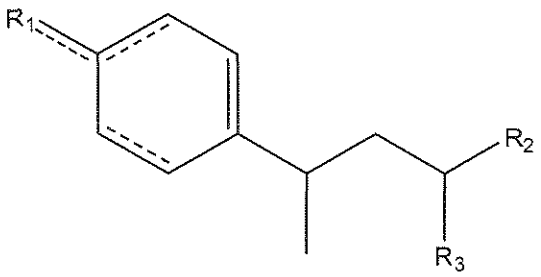
ISOLATED COMPOUNDS FROM TURMERIC OIL AND METHODS OF USE

[0001] This application claims the benefit of and priority to U.S. provisional patent application serial no. 61/438,916, filed on February 2, 2011, which is hereby incorporated by reference in its entirety.

SUMMARY

[0002] The present disclosure provides, *inter alia*, compounds and methods for preparation thereof useful for the inhibition, treatment, and/or abatement of cognitive decline. In a method called "chemical conditioning", certain compounds of the present disclosure are derived from naturally occurring compounds, such as those found in turmeric (*Curcuma longa*). The chemical conditioning process described herein is applicable to a large variety of biological extracts and may be used to create compound arrays for screening for potential new drug candidates. Further, in general, compounds derived by the chemical conditioning process are chemically stable and structurally diverse, and good candidates for use in drug screenings for pharmaceutical activity. In some embodiments, compounds derived from turmeric oil are provided. According to some embodiments of the present disclosure, compounds derived from turmeric oil by the chemical conditioning process described herein are provided. In another embodiment, the present disclosure provides a method of preparing an array of novel chemical compounds from turmeric oil. In some other embodiments, novel compounds useful for the inhibition, treatment, and/or abatement of cognitive decline are prepared by chemical synthesis.

[0002a] In a first aspect of the present disclosure, there is provided a compound comprising formula I-0



I-0

or pharmaceutically acceptable salt thereof, wherein:

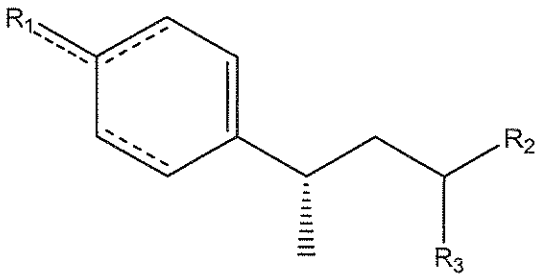
-------- is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and

R_3 is $NHCH_2CH(CH_3)_2$.

[0002b] In a second aspect of the present disclosure, there is provided a compound comprising formula I-1



I-1

or pharmaceutically acceptable salt thereof, wherein:

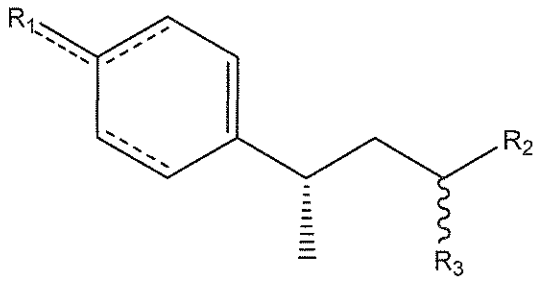
-------- is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and

R_3 is $NHCH_2CH(CH_3)_2$.

[0002c] In a third aspect of the present disclosure, there is provided a compound comprising formula I-2



I-2

or pharmaceutically acceptable salt thereof, wherein:

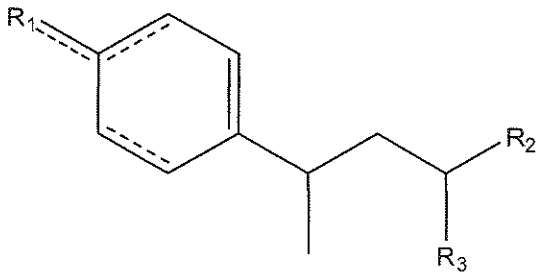
-------- is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and

R_3 is $NHCH_2CH(CH_3)_2$.

