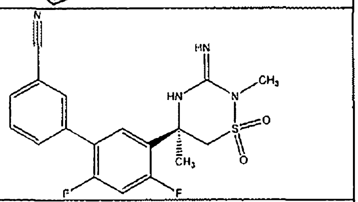
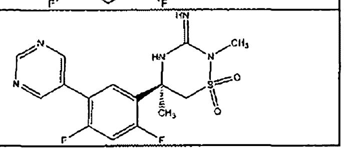
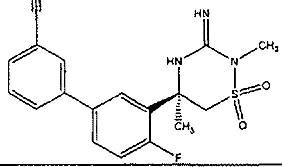
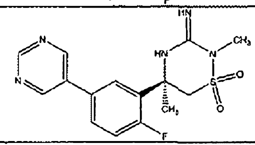
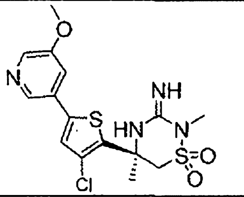
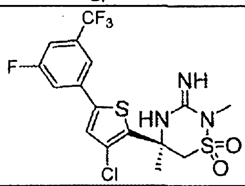
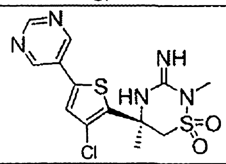
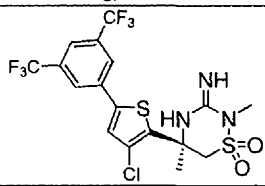
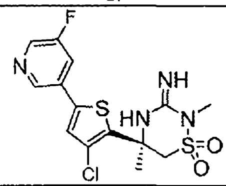
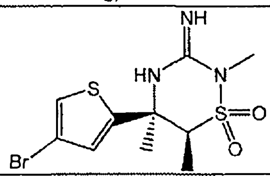
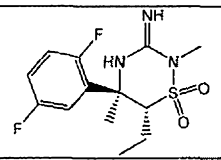
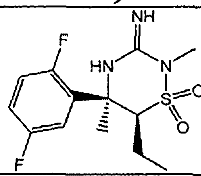
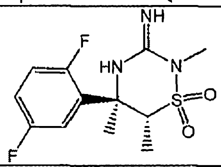
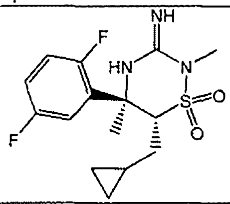
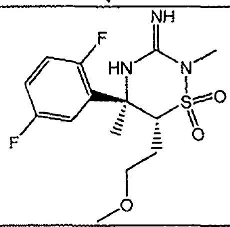
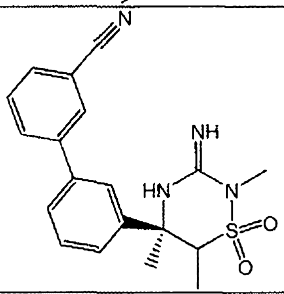
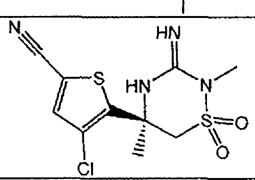
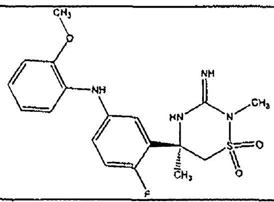
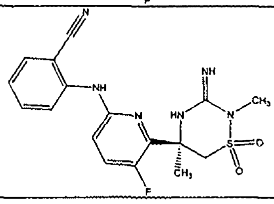
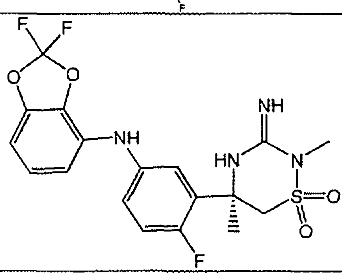
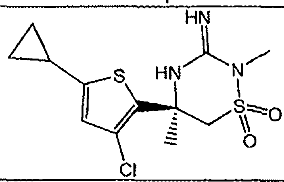
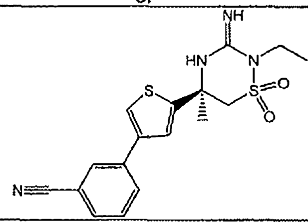
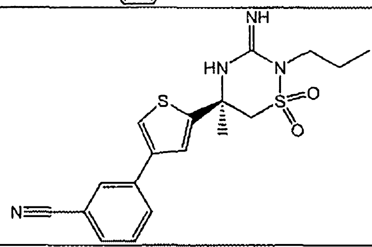
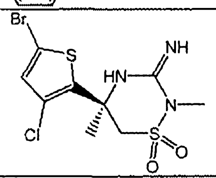
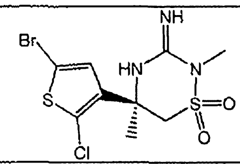
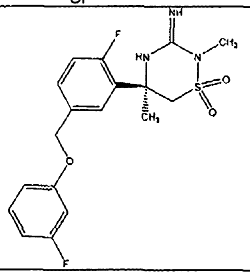
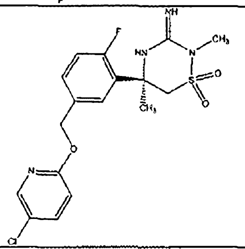
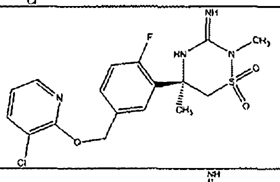
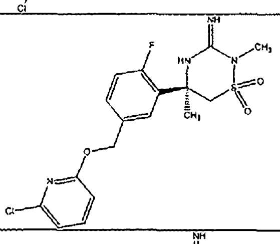
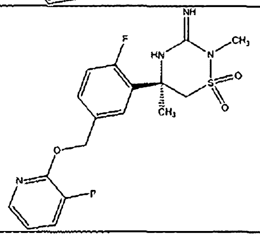
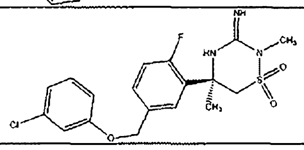
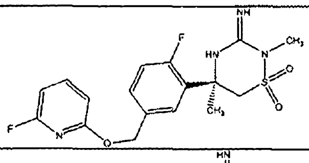
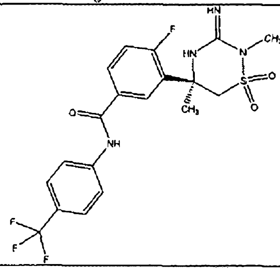
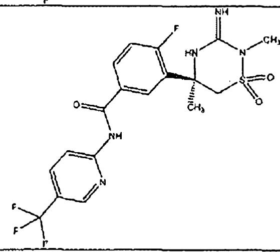
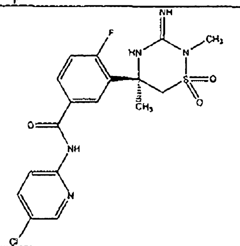
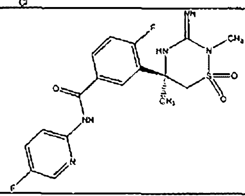
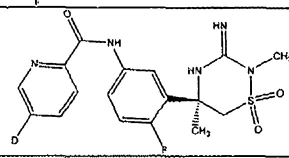
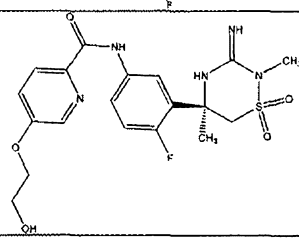
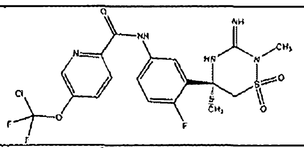
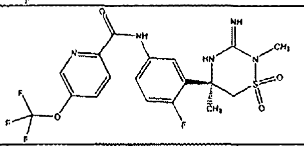
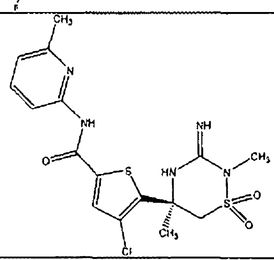
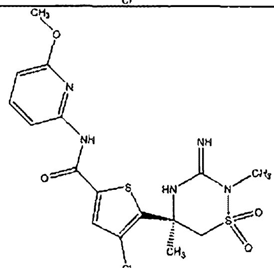
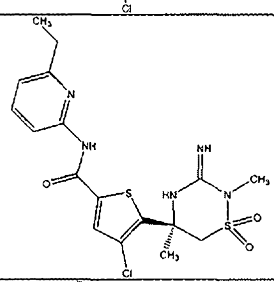
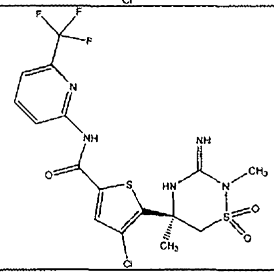
80	
81	
82	
83	
84	
85	

