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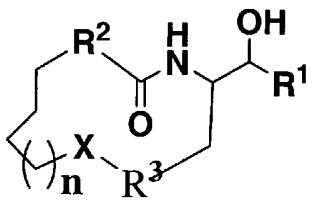
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(54) **Title:** MACROCYCLIC BETA-SECRETASE INHIBITORS



(I)

(57) **Abstract:** Disclosed are novel compounds of the formula (I): or a pharmaceutically acceptable salt or solvate thereof, wherein R^1, R^2, R^3, n and X are as defined in the specification. Also disclosed are pharmaceutical compositions comprising the compounds of formula (I). Also disclosed are methods of treating cognitive or neurodegenerative diseases such as Alzheimer's disease. Also disclosed are methods of treating a cognitive or neurodegenerative disease comprising administering to a patient I need of such treatment a combination of at least one compound of formula (I) and at least one compound selected from the group consisting of -secretase inhibitors other than those of formula (I), HMG-CoA reductase inhibitors, gamma-secretase inhibitors, non-steroidal anti-inflammatory agents, N-methyl-D-aspartate receptor antagonists, cholinesterase inhibitors and anti-amyloid antibodies.

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MACROCYCLIC BETA-SECRETASE INHIBITORS

FIELD OF THE INVENTION

This invention relates to substituted macrocyclic BACE-1 inhibitors, pharmaceutical compositions comprising said compounds, and their use in the treatment of Alzheimer's disease.

BACKGROUND

Alzheimer's disease (AD) is a progressive neurodegenerative disease that is ultimately fatal. Disease progression is associated with gradual loss of cognitive function related to memory, reasoning, orientation and judgment. Behavioral changes including confusion, depression and aggression also manifest as the disease progresses. The cognitive and behavioral dysfunction is believed to result from altered neuronal function and neuronal loss in the hippocampus and cerebral cortex. The currently available AD treatments are palliative, and while they ameliorate the cognitive and behavioral disorders, they do not prevent disease progression. Therefore there is an unmet medical need for AD treatments that halt disease progression.

Pathological hallmarks of AD are the deposition of extracellular β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles comprised of abnormally phosphorylated protein tau. Individuals with AD exhibit characteristic Aβ deposits, in brain regions known to be important for memory and cognition. It is believed that Aβ is the fundamental causative agent of neuronal cell loss and dysfunction, which is associated with cognitive and behavioral decline. Amyloid plaques consist predominantly of Aβ peptides comprised of 40 – 42 amino acid residues, which are derived from processing of amyloid precursor protein (APP). APP is processed by

multiple distinct protease activities. Aβ peptides result from the cleavage of APP by β-secretase at the position corresponding to the N-terminus of Aβ, and at the C-terminus by γ-secretase activity. APP is also cleaved by α-secretase activity resulting in the secreted, non-amyloidogenic fragment known as soluble APP.

An aspartyl protease known as BACE-1 has been identified as the β-secretase activity responsible for cleavage of APP at the position corresponding to the N-terminus of Aβ peptides.

Accumulated biochemical and genetic evidence supports a central role of Aβ in the etiology of AD. For example, Aβ has been shown to be toxic to neuronal cells in vitro and when injected into rodent brains. Furthermore inherited forms of early-onset AD are known in which well-defined mutations of APP or the presenilins are present. These mutations enhance the production of Aβ and are considered causative of AD.

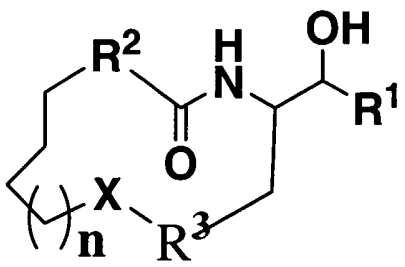
Since Aβ peptides are formed as a result of β-secretase activity, inhibition of BACE-1 should inhibit formation of Aβ peptides. Thus inhibition of BACE-1 is a therapeutic approach to the treatment of AD and other cognitive and neurodegenerative diseases caused by Aβ plaque deposition.

Substituted amine BACE-1 inhibitors are disclosed in, WO 04/04396, WO 02/02505, WO 02/02506, WO 02/02512, WO 02/02518 and WO 02/02520. Renin inhibitors comprising a (1-amino-2 hydroxy-2-heterocyclic)ethyl moiety are disclosed in WO 89/03842. WO 02/088101 discloses BACE inhibitors functionally described as being comprised of four hydrophobic moieties, as well as series of compounds preferably comprising a heterocyclic or heteroaryl moiety.

WO 02/100856 and WO 02/100399 disclose macrocycles and methods for preparing macrocycles useful in the treatment of Alzheimer's disease.

SUMMARY OF THE INVENTION

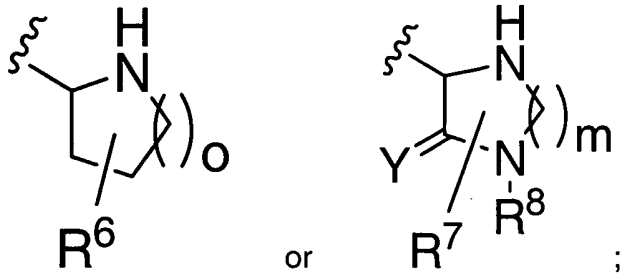
The present invention relates to compounds having the structural formula I



I

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 is



;

R^2 is $-N(R^5)C(O)R^4-$ or heterocyclylene ring;

R^3 is arylene, heteroarylene, heterocyclylene or cycloalkylene;

R^4 is arylene, heteroarylene, heterocyclylene or cycloalkylene;

R^5 is hydrogen, alkyl, aryl, heteroaryl or cycloalkyl;

R^6 and R^7 are independently selected from hydrogen, -OH, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroaralkyl, aralkoxy, heteroaralkoxy and alkoxy, with the proviso that when R^6 and R^7 are –OH, aralkoxy, heteroaralkoxy and alkoxy, R^6 and R^7 are not attached to a ring carbon adjacent to a ring nitrogen;

R^8 is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, $-C(O)R^9$, $-C(O)OR^{12}$, $-S(O)R^9$, $-S(O_2)R^9$ or –CN; with the proviso that when Y is =O, R^8 cannot be $-C(O)R^9$, $-C(O)OR^{12}$, $-S(O)R^9$, $-S(O_2)R^9$ or –CN;

R^9 is hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, cycloalkylalkyl, aralkyl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl or $-N(R^{10})(R^{11})$;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, alkenyl and alkynyl;

or R^{10} and R^{11} together with the nitrogen to which they are attached, form a 3-7 membered heterocyclyl ring;

R^{12} is alkyl, cycloalkyl, aryl, heteroaryl, cycloalkylalkyl, aralkyl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, alkenyl or alkynyl;

X is O, S, $C(R^5)$, or NH;

Y is =O, or (H,H);

m is 1, 2, or 3;

n is 0, 1, 2, or 3;

and

o is 0, 1, 2, or 3;

wherein each alkyl is optionally substituted with 1 to 3 moieties selected from the group consisting of halo, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, carboxy and –C(O)O-alkyl;

and

wherein each arylene, heteroarylene, heterocyclyl, heterocyclylalkyl, heterocyclylene, cycloalkylene, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, aralkoxy or heteroaralkoxy is optionally substituted with 1 to 4 moieties selected from the group consisting of –CF_3, alkyl, alkenyl, alkynyl, 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, -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, with the proviso that cycloalkylene and heterocyclylene can be substituted with =O.

Compounds represented by formula I are beta-secretase inhibitors useful for the prevention and treatment of Alzheimer's disease.

In another aspect, the invention relates to a pharmaceutical composition comprising at least one compound of formula I and a pharmaceutically acceptable carrier.

In another aspect, the invention comprises a method of inhibiting BACE-1 comprising administering at least one compound of formula I to a patient in need of such treatment. Also claimed is the method of inhibiting the formation, or formation and deposition, of β-amyloid plaques in, on or around neurological tissue (e.g., the brain) comprising administering at least one compound of formula I to a patient in need of such treatment.

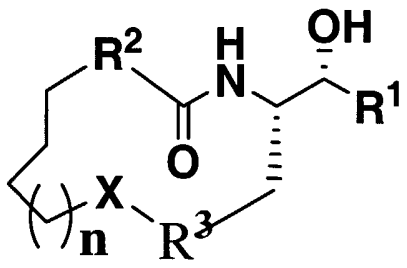
More specifically, the invention comprises a method of treating a cognitive or neurodegenerative disease comprising administering at least one compound of formula I to a patient in need of such treatment. Further, the invention comprises the method of treating Alzheimer's disease comprising administering at least one compound of formula I to a patient in need of such treatment.

In another aspect, the invention comprises the method of treating a cognitive or neurodegenerative disease comprising administering to a patient I need of such treatment a combination of at least one compound of formula I and at least one compound selected from the group consisting of β-secretase inhibitors other than those of formula I, HMG-CoA reductase inhibitors, gamma-secretase inhibitors, non-steroidal anti-inflammatory agents, N-methyl-D-aspartate receptor antagonists, cholinesterase inhibitors and anti-amyloid antibodies.

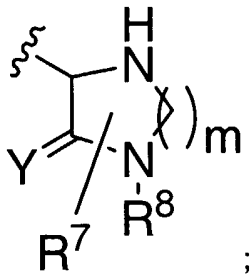
In a final aspect, the invention relates to a kit comprising in separate containers in a single package pharmaceutical compositions for use in combination, in which one container comprises at least one compound of formula I in a pharmaceutically acceptable carrier and a second container comprises at least one β-secretase inhibitor other than those of formula I, HMG-CoA reductase inhibitor, gamma-secretase inhibitor, non-steroidal anti-inflammatory agent, N-methyl-D-aspartate receptor antagonist, cholinesterase inhibitor and/or anti-amyloid antibody in a pharmaceutically acceptable carrier, the combined quantities being an effective amount to treat a cognitive disease or neurodegenerative disease such as Alzheimer's disease.

DETAILED DESCRIPTION:

Referring to formula I, above, preferred compounds of the invention are those with the following stereochemistry:

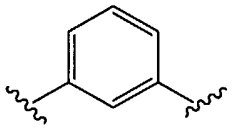


In preferred compounds of formula I, R^1 is



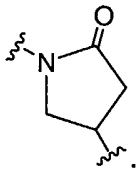
;

R^2 is preferably is $-N(R^5)C(O)R^4-$, wherein R^4 is preferably arylene and R^5 is preferably alkyl. More preferably, R^4 is phenylene and R^5 is propyl. In a preferred embodiment , R^4 is



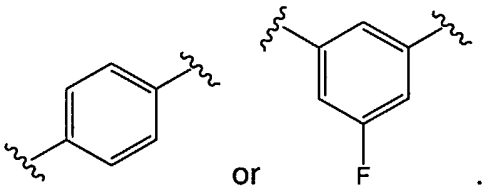
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Alternatively, R^2 is heterocyclylene, more preferably R^2 is heterocyclylene substituted with =O with the following structure:



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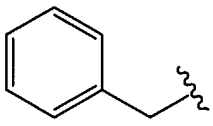
R^3 is preferably arylene, more preferably, R^3 is phenylene or halo-substituted phenylene. Even more preferably, R^3 is

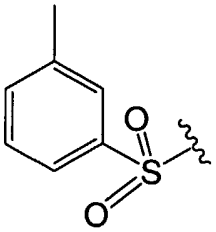


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Preferably, m is 2 and n is 1.

R^7 is preferably hydrogen.

R^8 is preferably aralkyl or $-S(O_2)R^9$ or more preferably R^8 is  or

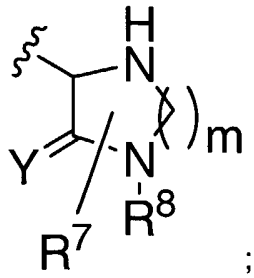


.

Preferably, X is O and Y is O.

In a preferred embodiment of the compound of formula I,

R^1 is



;

R^2 is $-N(R^5)C(O)R^4-$ or heterocyclylene;

R^3 is arylene;

R^4 is arylene or heterocyclylene;

R^5 is alkyl;

R^7 is hydrogen;

R^8 is aralkyl or $-S(O_2)R^9$;

m is 2;

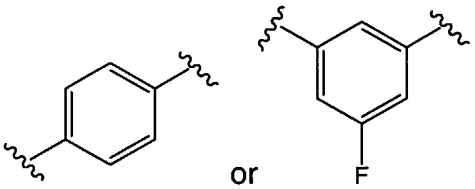
n is 1;

X is O;

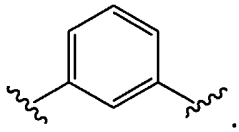
and

Y is O.

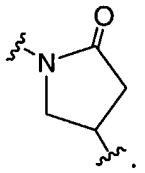
In the above-preferred embodiment, R^3 is preferably phenylene or halo-substituted phenylene. Specifically, R^3 is



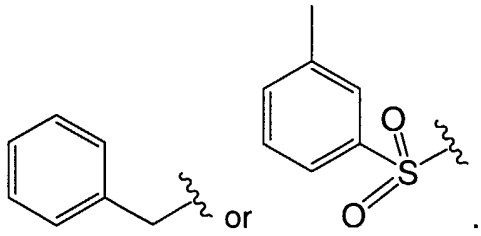
In the above-preferred embodiment, R^4 is preferably arylene, specifically, R^4 is



Alternatively, R^2 is heterocyclylene, more preferably R^2 is heterocyclylene substituted with =O with the following structure:



In the above-preferred embodiment, R^8 is



Except where stated otherwise, the following definitions apply throughout the present specification and claims. These definitions apply regardless of whether a term is used by itself or in combination with other terms. Hence the definition of "alkyl" applies to "alkyl" as well as to the "alkyl" portions of "alkoxy", "cycloalkyl" and so forth.

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

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"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.

"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 and ethylene.

"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. The term "substituted alkenyl" means that the alkenyl group may be 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.

"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. The term "substituted alkynyl" means that the alkynyl group may be 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.

"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.

“Arylene” means a difunctional group obtained by removal of a hydrogen atom from an aryl group that is defined above. Non-limiting examples of arylene include phenylene and naphthylene.

"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. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, 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.

"Heteroarylene" means a difunctional group obtained by removal of a hydrogen atom from a heteroaryl group that is defined above. Non-limiting examples of pyridylene, pyrazinylene, furanylene, thienylene and pyrimidinylene.

"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.

"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.

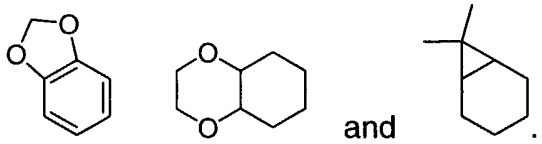
"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. 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, as well as partially saturated species such as, for example, indanyl, tetrahydronaphthyl and the like.