[0002d] In a fourth aspect of the present disclosure, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I-0



I-0

wherein:

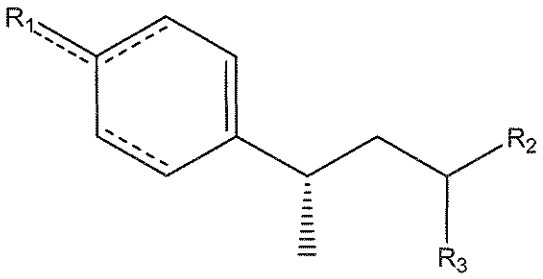
-------- is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH=C(CH_3)_2$ and

R_3 is $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

[0002e] In a fifth aspect of the present disclosure, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I-1



I-1

wherein:

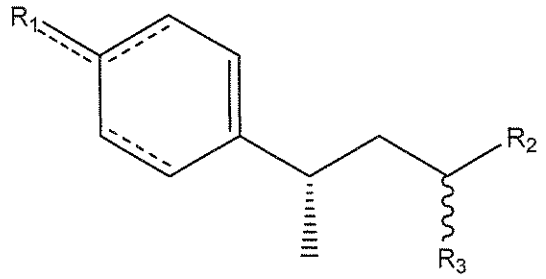
-------- is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH=C(CH_3)_2$; and

R_3 is $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

[0002f] In a sixth aspect of the present disclosure, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I-2



I-2

wherein:

⁼⁼⁼⁼⁼⁼⁼⁼ is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

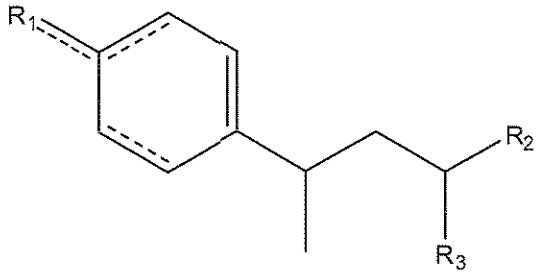
R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and

R_3 is $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

[0002g] In a seventh aspect of the present disclosure, there is provided a pharmaceutical composition comprising a mixture of a therapeutically effective amount of 4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol and a therapeutically effective amount of 4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

[0002h] In an eighth aspect of the present disclosure, there is provided a pharmaceutical composition comprising a mixture of a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol and a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

[0002i] In a ninth aspect of the present disclosure, there is provided a use of a compound of formula I-0



I-0

in the manufacture of a medicament for treating cognitive decline and/or Alzheimer's disease in a patient, wherein:

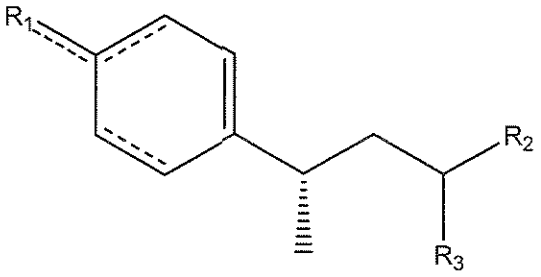
-------- is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and

R_3 is selected from OH and $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0002j] In a tenth aspect of the present disclosure, there is provided a use of a compound of formula I-1



I-1

in the manufacture of a medicament for treating cognitive decline and/or Alzheimer's disease in a patient, wherein:

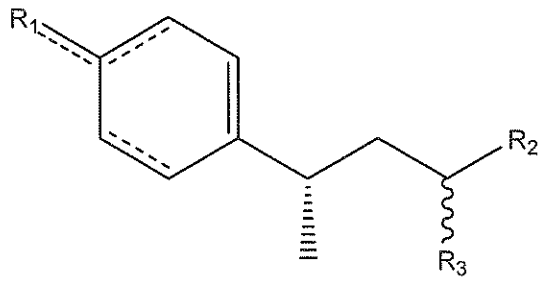
-------- is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and

R_3 is selected from OH and $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0002k] In an eleventh aspect of the present disclosure, there is provided a use of a compound of formula I-2



I-2

or pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cognitive decline and/or Alzheimer's disease in a patient, wherein:

-------- is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

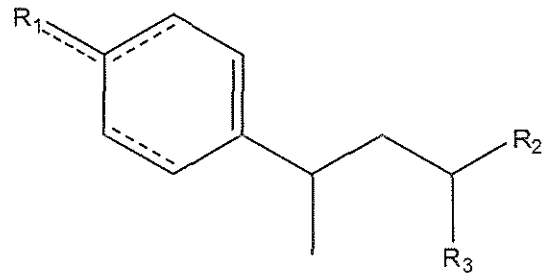
R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and

R_3 is selected from OH and $NHCH_2CH(CH_3)_2$.