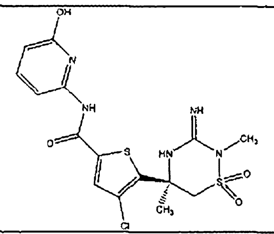
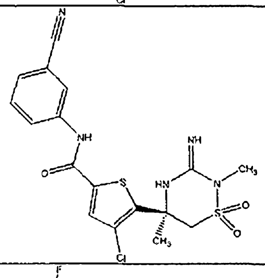
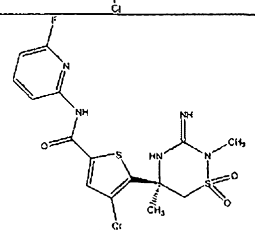
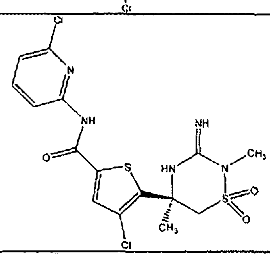
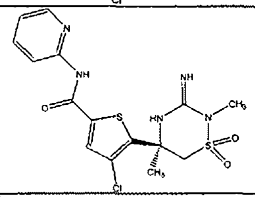
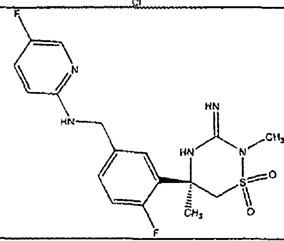
86	
87	
88	
89	
90	
90ig	

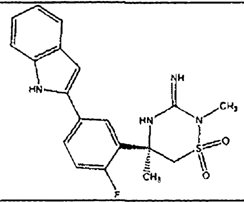
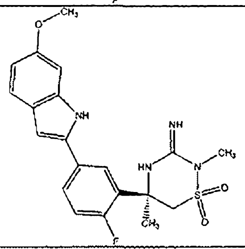
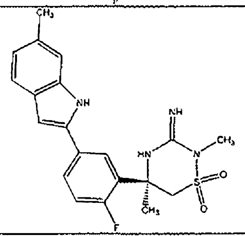
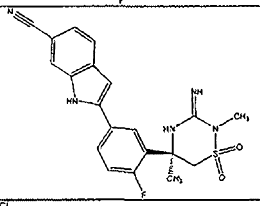
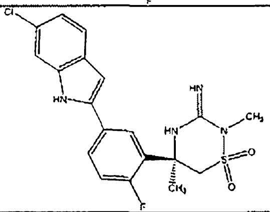
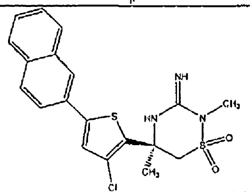
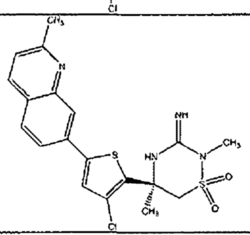
91	
92	
93	
94	
95	
95a	
95b	
95c	
95d	
95e	
95f	
95g	
95h	
95i	
96	