"Cycloalkylene" means a difunctional group obtained by removal of a hydrogen atom from a cycloalkyl group that is defined above. Non-limiting examples of cycloalkylene include cyclobutylene and cyclopropylene.

"Halo" means fluoro, chloro, bromo or iodo. Preferred are fluoro, chloro and bromo.

"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 independently selected from the group consisting of $-CF_3$, alkyl, alkenyl, alkynyl, 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, $-C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, $-C(=NH)-NH(alkyl)$, 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 methylene dioxy, ethylenedioxy, $-C(CH_3)_2-$ and the like which form moieties such as, for example:

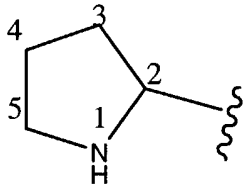
 and .

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 4 to about 7 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. 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.

"Heterocyclylene" means a difunctional group obtained by removal of a hydrogen atom from an heterocyclyl group that is defined above. Non-limiting examples of heterocyclylene include piperidylene, pyrrolidinylene, piperazinylene,

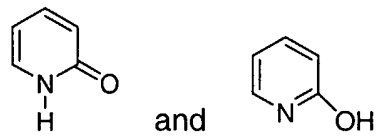
morpholinylene, thiomorpholinylene, thiazolidinylene, 1,4-dioxanylene, tetrahydrofuranylene and tetrahydrothiophenylene.

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, nor is there an N or S group on a carbon adjacent to another heteroatom. Thus, for example, in the ring:



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

It should also be noted that tautomeric forms such as, for example, the moieties:



are considered equivalent in certain embodiments of this invention.

"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 heteroaralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Heteroaralkylthio" means a heteroaralkyl-S- group in which the heteroaralkyl is as previously described. Preferred heteroaralkylthios contain a lower alkyl group. The bond to the parent moiety is through the sulfur.

"Heteroarylalkenyl" means a heteroaryl-alkenyl group in which the heteroaryl and the alkenyl are as previously described. Preferred heteroarylalkenyls contain a lower alkenyl group. The bond to the parent moiety is through the alkenyl.

"Heteroarylalkynyl" means a heteroaryl-alkynyl group in which the heteroaryl and the alkynyl are as previously described. Preferred heteroarylalkynyls contain a lower alkynyl group. The bond to the parent moiety is through the alkynyl.

"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.

"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.

"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.

"Alkoxyalkyl" means an alkoxy-alkyl group in which the alkoxy and alkyl groups are as previously described. Non-limiting examples of suitable alkoxyalkyl groups include ethoxyethyl, methoxymethyl and ethoxymethyl. The bond to the parent moiety is through the alkyl group.

"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.

"Aralkoxy" means an aralkyl-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.

"Alkylheteroaryl" means an alkyl-heteroaryl group in which the alkyl and heteroaryl groups are as previously described. The bond to the parent moiety is through the heteroaryl.

"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-C(O)- group in which the alkyl group is as previously described. 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 in which the aryl group is as previously described. 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 in which the aralkyl group is as previously described. 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 in which the alkyl group is as previously described. 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 in which the aryl group is as previously described. The bond to the parent moiety is through the sulfonyl.

"Cycloalkylalkyl" means a cycloalkyl-alkyl- group in which the cycloalkyl and alkyl group is as previously described. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the alkyl.

“Heteroaralkoxy” means an heteroaralkyl-O- group in which the heteroaralkyl group is as previously described. The bond to the parent moiety is through the ether oxygen.

"Heteroarylsulfonyl" means a heteroaryl-S(O_2)- group in which the heteroaryl group is as previously described. The bond to the parent moiety is through the sulfonyl.

“Heteroarylthio” means a heteroaryl-S- group in which the heteroaryl group is as previously described. The bond to the parent moiety is through the sulfur.

“Heterocyclylalkyl” means a heterocyclyl-alkyl group in which the heterocyclyl and the alkyl are as previously described. The bond to the parent moiety is through the alkyl.

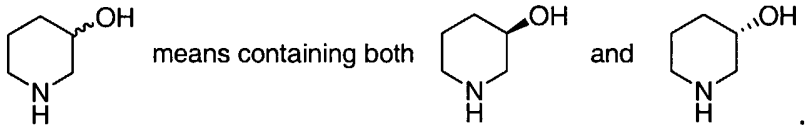
The term “substituted” means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the

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.

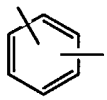
The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

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 formula I," one to three compounds of formula I can be administered at the same time, preferably one.

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

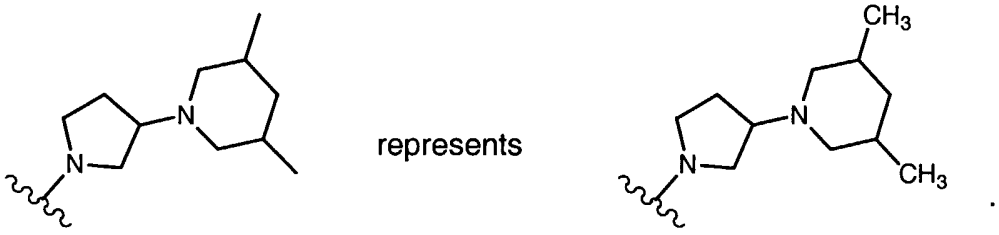


Lines drawn into the ring systems, such as, for example:



indicate that the indicated line (bond) may be attached to any of the substitutable ring carbon atoms.

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:



The term "isolated" or "in isolated form" for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. The term "purified" or "in purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan, in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the hydrogen atom(s) to satisfy the valences.

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.

When any variable (e.g., aryl, heterocycle, R^2, etc.) occurs more than one time in any constituent or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

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. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula I or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *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, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the

solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I 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 Formula I 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 Formula I may be formed, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, 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.

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

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

Compounds represented by formula **I** are beta-secretase inhibitors useful for the prevention and treatment of Alzheimer's disease.

An aspect of this invention is a method of treating a mammal (*e.g.*, human) having a disease or condition mediated or exacerbated by BACE-1 (an aspartyl protease) by administering a therapeutically effective amount of at least one compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound to the mammal.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting BACE-1 and thus producing the desired therapeutic effect in a suitable patient.

A preferred dosage is about 0.001 to 1000 mg/kg of body weight/day of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. An especially preferred dosage is about 0.01 to 30 mg/kg of body weight/day of a compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound.

Still yet another aspect of this invention is a method of treating a cognitive or neurodegenerative disease, such as Alzheimer's disease, comprising administering to a mammal in need of such treatment a therapeutically effective amount of at least one compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound.

A further aspect of this invention is a method for treating a cognitive or neurodegenerative disease such as Alzheimer's disease, comprising administering to a mammal a therapeutically effective amount of at least one compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound.

This invention is also directed to pharmaceutical compositions, which comprise at least one compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound and at least one pharmaceutically acceptable carrier.

This invention is also directed to pharmaceutical compositions for the treatment of neurodegenerative diseases such as Alzheimer's disease which comprise an effective treating amount of at least one compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound and at least one pharmaceutically acceptable carrier.

For the combination aspect, the use of any β-secretase inhibitor other than those of formula I is contemplated; β-secretase inhibitory activity can be determined by the procedures described below. Useful β-secretase inhibitors are those disclosed in, but are not limited to, WO 02/02505, WO 02/02506, WO 02/02512, WO 02/02518, WO 02/02520 and WO 02/088101.

Still yet other aspects of this invention are combinations of a compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound and other compounds as described below.

Accordingly, included within the invention is a method for treating neurodegenerative diseases such as Alzheimer's, comprising administering to a mammal (*e.g.*, a female or male human)

a. an amount of a first compound, said first compound being a compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound; and

b. an amount of a second compound, said second compound being a cholinesterase inhibitor.

Cholinesterase inhibitors for use in the combination include acetyl- and/or butyrylchlolinesterase inhibitors. Examples of cholinesterase inhibitors include tacrine, donepezil, rivastigmine, galantamine, pyridostigmine and neostigmine.

Accordingly, included within the invention is a method for treating neurodegenerative diseases such as Alzheimer's, comprising administering to a mammal (*e.g.*, a female or male human)

a. an amount of a first compound, said first compound being a compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound; and

b. an amount of a second compound, said second compound being an anti-amyloid antibody. Anti amyloid antibodies are described, for example, in Hock et al, *Nature Medicine, 8* (2002), p. 1270-1275.

Accordingly, included within the invention is a method for treating neurodegenerative diseases such as Alzheimer's, comprising administering to a mammal (*e.g.*, a female or male human)

a. an amount of a first compound, said first compound being a compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound; and

b. an amount of a second compound, said second compound being an anti-inflammatory compound. Examples of anti-inflammatory compounds include but are non limited to non-steroidal anti-inflammatory drugs such as diclofenac (Voltaren, Cataflam), diflunisal (Dolobid), etodolac (Lodine), flurbiprofen (Ansaid), ibuprofen (Motrin, Advil), indomethacin (Indocin), ketoprofen (Orudis, Oruvail), ketorolac (Toradol), nabumetone (Relafen), naproxen (Naprosyn, Alleve), oxaprozin (Daypro), piroxicam (Feldene), sulindac (Clinoril), tolmetin (Tolectin), celecoxib (Celebrex) and rofecoxib (Vioxx).

Accordingly, included within the invention is a method for treating neurodegenerative diseases such as Alzheimer's, comprising administering to a mammal (*e.g.*, a female or male human)

a. an amount of a first compound, said first compound being a compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound; and

b. an amount of a second compound, said second compound being a gamma secretase inhibitor. Gamma-secretase inhibitors for use in the combination of this invention can be determined by procedures known in the art. Typical gamma-secretase inhibitors include, but are not limited to, those described in WO 03/013527, US 6,683,091, WO 03/066592, USSN 10/663,042, filed September 16, 2003, WO 00/247671, WO 00/050391, WO 00/007995 and WO 03/018543.

Accordingly, included within the invention is a method for treating neurodegenerative diseases such as Alzheimer's, comprising administering to a mammal (*e.g.*, a female or male human)

a. an amount of a first compound, said first compound being a compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound; and

b. an amount of a second compound, said second compound being a HMG-CoA reductase inhibitor compound. HMG-CoA reductase inhibitors for use in combination with compounds of formula I include the "stains," e.g., atorvastatin, lovastatin, simvistatin, pravastatin, fluvastatin and rosuvastatin.

Accordingly, included within the invention is a method for treating neurodegenerative diseases such as Alzheimer's, comprising administering to a mammal (*e.g.*, a female or male human)

a. an amount of a first compound, said first compound being a compound of Formula I, or a pharmaceutically acceptable salt or solvate of said compound; and

b. an amount of a second compound, said second compound being a N-methyl-D-aspartate receptor antagonist. A suitable N-methyl-D-aspartate receptor antagonist is, for example, memantine.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, 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.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 1000 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.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the

proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 300 mg/day, preferably 1 mg/day to 50 mg/day, in two to four divided doses.

The amount and frequency of administration of the compounds of the combinations (beta secreatse inhibitors other than those of formula I, NSAIDS, statin drugs, cholinesterase inhibitors, etc.), 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.

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.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. 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.

Also included are solid form preparations which 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.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

When a compound of formula I is used in combination with a β-secretase inhibitors other than those of formula I, an HMG-CoA reductase inhibitor, a gamma-secretase inhibitor, a non-steroidal anti-inflammatory agent, an N-methyl-D-aspartate receptor antagonist, a cholinesterase inhibitor or an anti-amyloid antibody to treat a cognitive disorder or neurodegenerative disorder, the active components may be co-administered simultaneously or sequentially, or a single pharmaceutical composition comprising a compound of formula I and one of the other agents in a pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional oral or parenteral dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. The dosage of the β-secretase inhibitors other than those of formula I, HMG-CoA reductase inhibitor, gamma-secretase inhibitor, non-steroidal anti-inflammatory agent, N-methyl-D-aspartate receptor antagonist, cholinesterase inhibitor or anti-amyloid antibody can be determined from published material, and may range from 0.001 to 100 mg/kg body weight.

When separate pharmaceutical compositions of a compound of formula I and a β-secretase inhibitors other than those of formula I, an HMG-CoA reductase inhibitor, a gamma-secretase inhibitor, a non-steroidal anti-inflammatory agent, an N-methyl-D-aspartate receptor antagonist, a cholinesterase inhibitor or an anti-amyloid antibody are to be administered, they can be provided in a kit comprising in a single package, one container comprising a compound of formula I in a pharmaceutically acceptable

carrier, and a separate container comprising the other agent in a pharmaceutically acceptable carrier, with the compound of formula I and the other agent being present in amounts such that the combination is therapeutically effective. A kit is advantageous for administering a combination when, for example, the components must be administered at different time intervals or when they are in different dosage forms.

The invention also includes multi-agent compositions, kits and methods of treatment, e.g., a compound of formula I can be administed in combination with an HMG-CoA reductase inhibitor and a non-steroidal anti-inflammatory agent

Compounds of Formula I can be produced by processes known to those skilled in the art using either solution phase or solid phase synthesis as shown in the following reaction schemes, in the preparations and examples below, but those skilled in the art will recognize that other procedures can also be suitable.