[0002l] In a twelfth aspect of the present disclosure, there is provided a use of a pharmaceutical composition comprising a mixture of a therapeutically effective amount of 4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol and a therapeutically effective amount of 4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof in the manufacture of a medicament for treating cognitive decline and/or Alzheimer's disease in a patient.

[0002l] In a thirteenth aspect of the present disclosure, there is provided a use of a pharmaceutical composition comprising a mixture of a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol and a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof in the manufacture of a medicament for treating cognitive decline and/or Alzheimer's disease in a patient.

[0003] In some embodiments, the present disclosure provides compounds of Formula I-0:



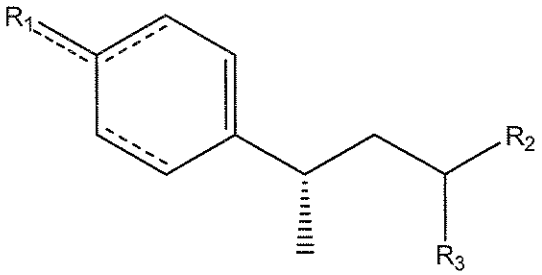
I-0

or pharmaceutically acceptable salts thereof, wherein: ⎓ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is

selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$. In some embodiments, R_1 is selected from CH_3 and CH_2.

[0004] In some embodiments compounds are selected from: 2-methyl-6-p-tolylhept-2-en-4-ol; 2-methyl-6-(4-methylcyclohexa-1,3-dienyl)hept-2-en-4-ol; 2-methyl-6-p-tolylheptane-2,4-diol; N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine; 4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol; 4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol and pharmaceutically acceptable salts thereof.

[0005] In some embodiments, the present disclosure provides compounds of Formula I-1:

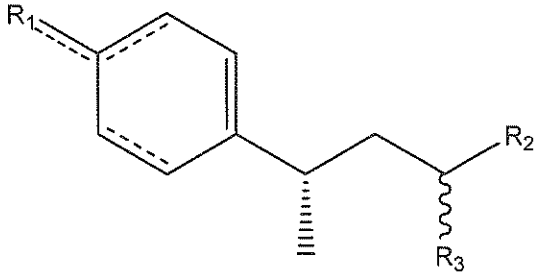


I-1

or pharmaceutically acceptable salts thereof, wherein: ⎯⎯⎯ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$. In some embodiments, R_1 is selected from CH_3 and CH_2.

[0006] In some embodiments compounds are selected from: (6S)-2-methyl-6-p-tolylhept-2-en-4-ol; (6S)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)hept-2-en-4-ol; (6S)-2-methyl-6-p-tolylheptane-2,4-diol; (6S)-N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine; (6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol;(6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol and pharmaceutically acceptable salts thereof.

[0007] In some embodiments, the present disclosure provides compounds of formula I-2:

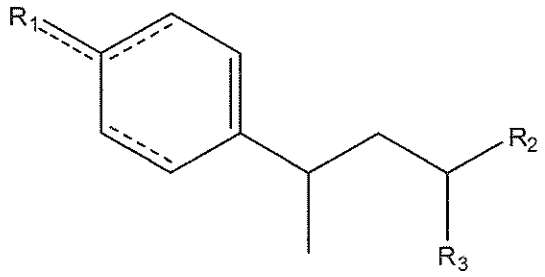


I-2

or pharmaceutically acceptable salts thereof, wherein: ⎓ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$. In some embodiments, R_1 is selected from CH_3 and CH_2.

[0008] In some embodiments, compounds are selected from: (4S,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine; (4R,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine and pharmaceutically acceptable salts thereof.

[0009] Some embodiments are a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I-0:

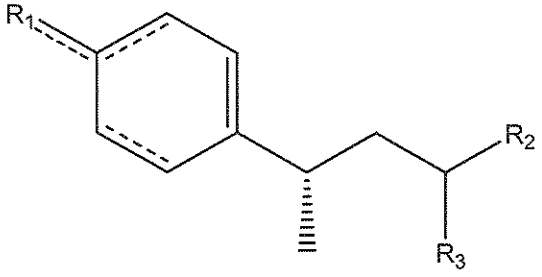


I-0

wherein: ⎓ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In some embodiments, R_1 is selected from CH_3 and CH_2.