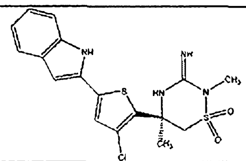
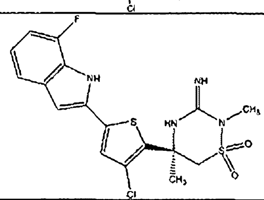
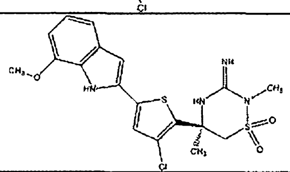
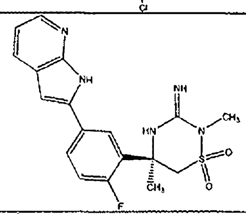
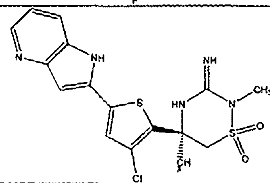
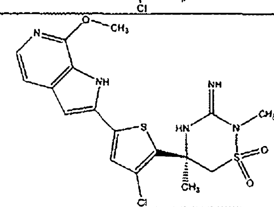
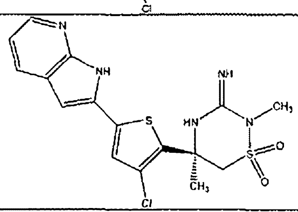
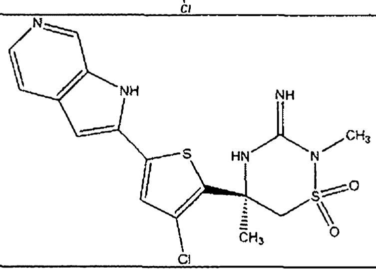
97	
98	
99	
100	
101	
102	
103	
103a	
103b	
104	
105	
106	
107	
108	

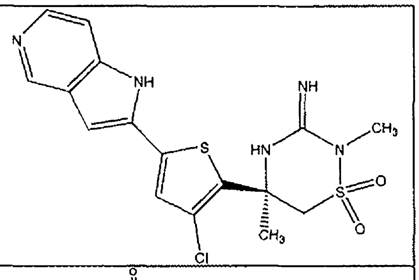
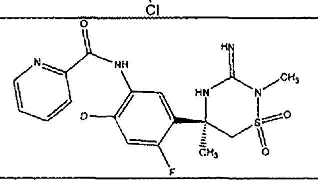
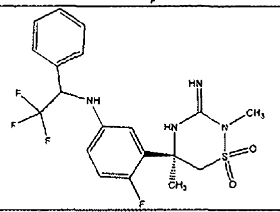
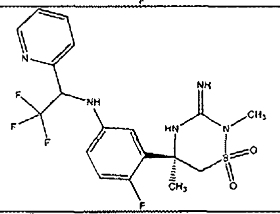
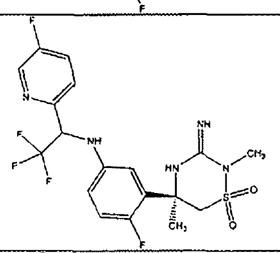
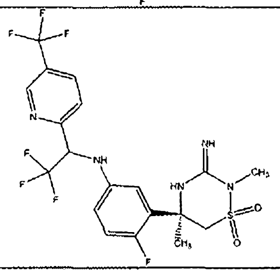
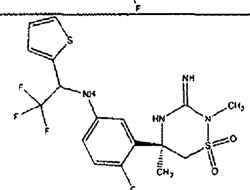
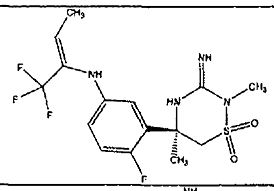
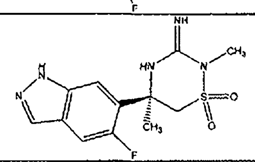
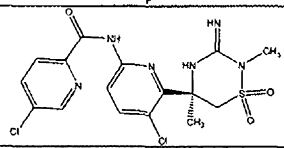
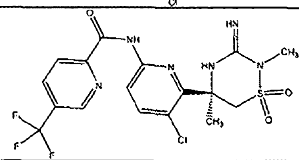
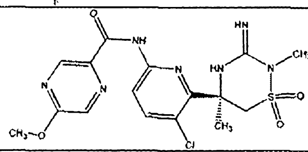
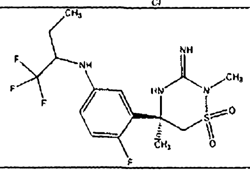
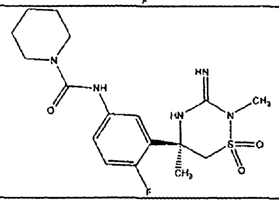
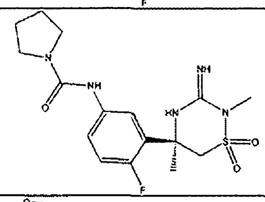
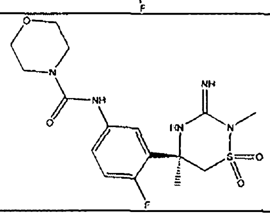
109	
109	
110	
111	
112	
113	
114	
115	
116	
117	
118	
119	
120	
121	