In the Schemes and in the Examples below, the following abbreviations are used:

methyl: Me; ethyl: Et; propyl: Pr; butyl: Bu; benzyl: Bn

ethyl acetate: EtOAc

benzyloxycarbonyl: Cbz

N,N-dimethylformamide: DMF:

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride: EDC or EDCI

room temperature: RT

hour: h

minute: min

retention time: t_R

trifluoroacetic acid: TFA

tetrahydrofuran: THF

1-hydroxybenzotriazole: HOBt

methanol: MeOH

ethanol: EtOH

acetic acid: AcOH

dimethylsulfoxide: DMSO

lithium diisopropylamide: LDA

tert-dimethylsilyl chloride: TBSCl

tert-dimethylsilyl: TBS

triphenyl phosphine: PPh_3

diisopropyl azodicarboxylate: DIAD

copper(I) bromide-dimethyl sulfide: CuBr-Me_2S

tertiary butyloxycarbonyl: Boc

Palladium tetrakis (Triphenylphosphine): $Pd(PPh_3)_4$

Triphenylphosphine: PPh_3

Tetrabutylammonium fluoride: TBAF

Triethylamine: Et_3N, NEt_3 or TEA

Lithium borohydride: $LiBH_4$

benzyl bromide: BnBr

Di-*tert*-butyl dicarbonate: $(Boc)_2O$

4-dimethylaminopyridine: DMAP

butyllithium: BuLi

Benzyl chloride: BnCl

oxalyl chloride: $(COCl)_2$

Preparative thin layer chromatography: PTLC

thin layer chromatography: TLC

nuclear magnetic resonance: NMR

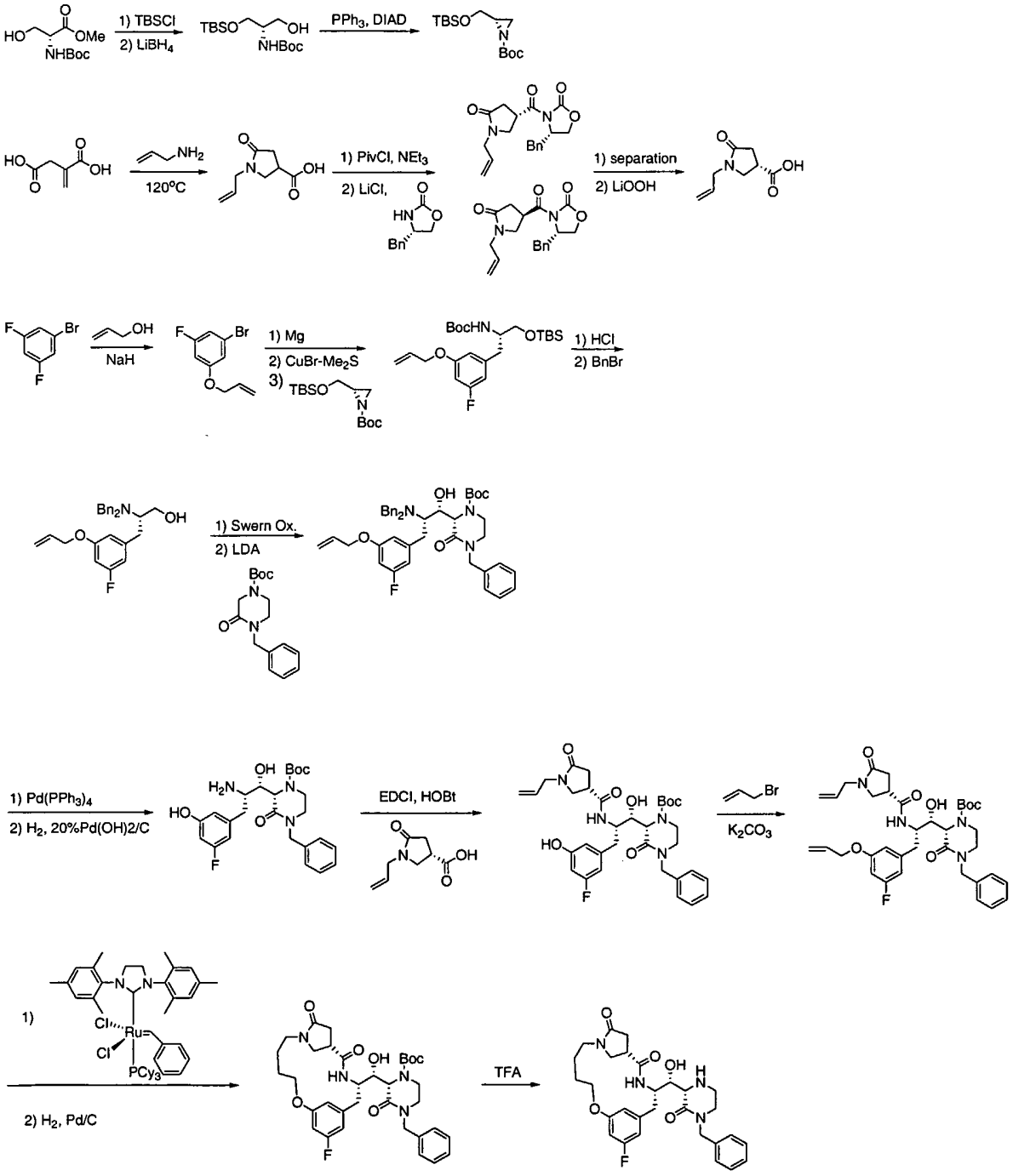
liquid chromatography mass spectrometry: LCMS

Diisopropylamine: DIPA

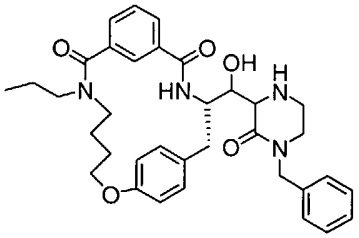
dimethylacetamide: DMA

pivaloyl chloride; PivCl.

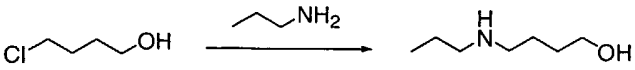
GENERAL SCHEMES:



Preparative Example 1

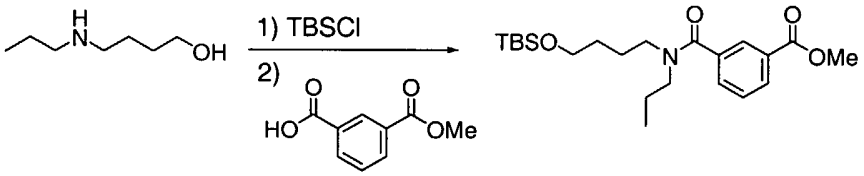


Step 1



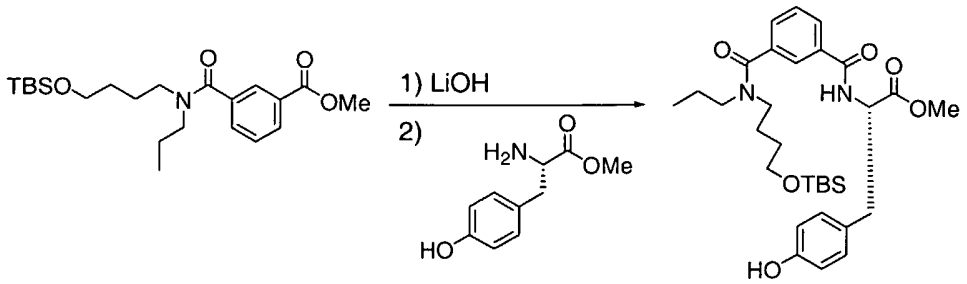
To 4-chloro-1-butanol (49.5 g, 0.456 mmol) in an ice-water bath was added propylamine (150 ml, 1.82 mol). The mixture was slowly warmed to RT and stirred for 64 h. Then the mixture was refluxed for 5 h and evaporated under reduced pressure. The residue was partitioned between ether (3x250 ml) and 40% aqueous NaOH (400 ml). The combined organic layer was dried ($MgSO_4$), concentrated, and distilled to give the product (14.87 g, 25%). ^{1}H-NMR ($CDCl_3$): δ=3.56 (m, 4H), 2.59 (m, 4H), 1.4-1.8 (m, 6H), 0.93 (m, 3H).

Step 2



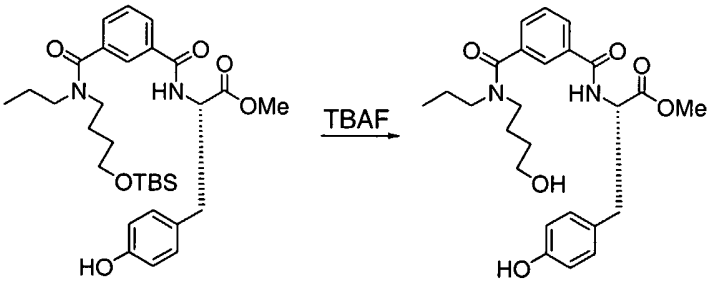
A solution of the product of Step 1(8.655 g, 66.07 mmol), TBSCl (20.12 g, 133.5 mmol), imidazole (13.50 g, 198.3 mmol), and catalytic amount of DMAP in anhydrous CH_2Cl_2 (180 ml) was stirred at RT for 16 h. The mixture was washed with 0.5N NaOH (100 ml), dried (Na_2SO_4), concentrated, and taken up in DMF (20 ml). To the resulting solution were added HOBt (10.73 g, 79.45 mmol), EDCI (15.38 g, 80.25 mmol), Triethylamine (Et_3N, NEt_3 or TEA) (29.0 ml, 208 mmol), and mono-methyl isophthalate (10.23 g, 56.78 mmol). The mixture was stirred at RT for 3 days and evaporated to dryness. The residue was partitioned between CH_2Cl_2 (200 ml) and 0.5N NaOH (200 ml). The organic layer was washed with aqueous NH_4Cl (100 ml), dried ($MgSO_4$), and purified by column chromatography (gradient MeOH/CH_2Cl_2 0-3%) to give the product (8.829 g, 38%). MS *m/e* 408 $(M+H)^+$

Step 3



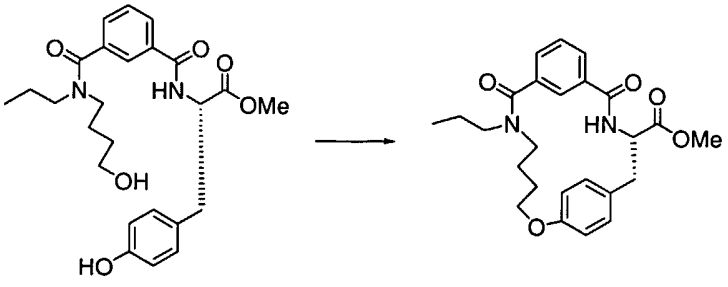
A mixture of the product of Step 2 (8.829 g, 21.69 mmol) and LiOH-H_2O (1.021 g, 24.33 mmol) in MeOH (75 ml) and water (25 ml) was stirred at RT for 16 h. The mixture was evaporated to dryness and the residue was taken up in DMF (80 ml). To the resulting solution were added triethylamine (3.0 ml, 21 mmol), EDCI (4.233 g, 22.08 mmol), HOBt (2.974 g, 22.01 mmol), and L-tyrosine methyl ester (4.235 g, 21.69 mmol). The mixture was stirred at RT for 16 h and concentrated. The residue was partitioned between CH_2Cl_2 (250 ml) and aqueous NH_4Cl (50 ml). The organic layer was washed with 5% sodium bicarbonate (100 ml), dried ($MgSO_4$), and purified by column chromatography (gradient MeOH/CH_2Cl_2 0-3.5%) to give the product (7.84 g, 63%). MS *m/e* 571 $(M+H)^+$

Step 4



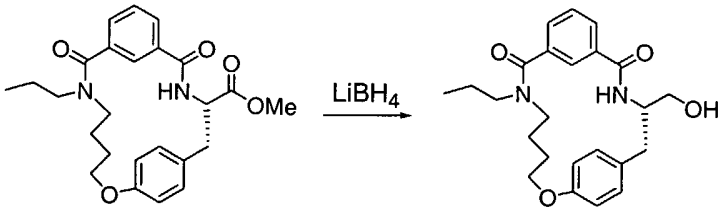
To a solution of the product of Step 3 (3.50 g, 6.14 mmol) in THF (100 ml) was added 1M TBAF in THF (9.2 ml) and the mixture was stirred at RT for 4.5 h. The mixture was concentrated and purified by column chromatography (gradient MeOH/CH_2Cl_2 0-4%) to give the product (2.40 g, 86%). MS *m/e* 457 $(M+H)^+$

Step 5



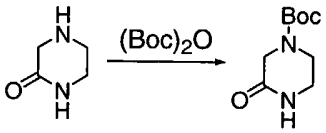
A mixture of the product of Step 4 (1.22 g, 2.68 mmol), tributylphosphine (995 µl, 4.01 mmol), and 1,1'-(azodicarbonyl)dipiperidine (1.01 g, 4.01 mmol) in benzene (150 ml) and THF (19 ml) was stirred at RT for 22 h. The mixture was concentrated and the residue was dissolved in EtOAc (200 ml) and washed with 1N HCl (100 ml). The organic layer was extracted with saturated sodium bicarbonate and brine, dried ($MgSO_4$), concentrated, and purified by column chromatography (gradient MeOH/CH_2Cl_2 0-2%) to give the product (0.583 g, 50%). MS *m/e* 439 $(M+H)^+$

Step 6



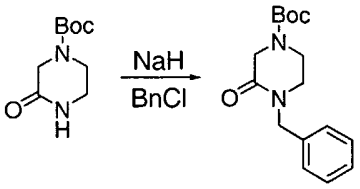
To a solution of the product of Step 5 (580 mg, 1.32 mmol) in absolute EtOH (20 ml) in an ice-water bath was added 2M lithium borohydride in THF (3.3 ml). The mixture was stirred in the ice-water bath for 10 min then at RT for 4 h. The reaction was quenched with water (1 ml) and 5% citric acid (5 ml). The mixture was concentrated and extracted with EtOAc (3x50 ml). The combined organic layer was washed with saturated sodium bicarbonate (20 ml) and brine, dried ($MgSO_4$), concentrated, and purified by column chromatography (gradient MeOH/CH_2Cl_2 0-5%) to give the product (502 mg, 93%). MS *m/e* 411 $(M+H)^+$

Step 7



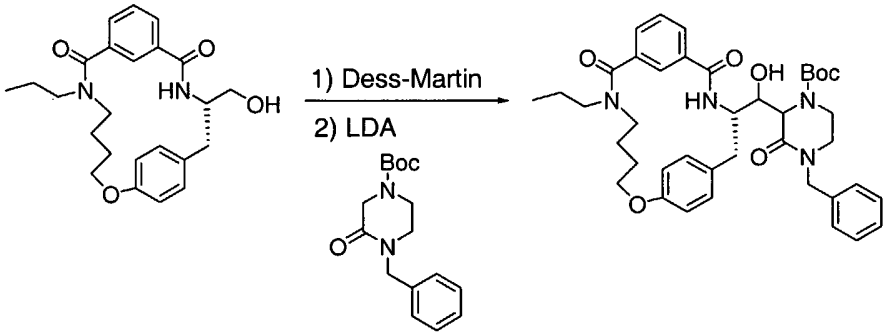
To a solution of piperazinone (10.0 g, 100 mmol), Triethylamine (20.2 g, 200 mmol), and DMAP (50 mg) in CH_2Cl_2 (250 ml) in an ice water bath was added $(Boc)_2O$ (22.9 g, 105 mmol) slowly. The mixture was stirred in the ice-water bath for 1 h and at RT for 4.5 h. The mixture was diluted with CH_2Cl_2 (250 ml), washed with water (200 ml), 5% citric acid (200 ml), 1N HCl (200 ml), saturated sodium bicarbonate (20 ml) and brine. The organic layer was dried ($MgSO_4$) and concentrated to give the product (18.0 g, 90%). MS *m/e* 201 $(M+H)^+$

Step 8



To a solution of the product of Step 7 (10.0 g, 50.0 mmol) in anhydrous DMF (250 ml) in an ice-water bath were added sodium hydride (2.40 g, 60.0 mmol) and benzyl chloride (6.60 g, 52.5 mmol). The mixture was stirred at RT for 4.5 h. The reaction was quenched with water (10 ml), diluted with CH_2Cl_2 (500 ml), and washed with water (2x250ml). The organic layer was extracted with saturated NH_4Cl (200 ml), dried ($MgSO_4$), concentrated, and purified by column chromatography (gradient MeOH/CH_2Cl_2 0-5%) to give the product (10.7 g, 74%). ^{1}H-NMR ($CDCl_3$): δ=7.2-7.3 (m, 5H), 4.57 (s, 2H), 4.10 (s, 2H), 3.53 (m, 2H), 3.19 (m, 2H), 1.41 (s, 9H).