[0010] In some embodiments, pharmaceutical compositions are selected from: 2-methyl-6-p-tolylhept-2-en-4-ol; 2-methyl-6-(4-methylcyclohexa-1,3-dienyl)hept-2-en-4-ol; 2-methyl-6-p-tolylheptane-2,4-diol; N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine; 4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol; 4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol and pharmaceutically acceptable salts thereof.

[0011] Some embodiments are a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I-1:

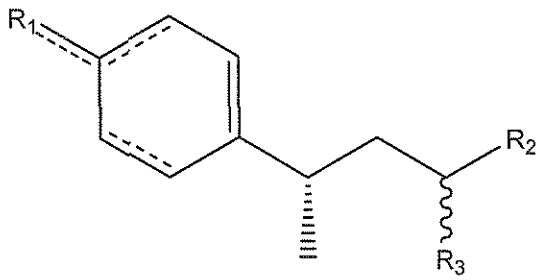


I-1

wherein: ⎯⎯⎯ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In some embodiments, R_1 is selected from CH_3 and CH_2.

[0012] In some embodiments pharmaceutical compositions are selected from: (6S)-2-methyl-6-p-tolylhept-2-en-4-ol; (6S)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)hept-2-en-4-ol; (6S)-2-methyl-6-p-tolylheptane-2,4-diol; (6S)-N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine; (6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol; and (6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

[0013] Some embodiments are a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I-2:



I-2

or pharmaceutically acceptable salt thereof, wherein: ⎯⎯⎯ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$. In some embodiments, R_1 is selected from CH_3 and CH_2.

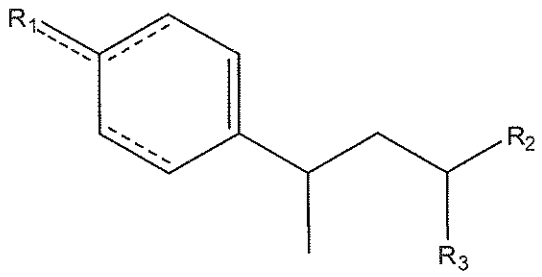
[0014] In some embodiments, pharmaceutical compositions are selected from: (4S,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine; (4R,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine and pharmaceutically acceptable salts thereof.

[0015] Some embodiments are a pharmaceutical composition comprising a mixture of a therapeutically effective amount of 4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol and a therapeutically effective amount of 4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

[0016] Some embodiments are a pharmaceutical composition comprising a mixture of a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol and

a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

[0017] In some embodiments, the present disclosure provides for a method for treating cognitive decline and/or Alzheimer's disease in a patient comprising administrating to the patient a therapeutically effective amount of a compound of formula I-0:



I-0

wherein: ⁻⁻⁻⁻⁻⁻⁻ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In some embodiments, R_1 is selected from CH_3 and CH_2.

[0018] In some embodiments, the compound is selected from: 2-methyl-6-p-tolylhept-2-en-4-ol; 2-methyl-6-(4-methylcyclohexa-1,3-dienyl)hept-2-en-4-ol; 2-methyl-6-p-tolylheptane-2,4-diol; N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine; 4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol; and 4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof.

[0019] In some embodiments one or more symptoms of cognitive decline selected from the group consisting of memory loss, confusion, impaired judgment, personality changes, disorientation, and loss of language skills is treated.

[0020] In yet other embodiments, treating comprises one or more of: (i) restoration of long term potentiation; (ii) inhibition, treatment, and/or abatement of neurodegeneration; (iii) inhibition, treatment, and/or abatement of general amyloidosis; (iv) inhibition, treatment, and/or abatement of one or more of amyloid production, amyloid assembly, amyloid aggregation, amyloid oligomer binding, and amyloid deposition; and (v) inhibition, treatment, and/or abatement of the activity/effect of one or more of Abeta oligomers on a neuron cell.