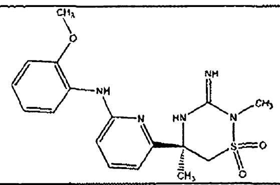
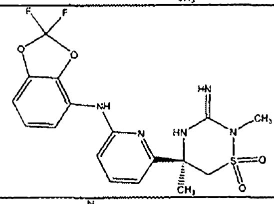
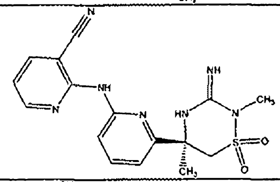
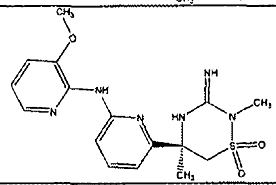
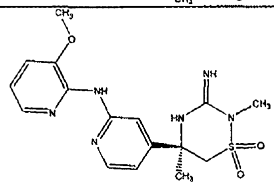
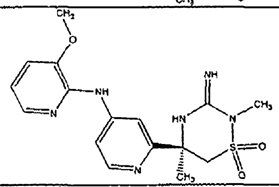
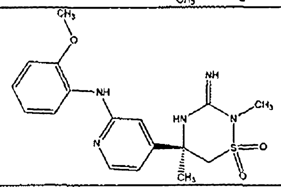
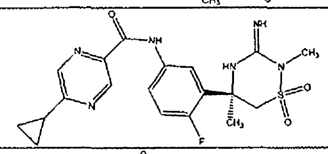
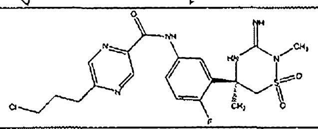
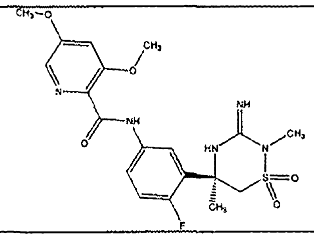
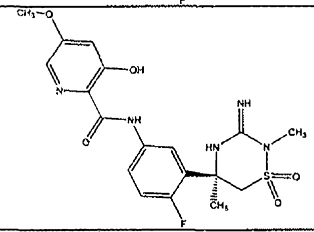
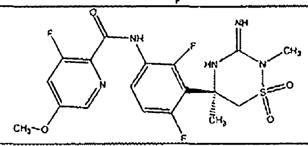
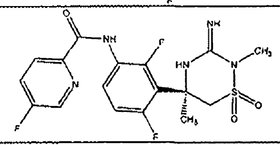
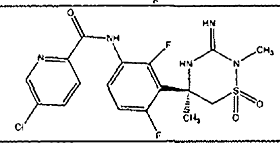
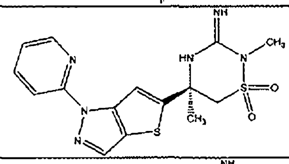
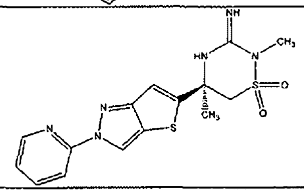
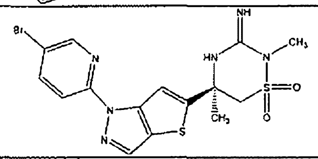
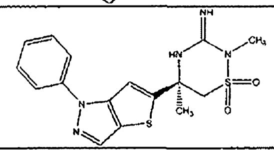
122	
123	
124	
125	
126	
127	

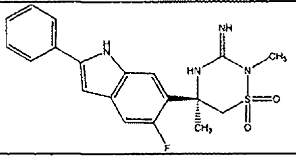
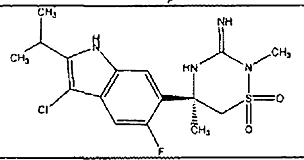
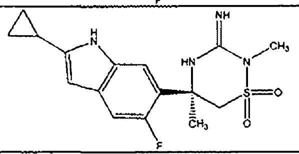
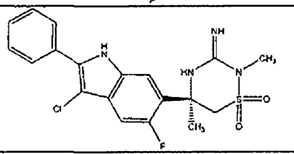
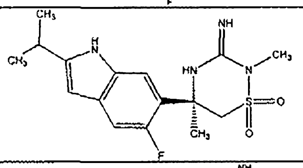
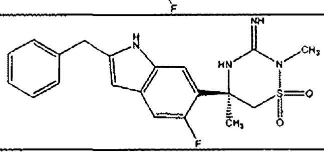
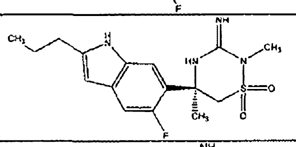
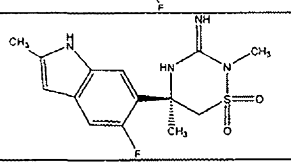
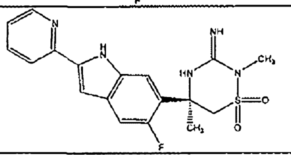
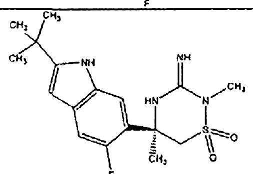
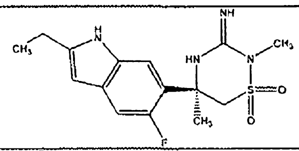
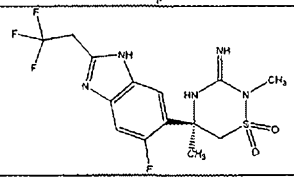
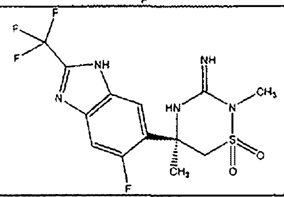
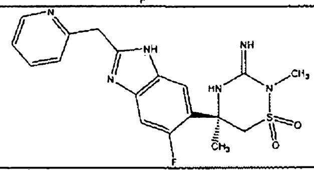
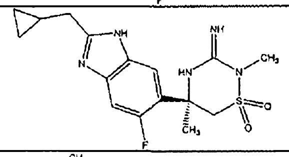
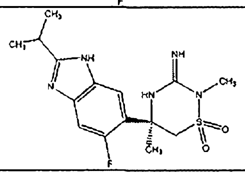
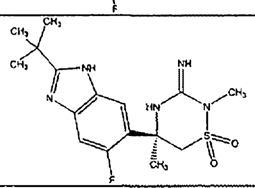
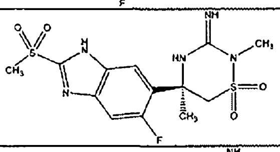
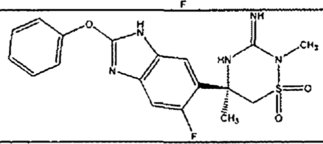
128	
129	
130	
130a	
130b	
131	