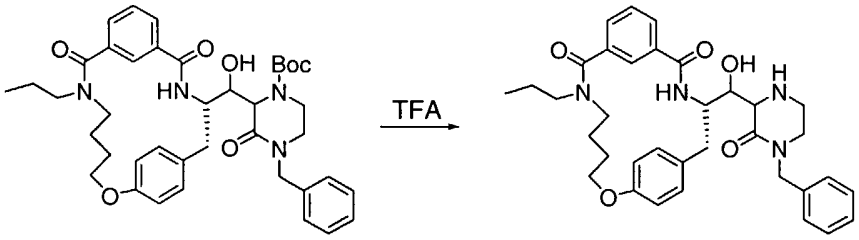
Step 9



A mixture of the product of Step 6 (123 mg, 0.300 mmol) and Dess-Martin periodinane (256 mg, 0.602 mmol) in CH_2Cl_2 (15 ml) was stirred at RT for 30 min. The mixture was diluted with CH_2Cl_2 (50 ml), washed with 1N $Na_2S_2O_3$ (20 ml) and saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated to give the crude aldehyde.

To a solution of the product of Step 8 (261 mg, 0.900 mmol) in anhydrous THF (5 ml) in a dry ice-acetone bath was added 2M LDA (0.45 ml) and the mixture was stirred for 1 h. A solution of the above aldehyde in THF (5 ml) was added and the mixture was stirred in the dry ice-acetone bath for 2 h. The reaction was quenched with saturated NH_4Cl (4 ml), diluted with CH_2Cl_2 (50 ml), and washed with water (30 ml). The organic layer was extracted with saturated NH_4Cl and brine, dried ($MgSO_4$), concentrated, and purified by PTLC (5% MeOH/CH_2Cl_2) to give the product (100 mg, 48%). MS *m/e* 699 $(M+H)^+$

Step 10

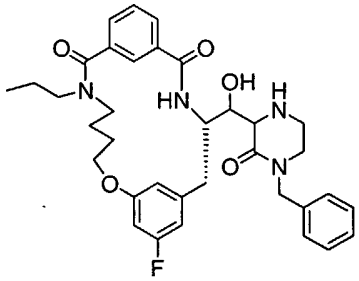


A solution of the product of Step 9 (100 mg, 0.143 mmol) in 15% TFA/CH_2Cl_2 (10 ml) was stirred at RT for 75 min. The mixture was concentrated and purified by PTLC (5% MeOH/CH_2Cl_2) to give:

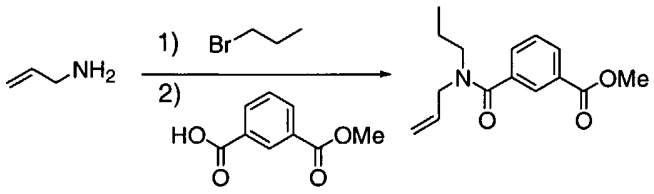
fraction A (15 mg, 18%). ^{1}H-NMR ($CDCl_3$): δ=6.4-7.8 (m, 13 H), 5.83 (m, 1H), 3.9-5.0 (m, 6H), 2.7-3.8 (m, 11H), 1.5-2.0 (m, 5H), 1.2-1.5 (m, 3H), 0.4-1.0 (m, 3H). MS *m/e* 599 $(M+H)^+$

fraction B (18 mg, 21%). ^{1}H-NMR ($CDCl_3$): δ=7.0-7.6 (m, 10H), 6.6-7.0 (m, 3H), 5.7-6.3 (m, 1H), 3.8-4.8 (m, 6H), 2.6-3.7 (m, 12H), 1.2-2.0 (m, 7H), 0.98 (m, 1H), 0.62 (m, 2H). MS *m/e* 599 $(M+H)^+$

Preparative Example 2



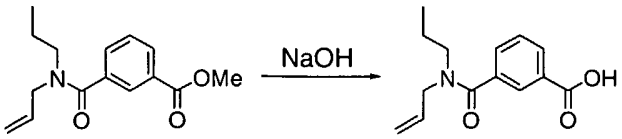
Step 1



n-Bromopropane (24.6 g, 0.200 mol) was added to allylamine (45.7 g, 0.800 mol) in an ice-water bath and the mixture was stirred at RT for 3 d. The mixture was distilled to give a solid, 5 g of which was dissolved in DMF (50 ml). To this solution were added mono-methyl isophthalate (1.86 g, 10.0 mmol), HOBt (2.70 g, 20.0 mmol), and EDCI (3.83 g, 20.0 mmol). The mixture was stirred at RT for 16 h and

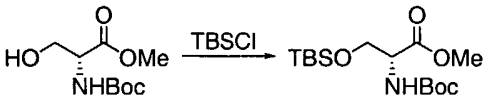
diluted with EtOAc (300 ml) and 1N NaOH (100 ml). The organic layer was washed with 1N HCl (100 ml), water (100 ml), saturated sodium bicarbonate (100 ml), and brine (100 ml), dried ($MgSO_4$), and concentrated to give the product (2.20 g, 84%). MS *m/e* 262 $(M+H)^+$

Step 2



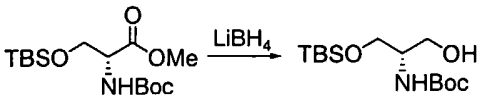
A mixture of the product of Step 1 (2.20 g, 8.42 mmol) in MeOH (25 ml) and 1N HCl (18 ml) was stirred at RT for 18 h. The mixture was concentrated and the residue was partitioned between 1N HCl (20 ml) and ether (2x100 ml). The combined organic layer was dried (Na_2SO_4) and concentrated to give the product (2.10 g, 100%). MS *m/e* 248 $(M+H)^+$

Step 3



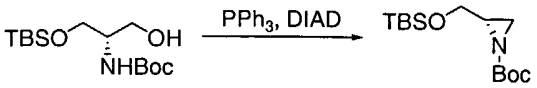
To an ice-cold solution of N-Boc-D-serine methyl ester (10.0 g, 45.6 mmol) in DMF (150 ml) were added imidazole (9.26 g, 136 mmol) and TBSCl (7.56 g, 50.16 mmol). The mixture was stirred at RT for 20 h and concentrated. The residue was dissolved with EtOAc (300 ml) and extracted with saturated NH_4Cl and sodium bicarbonate. The organic layer was dried ($MgSO_4$) and concentrated to give the product (16.5 g, 100%). MS *m/e* 356 $(M+Na)^+$

Step 4



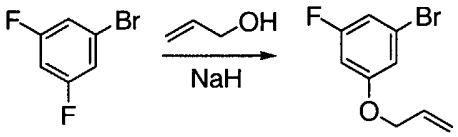
To a solution of the product of Step 3 (16.5 g, 45.6 mmol) in THF (150 ml) was added 2M lithium borohydride in THF (37.1 ml) slowly. The mixture was stirred at RT for 2.5 h. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (2x250 ml). The combined organic layer was washed with saturated NH_4Cl (100 ml), saturated sodium bicarbonate, and brine, dried, and concentrated to give the product (14.5 g, 100%). MS *m/e* 306 $(M+H)^+$

Step 5



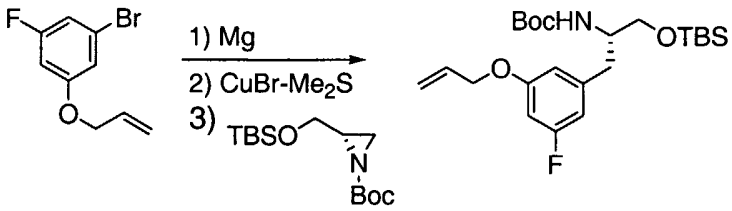
To an ice-cold solution of triphenylphosphine (13.95 g, 53.19 mmol) in THF (400 ml) and CH_3CN (50 ml) was added DIAD (10.76 g, 53.21 mmol). The mixture was stirred for 15 min and a solution of the product of Step 4 (8.20 g, 26.2 mmol) in THF (100 ml) was added over 15 min. After the addition was complete, the ice-water bath was removed and the mixture was stirred at RT for 2 d. The mixture was concentrated and purified by column chromatography (gradient EtOAc/Hexanes 0-5%) to give the product (3.75 g, 50%). MS *m/e* 288 $(M+H)^+$

Step 6



To a suspension of 60% NaH (6.40 g, 0.160 mol) in anhydrous DMA (400 ml) was added allyl alcohol (8.90 g, 0.154 mol) slowly. The mixture was stirred at RT for 1 h. 3,5-Difluorobromobenzene (30.0 g, 0.155 mol) was added and the mixture was stirred at RT for 24 h. The reaction was quenched with water (1.5 l) and extracted with ether (4x300 ml). The combined organic layer was washed with brine (500 ml), dried ($MgSO_4$), concentrated, and purified by column chromatography (Hexanes) to give the product (14.3 g, 40%). ^{1}H-NMR ($CDCl_3$): δ=6.81 (m, 2H), 6.53 (m, 1H), 5.96 (m, 1H), 5.34 (m, 2H), 4.46 (m, 2H).

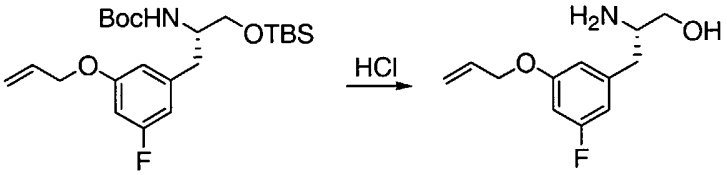
Step 7



To a flame-dried flask was added magnesium turnings (292 mg, 12.0 mmol) followed by one third of a solution of the product of Step 6 (2.31 g, 10.0 mmol) in THF (16 ml). The reaction was initiated with dibromoethane (50 µl) then the remaining solution of the product of Step 6 was added slowly. The mixture was stirred at RT for 30 min and added to a suspension of CuBr-Me_2S (310 mg, 1.51 mmol) in THF (30 ml) at -40°C. The mixture was stirred at 4°C for 30 min and a solution of the product of

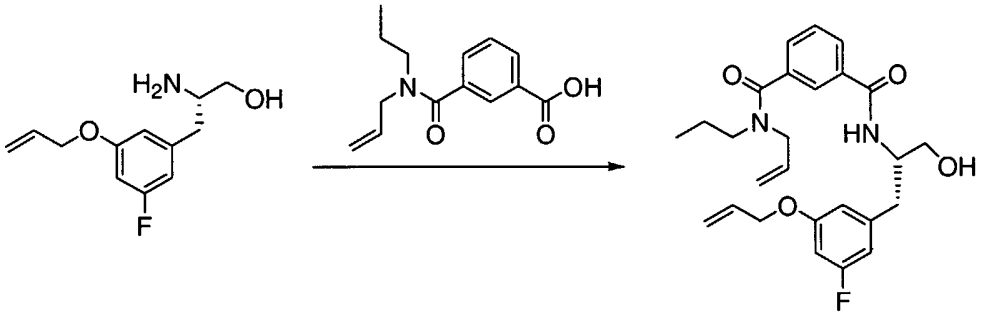
Step 5 (1.20 g, 4.17 mmol) in anhydrous ether (15 ml) was added. The resulting mixture was stirred at 4°C for 1 h then at RT for 3 d. The reaction was quenched with saturated NH_4Cl (100 ml) and extracted with EtOAc (2x150 ml). The combined organic layer was washed with saturated sodium bicarbonate and brine, dried ($MgSO_4$), concentrated, and purified by column chromatography (gradient EtOAc/Hexanes 0-5%) to give the product (1.00 g, 55%). MS *m/e* 440 $(M+H)^+$

Step 8



A solution of the product of Step 7 (500 mg, 1.14 mmol) in CH_2Cl_2 (12 ml) and 4N HCl/dioxane (6 ml) was stirred at RT for 20 h. The mixture was concentrated and the residue was partitioned between CH_2Cl_2 (50 ml) and 5N NH_4OH (20 ml). The organic layer was dried (K_2CO_3) and concentrated to give the product (345 mg, 100%). MS *m/e* 226 $(M+H)^+$

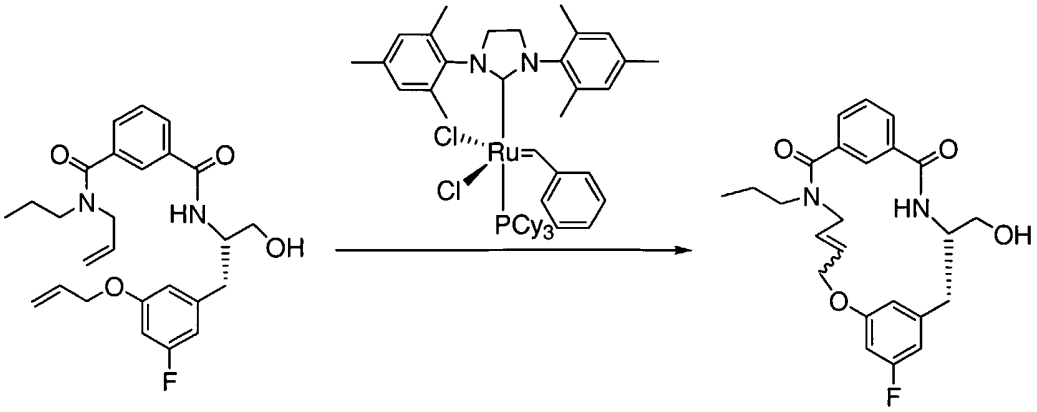
Step 9



A mixture of the product of Step 8 (445 mg, 1.98 mmol), the product of Step 2 (539 mg, 2.18 mmol), HOBt (442 mg, 3.27 mmol), and EDCI (627 mg, 3.27 mmol) in DMF (20 ml) was stirred at RT for 3 d. The mixture was concentrated and the residue was partitioned between CH_2Cl_2 (200 ml) and 1N NaOH. The organic layer was washed with 5% citric acid and brine, dried ($MgSO_4$), and concentrated. A solution of the residue in MeOH (20 ml) and 1N NaOH (10 ml) was stirred at RT for 4 h. The mixture was concentrated and the residue was partitioned between EtOAc (150 ml) and saturated $NaHCO_3$. The organic layer was washed with brine, dried ($MgSO_4$), concentrated, and purified by column chromatography (gradient MeOH/CH_2Cl_2 0-2.5%) to give the product (405 mg, 45%). ^{1}H-NMR ($CDCl_3$): δ=7.63 (m, 2H), 7.37 (m,

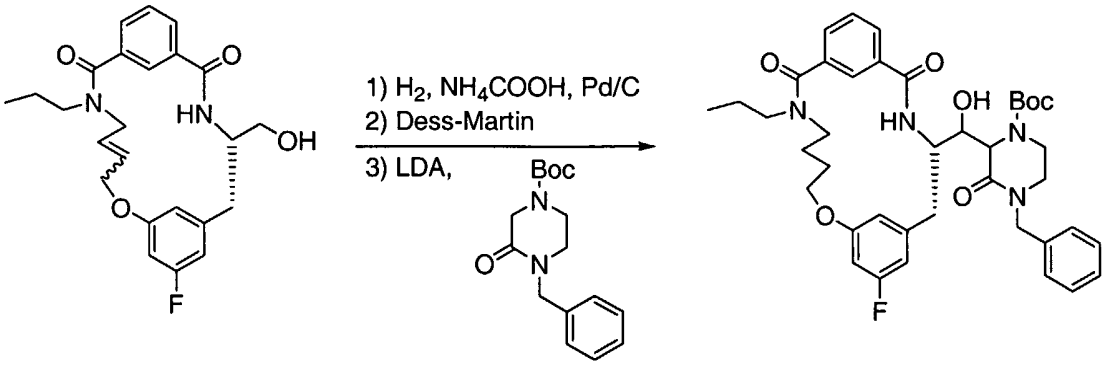
1H), 7.28 (m, 1H), 7.07 (m, 1H), 6.56 (m, 2H), 6.43 (m, 1H), 5.95 (m, 1H), 5.5-5.9 (m, 1H), 5.33 (m, 1H), 5.0-5.25 (m, 3H), 4.42 (m, 2H), 4.23 (m, 1H), 4.07 (m, 1H), 3.5-3.8 (m, 3H), 3.36 (m, 2H), 3.06 (m, 1H), 2.86 (m, 2H), 1.3-1.7 (m, 2H), 0.6-1.0 (m, 3H).

Step 10



A mixture of the product of Step 9 (400 mg, 0.880 mmol) and 2nd generation Grubb's catalyst (37 mg, 0.044 mmol) in CH_2Cl_2 (200 ml) was heated at 50°C for 2.5 h then at RT for 16 h. The mixture was concentrated and purified by column chromatography (gradient MeOH/CH_2Cl_2 0-2.5%) to give the product (340 mg, 91%). MS *m/e* 427 $(M+H)^+$

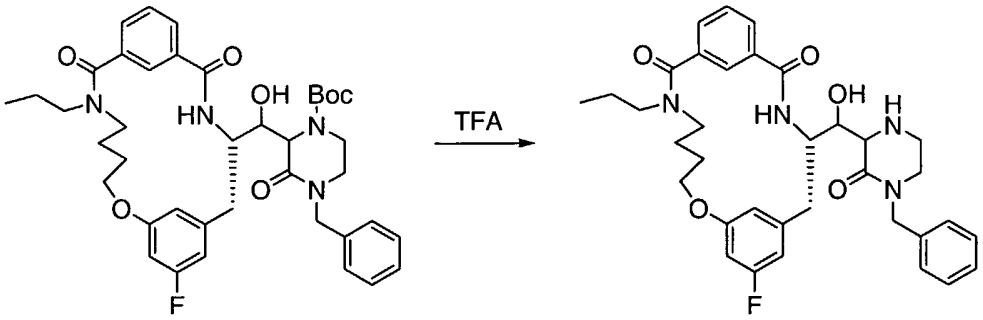
Step 11



A mixture of the product of Step 10 (340 mg, 0.797 mmol), ammonium formate (50 mg, 0.79 mmol), and 10% Pd/C (50 mg) was stirred under H_2 (1 atm) for 18 h. The mixture was filtered, concentrated, and used without further purification. A mixture of this material (129 mg, 0.301 mmol) and Dess-Martin periodinane (510 mg, 1.20 mmol) in CH_2Cl_2 (25 ml) was stirred at RT for 2 h. The reaction was quenched with 1N $Na_2S_2O_3$ and partitioned between saturated $NaHCO_3$ and CH_2Cl_2 (100 ml). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give the crude aldehyde.

To a solution of the product of Preparative Example 1, Step 8 (261 mg, 0.900 mmol) in anhydrous THF (5 ml) in a dry ice-acetone bath was added 2M LDA (0.45 ml) and the mixture was stirred for 1 h. A solution of the above aldehyde in THF (5 ml) was added and the mixture was stirred in the dry ice-acetone bath for 1 h. The reaction was quenched with saturated NH_4Cl (5 ml) and diluted with CH_2Cl_2 (50 ml). The organic layer was washed with water and brine, dried ($MgSO_4$), concentrated, and purified by PTLC (5% MeOH/CH_2Cl_2) to give the product (120 mg, 56%). MS *m/e* 717 $(M+H)^+$

Step 12



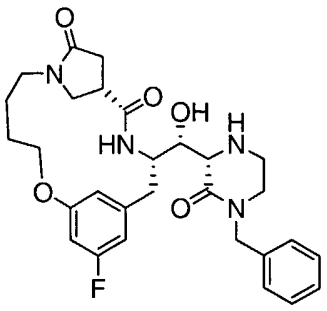
A mixture of the product of Step 11 (120 mg, 0.167 mmol) and TFA (2 ml) in CH_2Cl_2 (8 ml) was stirred at RT for 1.5 h. The mixture was concentrated and purified by PTLC (5% MeOH/CH_2Cl_2) to give:

fraction A (22 mg, 21%). ^{1}H-NMR ($CDCl_3$): δ=7.05-7.8 (m, 9H), 6.7-7.0 (m, 1H), 6.50 (m, 2H), 6.36 (m, 1H), 4.4-5.0 (m, 3H), 3.9-4.3 (m, 2H), 3.4-3.9 (m, 3H), 2.7-3.4 (m, 9H), 1.2-2.1 (m, 8H), 0.94 (m, 2H), 0.59 (m, 1H). MS *m/e* 617 $(M+H)^+$

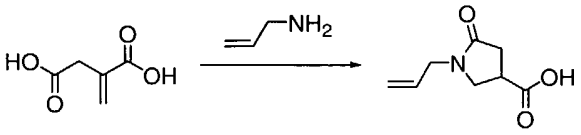
fraction B (17 mg, 16%). ^{1}H-NMR ($CDCl_3$): δ=7.45-7.65 (m, 2H), 7.1-7.3 (m, 8H), 6.95 (m, 1H), 6.56 (m, 1H), 6.37 (m, 1H), 4.68 (m, 2H), 3.9-4.4 (m, 3H), 2.7-3.9 (m, 13H), 1.2-2.2 (m, 7H), 1.04 (m, 2H), 0.58 (m, 1H). MS *m/e* 617 $(M+H)^+$

fraction C (12 mg, 12%). ^{1}H-NMR ($CDCl_3$): δ=7.2-7.8 (m, 8H), 6.75-7.0 (m, 1H), 6.5-6.7 (m, 2H), 6.2-6.4 (m, 2H), 4.4-4.8 (m, 3H), 3.6-4.2 (m, 3H), 2.7-3.4 (m, 10H), 1.2-2.2 (m, 8H), 0.95 (m, 2H), 0.61 (m, 1H). MS *m/e* 617 $(M+H)^+$

Preparative Example 3

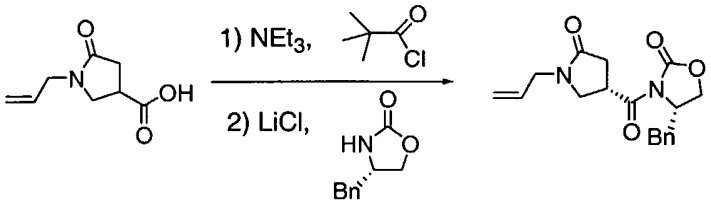


Step 1



A mixture of itaconic acid (13.0 g, 100.0 mmol) and allyl amine (5.71 g, 100 mmol) in anhydrous toluene (100 ml) was heated in a sealed tube at 125°C for 16 h. After the mixture was cooled down to RT, 1N aqueous NaOH (400 ml) was added and the aqueous layer was extracted with ether (2x200 ml). The aqueous layer was acidified with conc. HCl to pH 1 and extracted with ether (10x300 ml). The combined organic portion was concentrated and the residue was dissolved with CH_2Cl_2 (200 ml) and washed with brine. The organic layer was dried with $MgSO_4$, concentrated, and lyophilized to give a light yellow solid (9.60 g, 57%). MS *m/e* 170 $(M+H)^+$

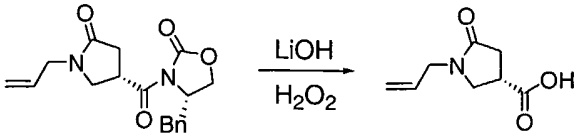
Step 2



To a solution of the product of Step 1 (8.60 g, 50.9 mmol) and triethylamine (15.4 g, 153 mmol) in anhydrous THF (200 ml) at -45°C was added pivaloyl chloride (6.45 g, 53.5 mmol). The mixture was stirred at -45°C for 1 h and then added into a suspension of lithium chloride (4.75 g, 112 mmol) and (*S*)-4-benzyl-2-oxazolidinone (9.02 g, 50.9 mmol) in THF (100 ml). The resulting mixture was stirred at RT for 16 h and filtered. The filtrate was concentrated, dissolved in EtOAc (700 ml), and washed with 1N HCl (200 ml), saturated sodium bicarbonate (200 ml), and brine. The organic layer was dried ($MgSO_4$), concentrated, and purified by column chromatography

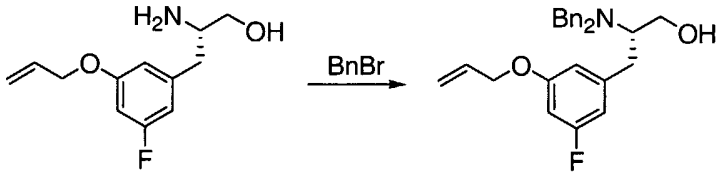
(gradient 0-75% EtOAc/Hexanes) to give the product (7.20 g, 43%). MS *m/e* 329 $(M+H)^+$

Step 3



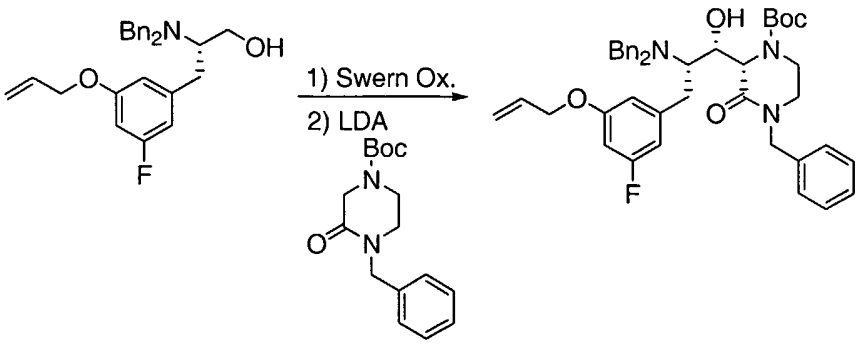
To a solution of the product of Step 2 (2.63 g, 8.01 mmol) in THF (30 ml) and water (8 ml) in an ice-water bath were added 30% hydrogen peroxide (4 ml) and lithium hydroxide (0.672 g, 16.0 mmol). The mixture was stirred at 0°C for 7 h. 10% Aqueous sodium bisulfite (40 ml) was added and the mixture was stirred at RT for 16 h. The mixture was concentrated and the residue was partitioned between 1N NaOH (8 ml) and CH_2Cl_2 (2x100 ml). The aqueous layer was acidified to pH 2 at 0°C and extracted with ether (5x100 ml). The combined organic portion was dried ($MgSO_4$) and concentrated to give the product (1.00 g, 74%). MS *m/e* 170 $(M+H)^+$

Step 4



A solution of the Preparative Example 2, Step 8 (3.10 g, 13.0 mmol) and potassium carbonate (5.39 g, 39.0 mmol) in EtOH (30 ml) and water (90 ml) was heated to 70°C. Benzyl bromide (3.42 ml, 28.6 mmol) was added and the mixture was stirred at 70°C for 2.5 h. EtOH was removed and the residue was extracted with ether (2x200 ml). The organic layer was washed with brine, dried (K_2CO_3), concentrated, and purified by column chromatography (gradient 0-10% EtOAc/Hexanes) to give the product (4.40 g, 83%). MS *m/e* 406 $(M+H)^+$

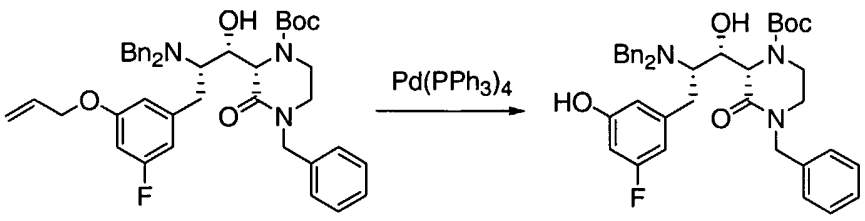
Step 5



To a solution of oxalyl chloride (762 mg, 6.00 mmol) in CH_2Cl_2 (10 ml) in a dry ice-acetone bath was added DMSO (938 mg, 12.0 mmol). After 5 min, a solution of the product of Step 4 (2.03 g, 5.01 mmol) in CH_2Cl_2 (20 ml) was added and the mixture was stirred for 1 h. Triethylamine (2.42 g, 23.9 mmol) was added and after 2 min the cooling bath was removed. The mixture was stirred for 30 min and diluted with water (50 ml). CH_2Cl_2 (100 ml) was added and the aqueous layer was extracted with CH_2Cl_2 (2x100 ml). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give the aldehyde, which was not further purified.