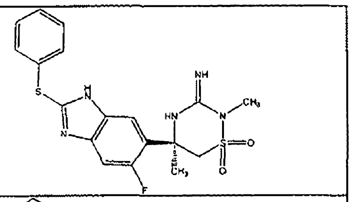
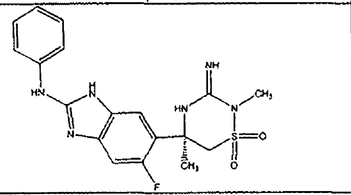
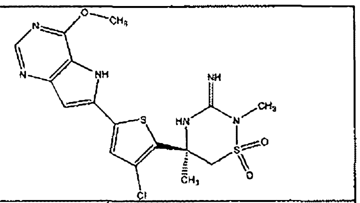
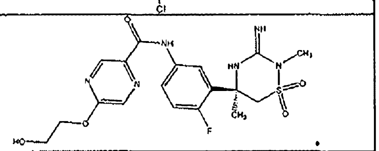
132	
133	
134	
135	
136	
137	
138	

139	
140	
141	
142	
143	
144	
145	
146	

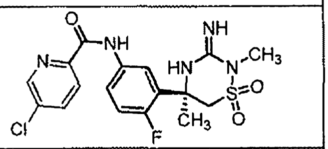
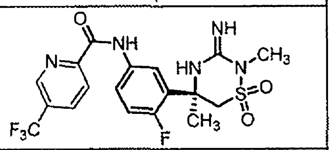
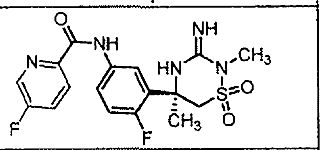
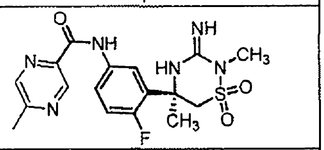
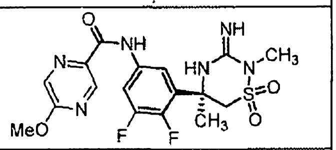
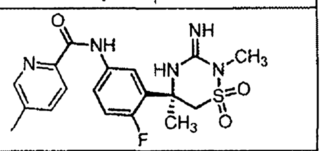
147	
148	
149	
150	
151	
152	
153	
154	
155	
156	
157	
158	
159	
160	
161a	
161b	

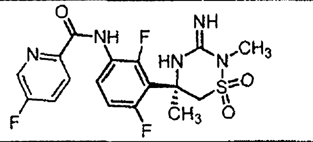
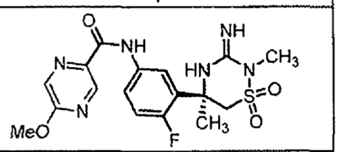
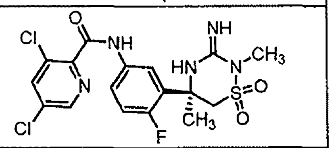
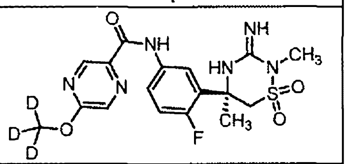
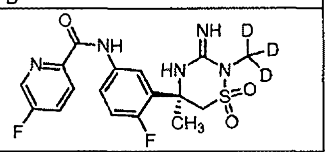
162	
163	
164	
165	
165	
166	
167	
168	
169	
170	
171	
172	
173	
174	
175	
176	
177	
178	

179	
180	
181	
182	
183	
184	
185	
186	
187	
188	
189	
190	
191	
192	
193	
194	
195	
196	
197	

198	
199	
200	
201	

9. A compound, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, said compound being selected from the group consisting of:

Ex. #	Structure
34	
26	
25	
36	
40di	
35	

Ex. #	Structure
173	
40ai	
40ag	
40aq	
40ax	

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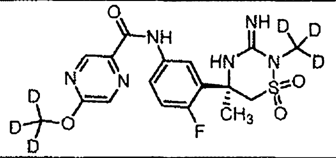
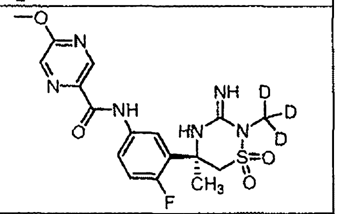
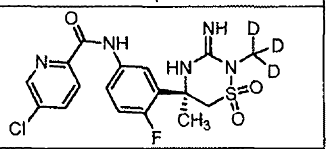
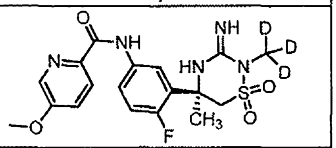
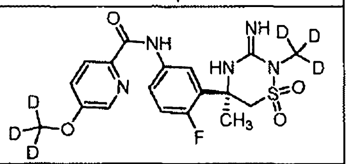
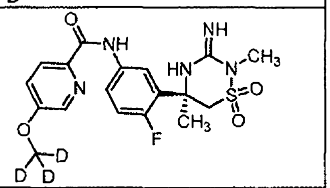
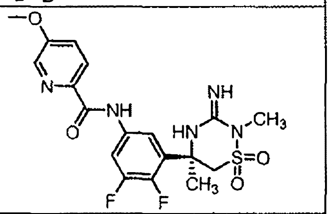
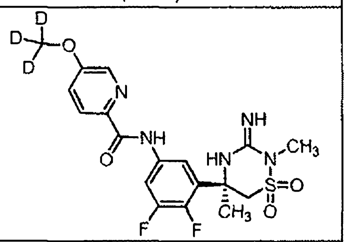
Ex. #	Structure
40ay	
40az	
40bb	
40bc	
40bd	
40cz	
40el	
40es	

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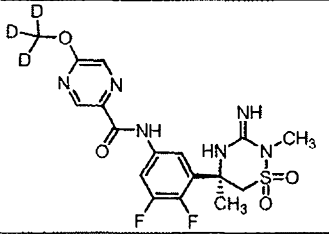
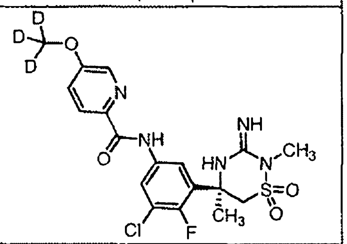
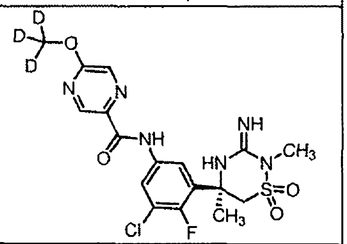
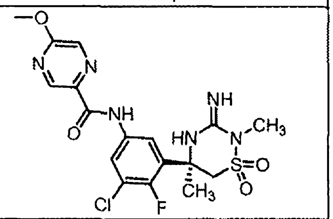
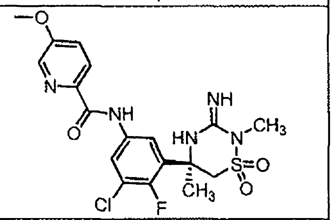
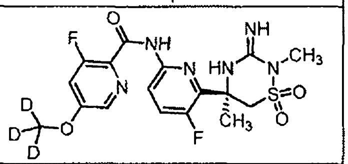
40et	
40ff	
40fg	
40fh	
40fi	
40fl	

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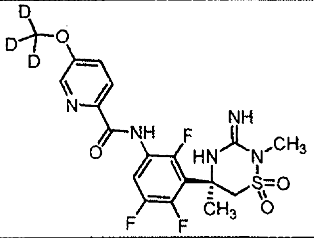
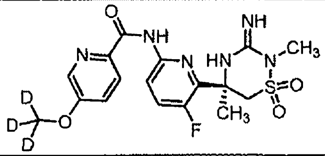
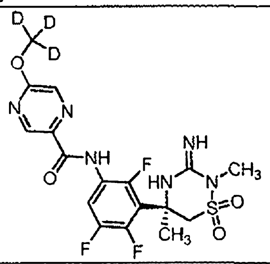
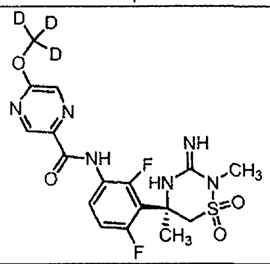
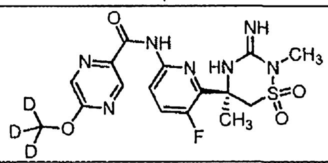
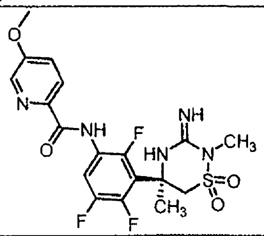
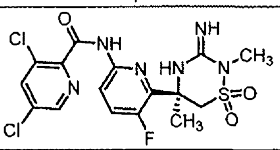
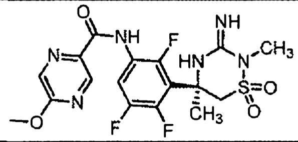
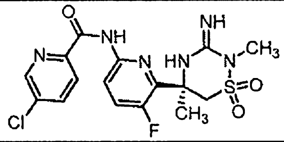
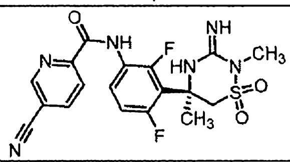
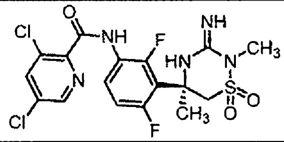
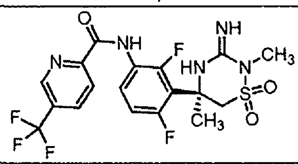
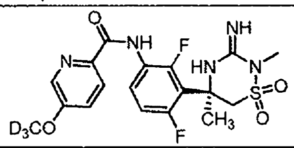
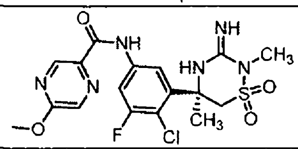
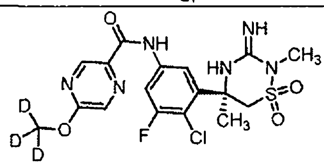
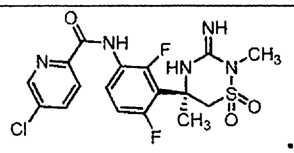
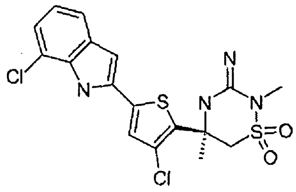
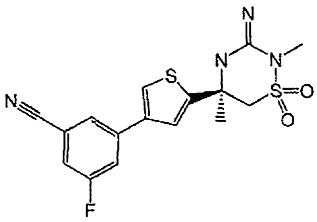
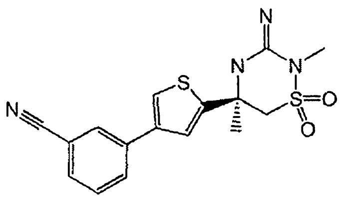
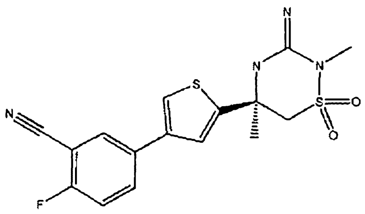
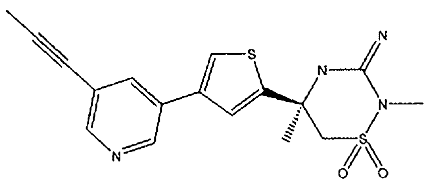
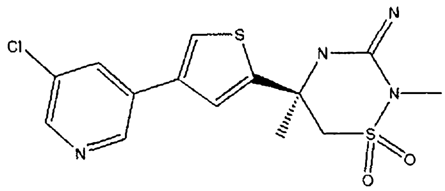
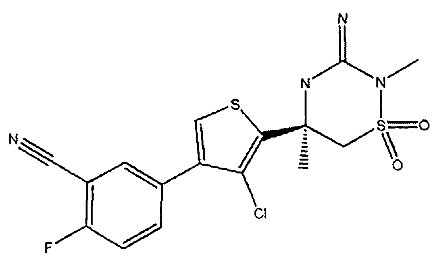
Ex. #	Structure
40fn	
40fo	
40fp	
40fq	
40fr	
40ge	
40gi	
40go	
40gs	
40hm	
40hp	
40hr	
40ii	
42n	
42p	 , and
174	 .