To a solution of diisopropylamine (667 mg, 6.59 mmol) in THF (5 ml) in a dry ice-acetone bath was added 1.6 M butyllithium in hexanes (4.13 ml, 6.61 mmol). After 5 min the mixture was put in an ice-water bath and stirred for 20 min. The solution was cooled in the dry ice-acetone bath again and a solution of the product of Preparative Example 1, Step 8 (1.74 g, 5.99 mmol) in THF (20 ml) was added. The mixture was stirred for 1 h. A solution of the above aldehyde in THF (30 ml) was added and the mixture was allowed to warm up to RT slowly and stirred for 16 h. The reaction was quenched with saturated NH_4Cl (20 ml) and extracted with ether (3x100 ml). The combined organic layer was washed with 5% citric acid, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), concentrated, and purified by column chromatography (gradient EtOAc/Hexanes 0-40%) to give the product (1.20 g, 35%). MS *m/e* 694 $(M+H)^+$

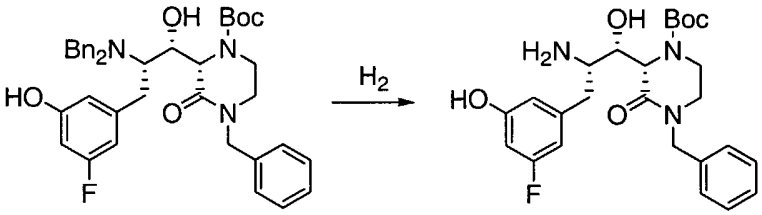
Step 6



A solution of the product of Step 5 (1.00 g, 1.44 mmol) in MeOH (15 ml) was degassed with N_2. Anhydrous potassium carbonate (594 mg, 4.30 mmol) and

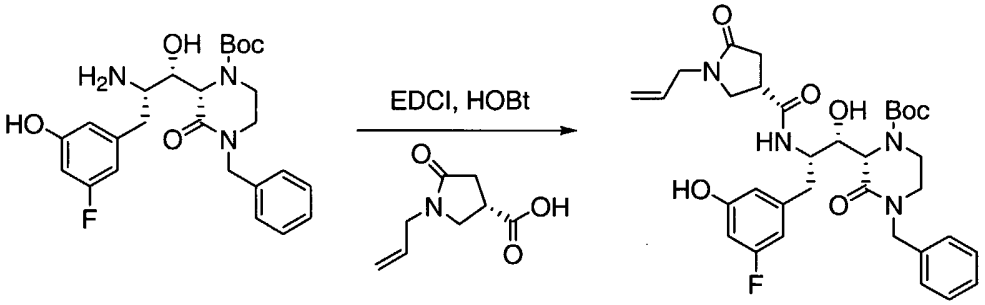
$Pd(PPh_3)_4$ (324 mg, 0.280 mmol) were added and the mixture was stirred at RT for 5 h. The mixture was filtered and concentrated. The residue was dissolved in CH_2Cl_2 (150 ml) and washed with 5% citric acid, saturated $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and concentrated to give the product (980 mg, 100%). MS *m/e* 654 $(M+H)^+$

Step 7



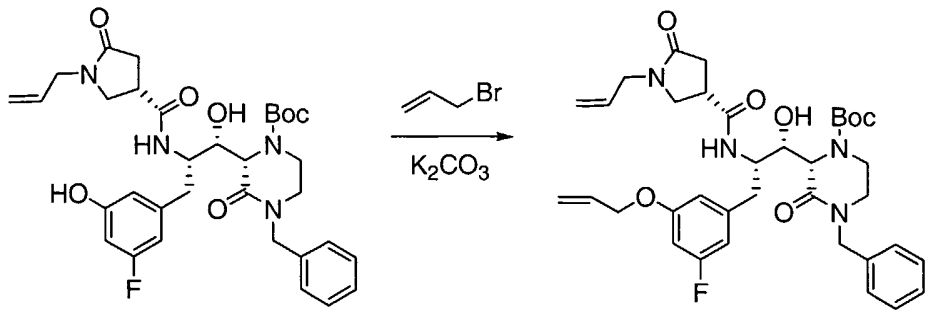
A mixture of the product of Step 6 (980 mg, 1.44 mmol), 20% $Pd(OH)_2/C$ (980 mg), and AcOH (1 ml) in EtOH (50 ml) was stirred under H_2 (1 atm) for 12 h. The mixture was filtered and concentrated to give the product (682 mg, 100%). MS *m/e* 474 $(M+H)^+$

Step 8



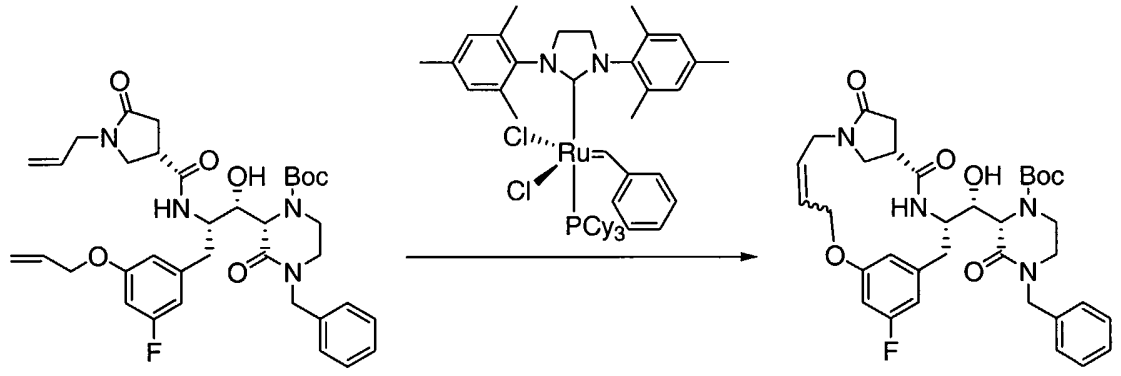
A mixture of the product of Step 7 (66 mg, 0.14 mmol), the product of Step 3 (28 mg, 0.17 mmol), HOBt (38 mg, 0.28 mmol), EDCI (53 mg, 0.28 mmol), and triethylamine (40 µl, 0.28 mmol) in CH_2Cl_2 (5 ml) was stirred at RT for 22 h. 1N NaOH (10 ml) was added and the mixture was stirred for 30 min. The mixture was diluted with CH_2Cl_2 (50 ml), washed with 5% citric acid, water and brine, dried ($MgSO_4$), concentrated, and purified by PTLC (5% MeOH/CH_2Cl_2) to give the product (66 mg, 76%). MS *m/e* 625 $(M+H)^+$

Step 9



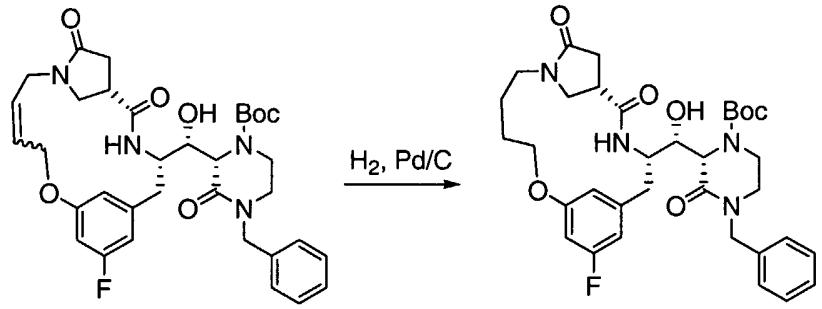
A mixture of the product of Step 8 (66 mg, 0.11 mmol), potassium carbonate (146 mg, 1.06 mmol), and allyl bromide (14 mg, 0.12 mmol) in acetone (4 ml) was stirred at RT for 18 h. The mixture was partitioned between 5% citric acid and CH_2Cl_2 (50 ml). The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), concentrated, and purified by PTLC (5% MeOH/CH_2Cl_2) to give the product (40 mg, 57%). MS *m/e* 665 $(M+H)^+$

Step 10



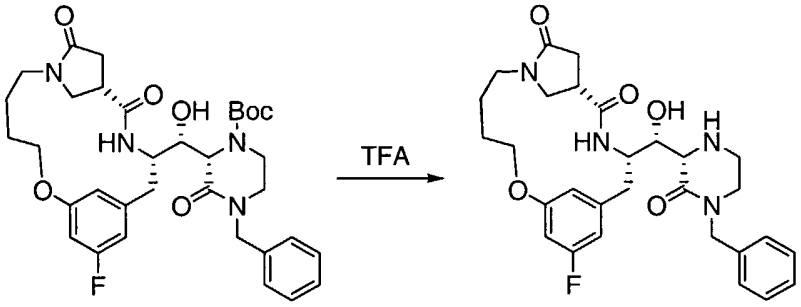
To a solution of the product of Step 9 (40 mg, 0.060 mmol) in CH_2Cl_2 (20 ml) was added the 2nd generation Grubb's catalyst (5 mg, 0.006 mmol). The mixture was degassed for 5 min with N_2 and then heated to 50°C for 2 h. The mixture was concentrated and purified by PTLC (5% MeOH/CH_2Cl_2) to give the product (30 mg, 79%). MS *m/e* 637 $(M+H)^+$

Step 11



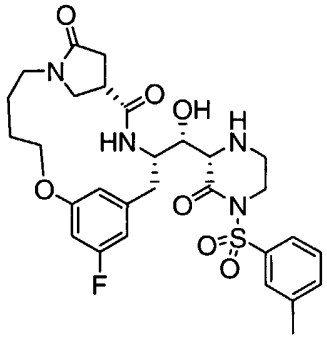
A mixture of the product of Step 10 (30 mg, 0.047 mmol) and 10% Pd/C (30 mg) in EtOH (5 ml) was stirred under H_2 (1 atm) for 75 min. The mixture was filtered and concentrated to give the product (30 mg, 100%). MS *m/e* 639 $(M+H)^+$

Step 12

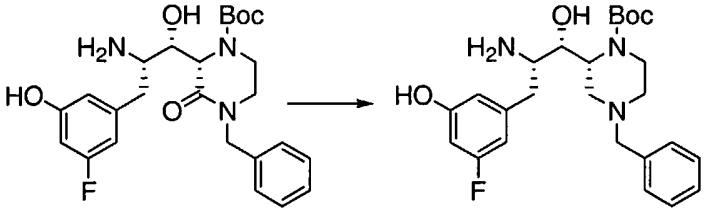


A solution of the product of Step 11 (30 mg, 0.047 mmol) and TFA (1 ml) in CH_2Cl_2 (4 ml) was stirred at RT for 1.5 h. The mixture was concentrated and purified by PTLC (5% 2M NH_3/MeOH-95% CH_2Cl_2) to give the product (20 mg, 79%). ^{1}H-NMR ($CDCl_3$): δ=7.25-7.35 (m, 5H), 6.53 (m, 1H), 6.42 (m, 2H), 4.67 (d, 1H, *J*=14.4 Hz), 4.44 (d, 1H, *J*=14.4 Hz), 4.36 (m, 1H), 3.8-4.2 (m, 4H), 3.60 (m, 1H), 2.8-3.4 (m, 9H), 2.69 (m, 1H), 2.54 (m, 2H), 1.84 (m, 2H), 1.66 (m, 1H), 1.47 (m, 2H). LCMS t_R=2.88 min *m/e* 539 $(M+H)^+$

Preparative Example 4

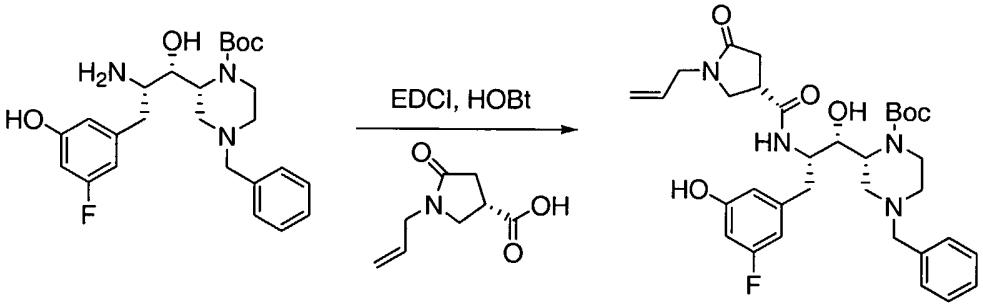


Step 1



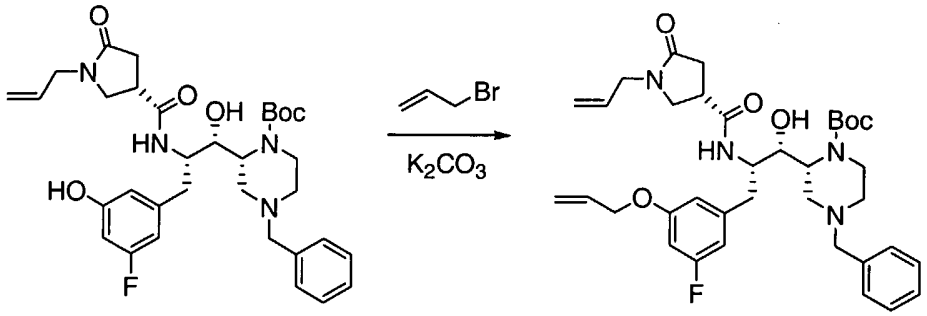
To a solution of the product of step 7 in Preparative Example 3 (236 mg, 0.5 mmol, crude product from previous step) in anhydrous THF (20 mL) was added 2.0 mL of 2 M borane-dimethylsufide in THF at RT. The mixture was heated at 60-70°C overnight. After addition of MeOH (30 mL), the mixture was heated at 70°C for additional 2 h. Cooled to RT and concentrated to dryness in a rotavapor. Additional MeOH (30 mL) was added and concentrated to dryness. The product was used directly in the next step without further purification. MS *m/e* 460 $(M+H)^+$

Step 2



A solution of the product of Step 3 in Preparative Example 3 (102 mg, 0.60 mmol), HOBt (162 mg, 1.2 mmol), and EDCI (230 mg, 1.2 mmol) in CH_2Cl_2 (6 ml) was stirred at RT for 1.5 h. Then a solution of the product of Step 1 (crude, ~0.5 mmol) in CH_2Cl_2 (20 mL) was added, followed by triethylamine (240 mg, 2.4 mmol). The mixture was stirred at RT for 22 h. 1N NaOH (20 ml) was added and the mixture was stirred for 45 min. The mixture was diluted with CH_2Cl_2 (150 ml), washed with H_2O, 5% citric acid, and brine, dried ($MgSO_4$), concentrated, and purified by ISCO (elution with CH_2Cl_2 for 10 min., 0-2.5% MeOH/CH_2Cl_2 for 35 min.) to give the product (90 mg, 29% for 3 steps). ^{1}H-NMR ($CDCl_3$): δ=7.22-7.32 (m, 5H), 6.58 (d, 1H, *J*=8.8 Hz), 6.39 (m, 2H), 6.25 (m, 1H), 3.79-3.93 (m, 5H), 3.27-3.58 (m,7H), 3.06 (d,1H, *J*=10 Hz), 2.96 (m, 1H), 2.77 (d, 1H, *J*= 10.8 Hz), 2.50-2.56 (m, 2H), 2.05-2.32(m, 4H), 1.38 (s, 9H). MS *m/e* 611 $(M+H)^+$.