10. A compound, or a tautomer thereof,

10. A compound, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, said compound being selected from the group consisting of

Ex.	Structure
141a	
44	
45	
46	
47	
48	
51	

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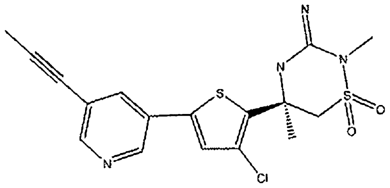
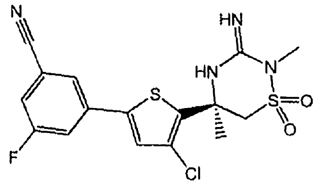
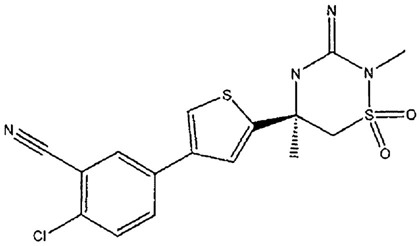
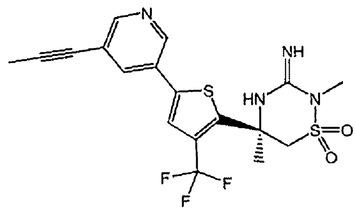
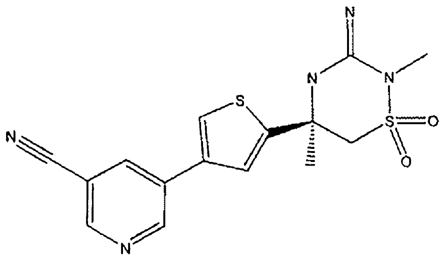
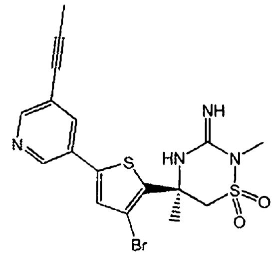
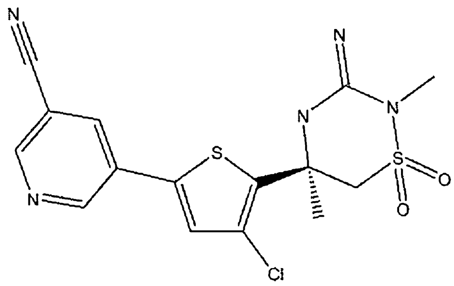
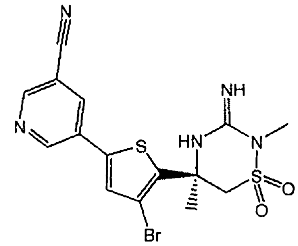
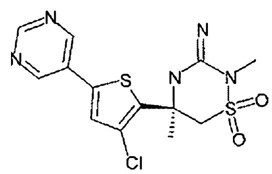
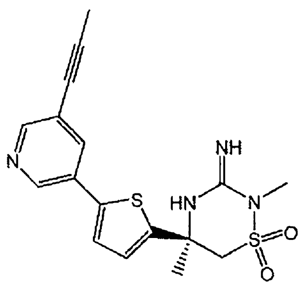
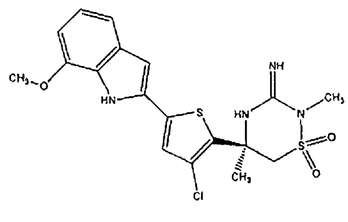
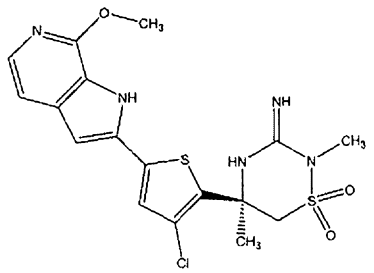
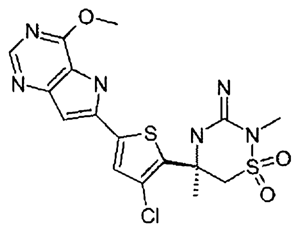
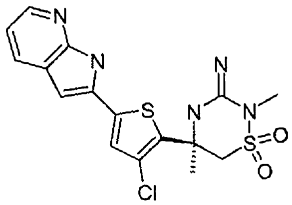
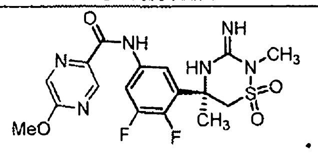
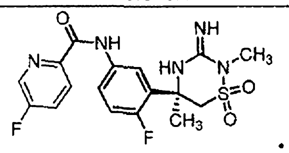
Ex.	Structure	Ex.	Structure
52		82	
54		87	
55		88	
66		89	
		95g	
80		141	

Ex.	Structure	Ex.	Structure
144		200	 .
145	 , and		

11. A compound, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound having a structure:

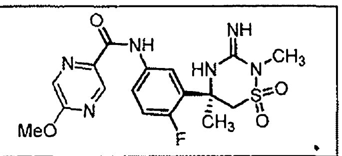
Ex #	Structure
40di	 .

12. A compound, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound having a structure:

Ex #	Structure
25	 .

13. A compound, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound having a structure:

Ex #	Structure

40ai	

14. A pharmaceutical composition comprising at least one compound of any one of claims 1-13, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

15. A pharmaceutical composition comprising a compound of any one of claims 1-13, or a tautomer thereof, or a stereoisomer of said compound or said tautomer, or a pharmaceutically acceptable salt thereof, together with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier or diluent.

16. A pharmaceutical composition of claim 15, wherein said at least one additional therapeutic agent is at least one agent selected from:

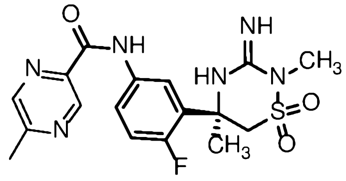
m_1 agonists; m_2 antagonists; cholinesterase inhibitors; galantamine; rivastigimine; N-methyl-D-aspartate receptor antagonists; combinations of cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists; gamma secretase modulators; gamma secretase inhibitors; non-steroidal anti-inflammatory agents; anti-inflammatory agents that can reduce neuroinflammation; anti-amyloid antibodies; vitamin E; nicotinic acetylcholine receptor agonists; CB1 receptor inverse agonists; 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; Tau aggregation inhibitors; RAGE inhibitors; anti-Abeta vaccine; APP ligands; agents that upregulate insulin, cholesterol lowering agents; cholesterol absorption inhibitors; combinations of HMG-CoA reductase inhibitors and cholesterol absorption inhibitors; fibrates; 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; LXR agonists; LRP mimics; H3 receptor antagonists; histone deacetylase inhibitors; hsp90 inhibitors; 5-HT4 agonists; 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; Metal-protein attenuating compound; GPR3 modulators; and antihistamines.

17. A method of treating, preventing, and/or delaying the onset of an amyloid β pathology ("Aβ pathology") and/or one or more symptoms of said pathology comprising administering at least one compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, to a patient in need thereof in an amount effective to treat said pathology.

18. A method of claim 17, wherein said Aβ pathology is selected from 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, Parkinson's disease, and/or Down'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, diabetes-associated amyloidogenesis, hemodialysis complications (from β_2 microglobulins and complications arising therefrom in hemodialysis patients), scrapie, bovine spongiform encephalitis, traumatic brain injury ("TBI"), Creutzfeld-Jakob disease, and traumatic brain injury.

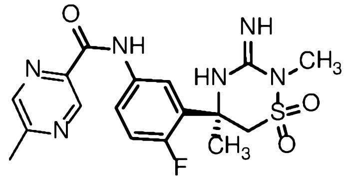
19. A method of claim 18, wherein said Aβ pathology is Alzheimer's disease.

1. A compound, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound having a structure:



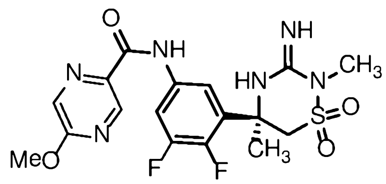
.

2. A pharmaceutically acceptable salt of a compound, or a tautomer thereof, said compound having a structure:



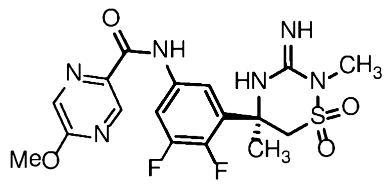
.

3. A compound, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound having a structure:



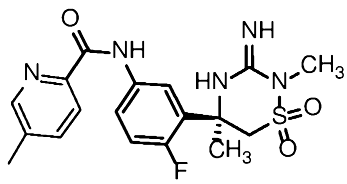
.

4. A pharmaceutically acceptable salt of a compound, or a tautomer thereof, said compound having a structure:



.

5. A compound, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound having a structure:



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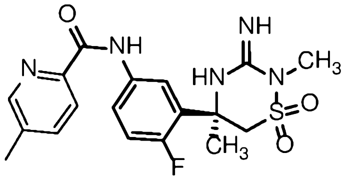
6. A pharmaceutically acceptable salt of a compound, or a tautomer thereof, said compound having a structure:



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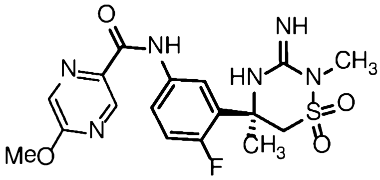
7. A compound, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound having a structure:



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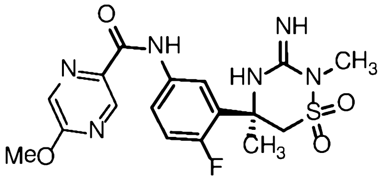
8. A pharmaceutically acceptable salt of a compound, or a tautomer thereof, said compound having a structure:



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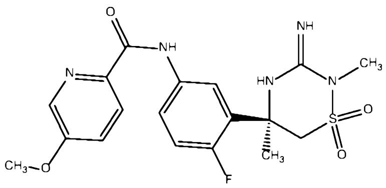
9. A compound, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, said compound having a structure:



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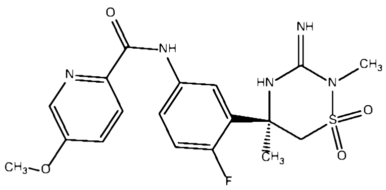
10. A pharmaceutically acceptable salt of a compound, or a tautomer thereof, said compound having a structure:



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11. A pharmaceutically acceptable salt of the compound of any one of claims 1 to 10 or a tautomer thereof, wherein said salt is selected from the group consisting of acetate, ascorbate, benzoate, benzenesulfonate, bisulfate, borate, butyrate, citrate, camphorate, camphorsulfonate, fumarate, hydrochloride, hydrobromide, hydroiodide, lactate, maleate, methanesulfonate, naphthalenesulfonate, nitrate, oxalate, phosphate, propionate, salicylate, succinate, sulfate, tartarate, thiocyanate, and tosylate.

12. A pharmaceutically acceptable salt of the compound of any one of claims 1 to 10 or a tautomer thereof, wherein said salt is a hydrochloride salt.

13. A pharmaceutically acceptable salt of the compound of any one of claims 1 to 10 or a tautomer thereof, wherein said salt is a tosylate salt.

14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound of any one of claims 1, 3, 5, 7 or 9, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer.

15. Use of a compound of any one of claims 1, 3, 5, 7 or 9, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, for the manufacture of a medicament the treatment of an amyloid β pathology.

16. The use according to claim 15 wherein said amyloid β pathology is 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.

17. The use according to claim 16 wherein said amyloid β pathology is Alzheimer's disease.

18. A method of treating an amyloid β pathology comprising administering a compound of any one of claims 1, 3, 5, 7 or 9, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or said tautomer, or a pharmaceutical composition of claim 14, to a patient in need thereof in an amount effective to treat said pathology.

19. The method according to claim 18 wherein said amyloid β pathology is 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.

20. The method according to claim 18 wherein said amyloid β pathology is Alzheimer's disease.

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