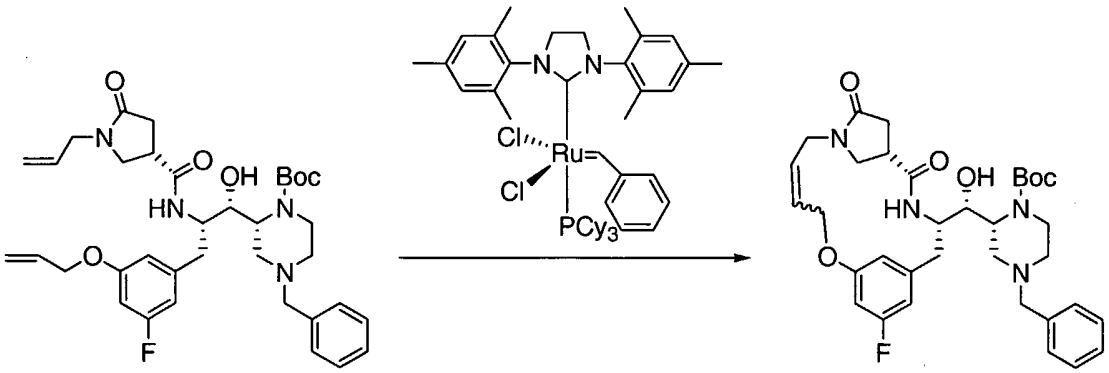
Step 3



A mixture of the product of Step 3 (40 mg, 0.066 mmol), potassium carbonate (91 mg, 0.66 mmol), and allyl bromide (18 mg, 0.15mmol) in acetone (5 ml) was at 60-

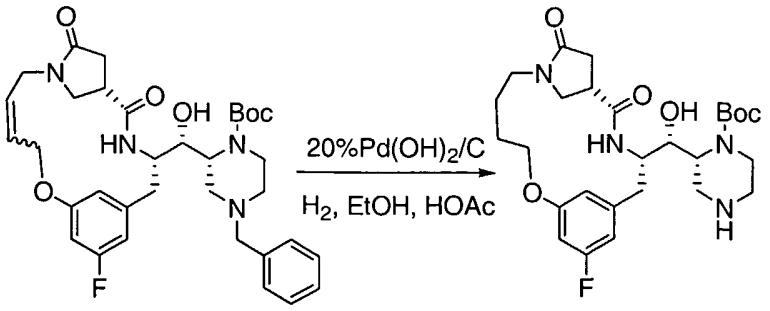
70°C for 18 h. Cooled to RT, filtered and concentrated. The residue was dissolved in CH_2Cl_2 (50 ml). The organic layer was washed with brine and dried ($MgSO_4$), concentrated, and purified by PTLC (5% MeOH/CH_2Cl_2) to give the product (27 mg, 63%). ^{1}H-NMR ($CDCl_3$): δ=7.22-7.30 (m, 5H), 6.41 (m, 3H), 5.96 (m, 1H), 5.84 (d,1H, *J* =8.9 Hz), 5.62 (m, 1H), 5.37 (dd, 1H, *J* = 1.6 Hz), 5.33 (dd, 1H, *J* = 1.6 Hz), 5.23(dd, 1H, *J*=1.2 Hz, *J* = 10Hz), 5.09-5.14 (m, 2H), 4.43(dt, 2H, *J* =6.4 Hz, *J*=1.5 Hz), 3.69-3.95 (m, 5H), 3.26-3.58 (m,7H), 3.08 (d, 1H, *J*=10 Hz), 2.92 (m,1H), 2.77 (d, 1H, *J*=11 Hz), 2.63 (m,1H), 2.42(m, 2H),2.22(d, 1H, *J*= 9Hz), 2.06 (m, 1H), 1.37 (s, 9H). MS *m/e* 651 $(M+H)^+$

Step 4



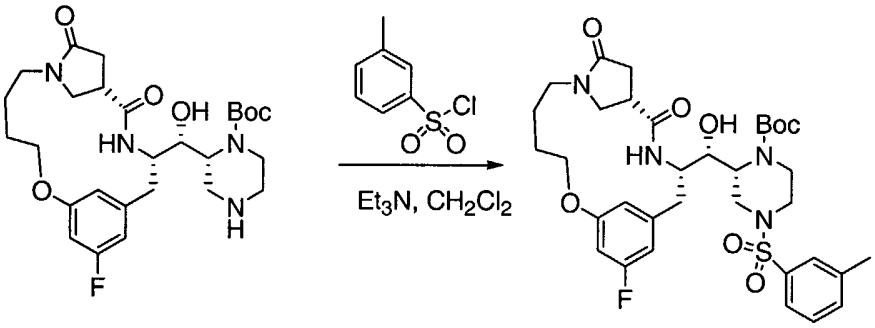
To a solution of the product of Step 3 (60 mg, 0.092 mmol) in CH_2Cl_2 (40 ml) was added the 2nd generation Grubb's catalyst (7.8 mg, 0.0092 mmol). The mixture was degassed for 5 min with N_2 and then heated to 40-50°C for 1 h. The mixture was concentrated and purified by PTLC (5% MeOH/CH_2Cl_2) to give the product (52 mg, 91%). ^{1}H-NMR ($CDCl_3$): δ=7.22-7.32 (m, 5H), 6.51 (d, 1H, *J*=8.8 Hz), 6.40 (d, 1H, *J* = 10Hz), 6.32 (s, 1H), 6.26 (d, 1H, *J* = 8.8 Hz), 5.65 (m, 2H), 4.60 (s, 2H), 4.56(d, 1H, *J* = 3.2 Hz), 4.00(s, 1H), 3.85 (d, 2H, *J*= 10 Hz), 3.17-3.51 (m, 6H), 2.62-2.97 (m, 6H), 2.47 (t, 1H, *J* =12 Hz), 2.05-2.15 (m, 2H), 1.78-1.88(m, 2H), 1.41 (s, 9H). MS *m/e* 623 $(M+H)^+$.

Step 5



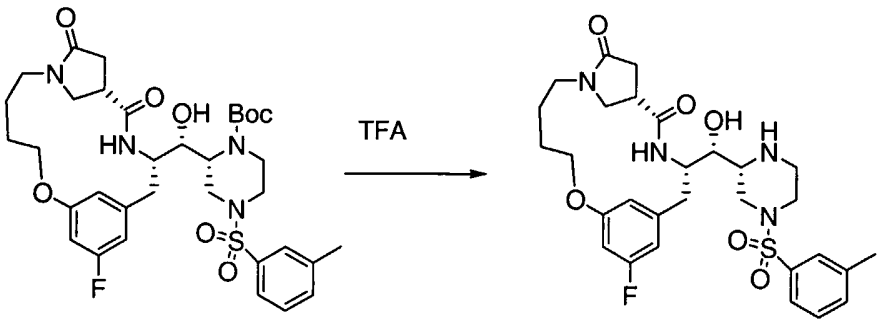
A mixture of the product of Step 4 (52 mg, 0.084 mmol) and 20% $Pd(OH)_2/C$ (52 mg) in EtOH (5 ml) and acetic acid (0.4 mL) was stirred under H_2 (1 atm) for 90 min. The mixture was filtered and concentrated. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ and brine, then dried (K_2CO_3) and concentrated to give the product (33 mg, 74%). MS *m/e* 535 $(M+H)^+$.

Step 6



To an ice-cooled solution of the product of step 5 (33 mg, 0.062 mmol) in anhydrous CH_2Cl_2 (6 mL) was added triethylamine (20 mg), followed by a solution of *m*-toluenesufonyl chloride (13mg, 0.068 mmol) in CH_2Cl_2. The mixture was stirred at 0 °C for 1h. Then diluted with CH_2Cl_2 (50 mL), washed with 5% of citric acid, saturated $NaHCO_3$ and brine, and dried ($MgSO_4$). The solution was concentrated and purified by PTLC (5% MeOH/CH_2Cl_2) to give the product (27 mg, 63%). MS *m/e* 689 $(M+H)^+$.

Step 7



A solution of the product of Step 6 (27 mg, 0.039 mmol) and TFA (1 ml) in CH_2Cl_2 (4 ml) was stirred at RT for 1 h. The mixture was concentrated and purified by

PTLC (5% 2M NH_3/MeOH-95% CH_2Cl_2) to give the product (23 mg, 94%). ^{1}H-NMR ($CDCl_3$): δ=7.49 (m, 2H), 7.38 (m, 2H), 6.53 (d, 1H, *J* = 8 Hz), 6.45 (s, 1H), 6.39 (m, 1H), 4.01-4.17 (m, 3H), 3.82-3.85 (m,2H), 3.64 (m, 1H), 3.23-3.43 (m, 3H), 2.85-3.10 (m, 7H), 2.66-2.70 (m, 2H), 2.50-2.57 (m, 2H), 2.40 (s, 3H), 1.88 (s, broad, 1H), 1.65 (m, 1H), 1.39-1.47 (m, 2H). LCMS t_R=2.99 min *m/e* 589 $(M+H)^+$

BACE-1 Cloning, Protein Expression and Purification.

A predicted soluble form of human BACE1 (sBACE1, corresponding to amino acids 1-454) was generated from the full length BACE1 cDNA (full length human BACE1 cDNA in pCDNA4/mycHisA construct; University of Toronto) by PCR using the advantage-GC cDNA PCR kit (Clontech, Palo Alto, CA). A HindIII/PmeI fragment from pCDNA4-sBACE1myc/His was blunt ended using Klenow and subcloned into the Stu I site of pFASTBACI(A) (Invitrogen). A sBACE1mycHis recombinant bacmid was generated by transposition in DH10Bac cells(GIBCO/BRL). Subsequently, the sBACE1mycHis bacmid construct was transfected into sf9 cells using CellFectin (Invitrogen, San Diego, CA) in order to generate recombinant baculovirus. Sf9 cells were grown in SF 900-II medium (Invitrogen) supplemented with 3% heat inactivated FBS and 0.5X penicillin/streptomycin solution (Invitrogen). Five milliliters of high titer plaque purified sBACEmyc/His virus was used to infect 1L of logarithmically growing sf9 cells for 72 hours. Intact cells were pelleted by centrifugation at 3000xg for 15 minutes. The supernatant, containing secreted sBACE1, was collected and diluted 50% v/v with 100 mM HEPES, pH 8.0. The diluted medium was loaded onto a Q-sepharose column. The Q-sepharose column was washed with Buffer A (20 mM HEPES, pH 8.0, 50 mM NaCl).

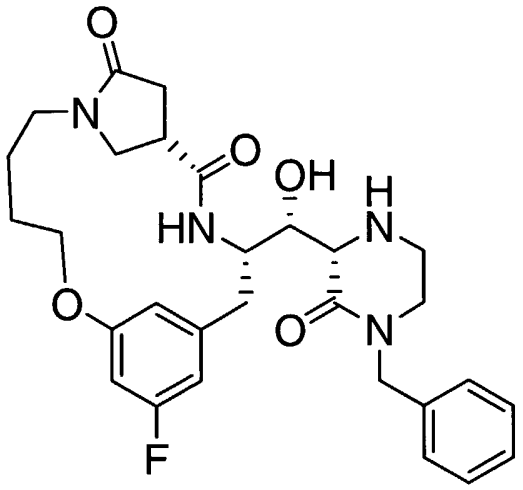
Proteins, were eluted from the Q-sepharose column with Buffer B (20 mM HEPES, pH 8.0, 500 mM NaCl). The protein peaks from the Q-sepharose column were pooled and loaded onto a Ni-NTA agarose column. The Ni-NTA column was then washed with Buffer C (20 mM HEPES, pH 8.0, 500 mM NaCl). Bound proteins were then eluted with Buffer D (Buffer C+250 mM imidazole). Peak protein fractions as determined by the Bradford Assay (Biorad, CA) were concentrated using a Centricon 30 concentrator (Millipore). sBACE1 purity was estimated to be ~90% as assessed by SDS-PAGE and Commassie Blue staining. N-terminal sequencing indicated that greater than 90% of the purified sBACE1 contained the prodomain; hence this protein is referred to as sproBACE1.

Peptide Hydrolysis Assay.

The inhibitor, 25 nM EuK-biotin labeled APPsw substrate (EuK-KTEEISEVNLDAEFRHDKC-biotin; CIS-Bio International, France), 5 μM unlabeled APPsw peptide (KTEEISEVNLDAEFRHDK; American Peptide Company, Sunnyvale, CA), 7 nM sproBACE1, 20 mM PIPES pH 5.0, 0.1%Brij-35 (protein grade, Calbiochem, San Diego, CA), and 10% glycerol were preincubated for 30 min at 30°C. Reactions were initiated by addition of substrate in a 5 μl aliquot resulting in a total volume of 25 μl. After 3 hr at 30° C reactions were terminated by addition of an equal volume of 2x stop buffer containing 50 mM Tris-HCl pH 8.0, 0.5 M KF, 0.001% Brij-35, 20 μg/ml SA-XL665 (cross-linked allophycocyanin protein coupled to streptavidin; CIS-Bio International, France) (0.5 μg/well). Plates were shaken briefly and spun at 1200xg for 10 seconds to pellet all liquid to the bottom of the plate before the incubation. HTRF measurements were made on a Packard Discovery® HTRF plate reader using 337 nm laser light to excite the sample followed by a 50 μs delay and simultaneous measurements of both 620 nm and 665 nm emissions for 400 μs.

IC_{50} determinations for inhibitors, (*I*), were determined by measuring the percent change of the relative fluorescence at 665 nm divided by the relative fluorescence at 620 nm, (665/620 ratio), in the presence of varying concentrations of *I* and a fixed concentration of enzyme and substrate. Nonlinear regression analysis of this data was performed using GraphPad Prism 3.0 software selecting four parameter logistic equation, that allows for a variable slope. Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*Hill Slope)); X is the logarithm of concentration of I, Y is the percent change in ratio and Y starts at bottom and goes to top with a sigmoid shape.

Compounds of the present invention have an IC_{50} range from about 100 to about 10,000 nM, preferably about 100 to about 1000 nM, more preferably about 100 to about 500 nM. Compounds of the preferred stereochemistry have IC_{50} values in a range of about 2 to about 500 nM, preferably about 2 to about 100 nM. The compound of the following formula



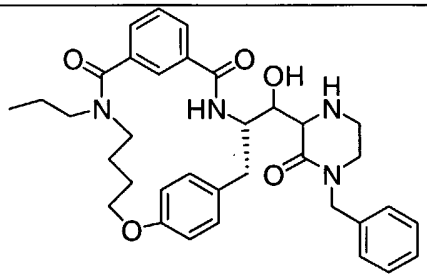
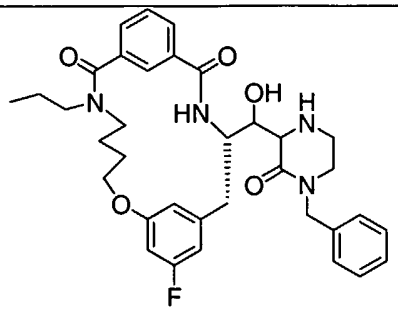
has an IC_{50} of 4 nM.

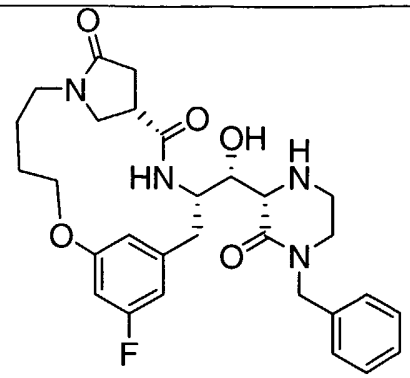
The following table demonstrates the IC_{50} classifications for the following compounds.

Compounds with an IC_{50} of 2 to 1000 nM are A class compounds.

Compounds with an IC_{50} of 1000 to 10000 nM are B class compounds.

Compounds with an IC_{50} over 10000 nM are C class compounds.

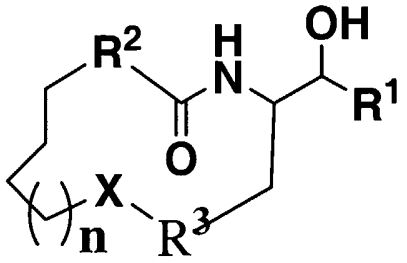
COMPOUND	Activity
	B
	A or B

	A

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and 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.

We claim:

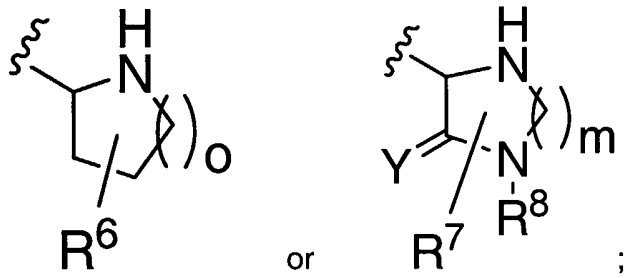
1. A compound having the structural formula



I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is



;

R^2 is $-N(R^5)C(O)R^4-$ or heterocyclylene ring;

R^3 is arylene, heteroarylene, heterocyclylene or cycloalkylene;

R^4 is arylene, heteroarylene, heterocyclylene or cycloalkylene;

R^5 is hydrogen, alkyl, aryl, heteroaryl or cycloalkyl;

R^6 and R^7 are independently selected from hydrogen, -OH, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroaralkyl, aralkoxy, heteroaralkoxy and alkoxy, with the proviso that when R^6 and R^7 are –OH, aralkoxy, heteroaralkoxy and alkoxy, R^6 and R^7 are not attached to a ring carbon adjacent to a ring nitrogen;

R^8 is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, $-C(O)R^9$, $-C(O)OR^{12}$, $-S(O)R^9$, $-S(O_2)R^9$ or –CN; with the proviso that when Y is =O, R^8 cannot be $-C(O)R^9$, $-C(O)OR^{12}$, $-S(O)R^9$, $-S(O_2)R^9$ or –CN;

R^9 is hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, cycloalkylalkyl, aralkyl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl or $-N(R^{10})(R^{11})$;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, alkenyl and alkynyl;

or R^{10} and R^{11} together with the nitrogen to which they are attached, form a 3-7 membered heterocyclyl ring;

R^{12} is alkyl, cycloalkyl, aryl, heteroaryl, cycloalkylalkyl, aralkyl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, alkenyl or alkynyl;

X is O, S, $C(R^5)$, or NH;

Y is =O, or (H,H);

m is 1, 2, or 3;

n is 0, 1, 2, or 3;

and

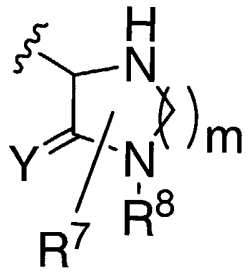
o is 0, 1, 2, or 3;

wherein each alkyl is optionally substituted with 1 to 3 moieties selected from the group consisting of halo, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), $-N(alkyl)_2$, carboxy and –C(O)O-alkyl;

and

wherein each arylene, heteroarylene, heterocyclyl, heterocyclylalkyl, heterocyclylene, cycloalkylene, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, aralkoxy or heteroaralkoxy is optionally substituted with 1 to 4 moieties selected from the group consisting of $–CF_3$, alkyl, alkenyl, alkynyl, 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, $-C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, -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, with the proviso that cycloalkylene and heterocyclylene can be substituted with =O.

2. The compound of claim 1 wherein R^1 is

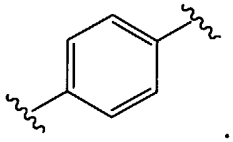


3. The compound of claim 1 wherein R^2 is $-N(R^5)C(O)R^4-$.

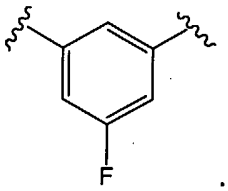
4. The compound of claim 1 wherein R^3 is arylene.

5. The compound of claim 4 wherein R^3 is phenylene or halo-substituted phenylene.

6. The compound of claim 4 wherein R^3 is



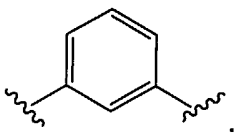
7. The compound of claim 4 wherein R^3 is



8. The compound of claim 1 wherein R^4 is arylene.

9. The compound of claim 1 wherein R^4 is phenylene.

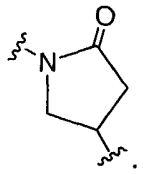
10. The compound of claim 1 wherein R^4 is



11. The compound of claim 1 wherein R^2 is heterocyclylene.

12. The compound of claim 11 wherein R^2 is heterocyclylene substituted with =O.

13. The compound of claim 12 wherein R^2 is



14. The compound of claim 3 wherein R^5 is alkyl.

15. The compound of claim 14 wherein R^5 is propyl.

16. The compound of claim 1 wherein m is 2 and n is 1.

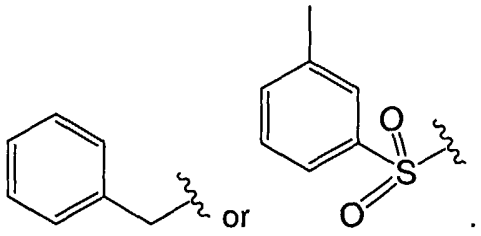
17. The compound of claim 1 wherein R^7 is hydrogen.

18. The compound of claim 1 wherein X is O.

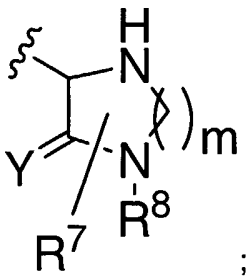
19. The compound of claim 1 wherein Y is O.

20. The compound of claim 1 wherein R^8 is aralkyl or $-S(O_2)R^9$.

21. The compound of claim 1 wherein R^8 is



22. The compound of claim 1 wherein
R^1 is



;

R^2 is $-N(R^5)C(O)R^4-$ or heterocyclylene;

R^3 is arylene

R^4 is arylene or heterocyclylene;

R^5 is alkyl;

R^7 is hydrogen;

R^8 is aralkyl or $-S(O_2)R^9$;

m is 2;

n is 1;

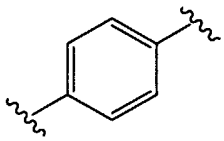
X is O;

and

Y is O.

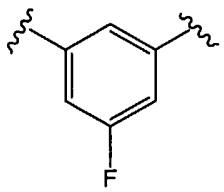
23. The compound of claim 22 wherein R^3 is phenylene or halo-substituted phenylene.

24. The compound of claim 23 wherein R^3 is



.

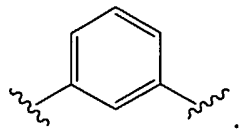
25. The compound of claim 24 wherein R^3 is



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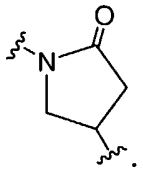
26. The compound of claim 22 wherein R^4 is arylene.

27. The compound of claim 22 wherein R^4 is



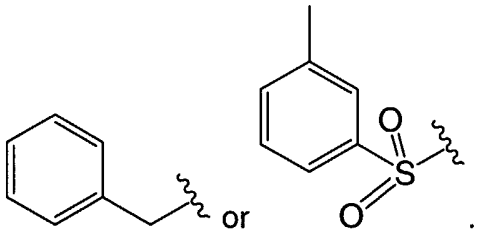
28. The compound of claim 22 wherein R^2 is heterocyclylene or heterocyclylene substituted with =O.

29. The compound of claim 28 wherein R^2 is

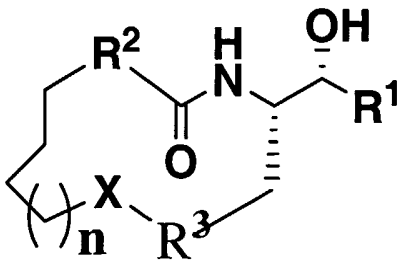


30. The compound of claim 13 wherein R^5 is propyl.

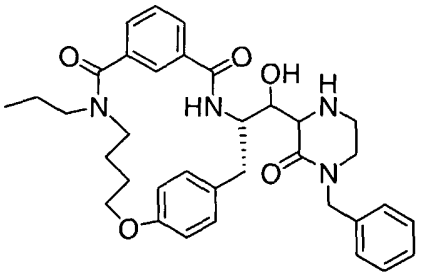
31. The compound of claim 22 wherein R^8 is

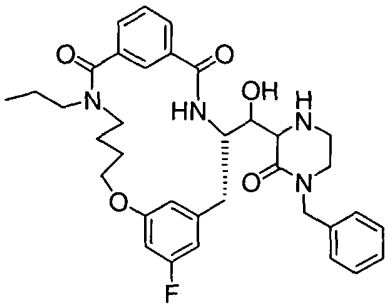


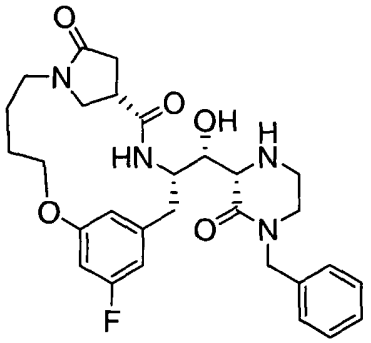
32. A compound of claim 1 having the stereochemical structure

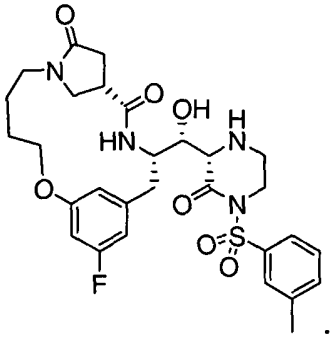


33. A compound of claim 1 selected from the group consisting of









and .

34. A compound of claim 1 in purified form.

35. A compound of claim 1 in isolated form.

36. A pharmaceutical composition comprising an effective amount of a compound of claim 1 and a pharmaceutically effective carrier.

37. A method of inhibiting the formation, or the formation and deposition of β-amyloid plaques in, on or around neurological tissue comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1.

38. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1.

39. The method of claim 38 wherein Alzheimer's disease is treated.

40. A pharmaceutical composition comprising an effective amount of a compound of claim 1, and an effective amount of a cholinesterase inhibitor in a pharmaceutically effective carrier.

41. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1 in combination with an effective amount of a cholinesterase inhibitor.

42. The method of claim 41 wherein said cholinesterase inhibitor is acetyl-cholinesterase or butyrylchlolinesterase.

43. The method of claim 41 wherein said cholinesterase inhibitor is selected from the group consisting of tacrine, donepezil, rivastigmine, galantamine, pyridostigmine and neostigmine.

44. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1 in combination with an effective amount of an anti-inflammatory compound.

45. The method of claim 44 wherein said anti-inflammatory compound is a non-steroidal anti-inflammatory drug.

46. The method of claim 45 wherein said non-steroid anti-inflammatory drug is diclofenac, diflunisal, etodolac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, tolmetin, celecoxib or rofecoxib.

47. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1 in combination with an effective amount of a gamma secreatse inhibitor.

48. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1 in combination with an effective amount of an HMG-CoA reductase inhibitor compound.

49. The method of claim 48 wherein said HMG-CoA reductase inhibitor compound is atorvastatin, lovastatin, simvistatin, pravastatin, fluvastatin or rosuvastatin.

50. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1 in combination with an effective amount of a N-methyl-D-aspartate receptor antagonist.

51. The method of claim 50 wherein said N-methyl-D-aspartate receptor antagonist is memantine.

52. A method of treating a cognitive or neurodegenerative disease comprising administering to a patient in need of such treatment an effective amount of a compound of claim 1 in combination with an effective amount of an anti-amyloid antibody.

INTERNATIONAL SEARCH REPORT

ational Application No
PCT/US2005/026468

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/06 C07D498/04 A61K31/00 A61P25/28

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/100856 A (ELAN PHARMACEUTICALS, INC; PHARMACIA & UPJOHN COMPANY; PULLEY, SHON, R) 19 December 2002 (2002-12-19) cited in the application the whole document	1-52
A	WO 02/100399 A (ELAN PHARMACEUTICALS, INC; PHARMACIA & UPJOHN COMPANY; PULLEY, SHON, R) 19 December 2002 (2002-12-19) cited in the application the whole document	1-52

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

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 2005	04/11/2005

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

INTERNATIONAL SEARCH REPORT

ıtional Application No
PCT/US2005/026468

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02100856 A	19-12-2002	BR 0210392 A	13-10-2004
		CA 2450202 A1	19-12-2002
		EP 1404671 A1	07-04-2004
		JP 2004534064 T	11-11-2004
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