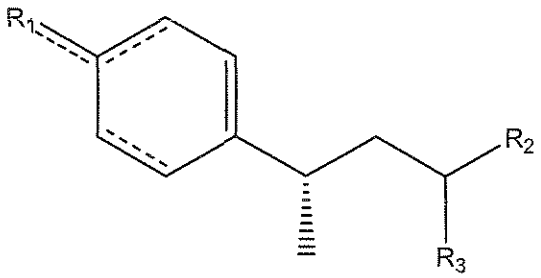
[0021] In some embodiments treating comprises one or more of inhibition of amyloid production, inhibition of amyloid assembly, inhibition of the activity of one or more of Abeta

oligomers on a neuron cell, inhibition of amyloid aggregation, inhibition of amyloid binding, and inhibition of amyloid deposition.

[0022] In some embodiments, treating comprises inhibition of the activity of one or more of Abeta oligomers on a neuron cell, inhibition of amyloid aggregation, inhibition of amyloid binding, and inhibition of amyloid deposition.

[0023] In some embodiments said compound is in a pharmaceutical composition comprising a pharmaceutically acceptable excipient.

[0024] In some embodiments, the present disclosure provides for a method for treating cognitive decline and/or Alzheimer's disease in a patient comprising administrating to the patient a therapeutically effective amount of a compound of formula I-1:



I-1

wherein: ⋯⋯⋯ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In some embodiments, R_1 is selected from CH_3 and CH_2.

In some embodiments, the compound is selected from: (6S)-2-methyl-6-p-tolylhept-2-en-4-ol; (6S)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)hept-2-en-4-ol; (6S)-2-methyl-6-p-tolylheptane-2,4-diol; (6S)-N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine; (6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol; and (6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof.

[0025] In some embodiments one or more symptoms of cognitive decline selected from the group consisting of memory loss, confusion, impaired judgment, personality changes, disorientation, and loss of language skills is treated.

[0026] In some embodiments treating comprises one or more of: (i) restoration of long term potentiation; (ii) inhibition, treatment, and/or abatement of neurodegeneration; (iii) inhibition, treatment, and/or abatement of general amyloidosis; (iv) inhibition, treatment, and/or abatement of one or more of amyloid production, amyloid assembly, amyloid

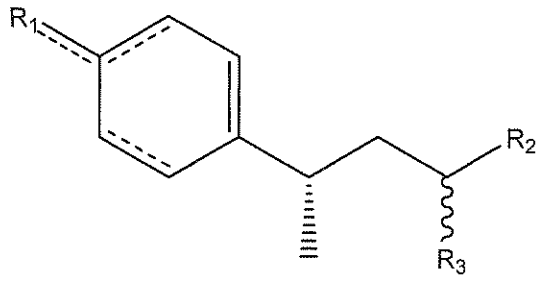
aggregation, amyloid oligomer binding, and amyloid deposition; and (v) inhibition, treatment, and/or abatement of the activity/effect of one or more of Abeta oligomers on a neuron cell.

[0027] In some embodiments, treating comprises one or more of inhibition of amyloid production, inhibition of amyloid assembly, inhibition of the activity of one or more of Abeta oligomers on a neuron cell, inhibition of amyloid aggregation, inhibition of amyloid binding, and inhibition of amyloid deposition.

[0028] In yet other embodiments, treating comprises inhibition of the activity of one or more of Abeta oligomers on a neuron cell, inhibition of amyloid aggregation, inhibition of amyloid binding, and inhibition of amyloid deposition.

[0029] In some embodiments, said compound is in a pharmaceutical composition comprising a pharmaceutically acceptable excipient.

[0030] In some embodiments, the present disclosure provides for a method for treating cognitive decline and/or Alzheimer's disease in a patient comprising administrating to the patient a therapeutically effective amount of a compound of formula I-2:



I-2

or pharmaceutically acceptable salt thereof, wherein: ⁻⁻⁻⁻⁻⁻⁻⁻ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$. In some embodiments, R_1 is selected from CH_3 and CH_2.

[0031] In some embodiments, the compound is selected from: (4S,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine; (4R,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine and pharmaceutically acceptable salts thereof.

[0032] In some embodiments one or more symptoms of cognitive decline selected from the group consisting of memory loss, confusion, impaired judgment, personality changes, disorientation, and loss of language skills is treated.

[0033] In some embodiments treating comprises one or more of: (i) restoration of long term potentiation; (ii) inhibition, treatment, and/or abatement of neurodegeneration; (iii) inhibition, treatment, and/or abatement of general amyloidosis; (iv) inhibition, treatment,

and/or abatement of one or more of amyloid production, amyloid assembly, amyloid aggregation, amyloid oligomer binding, and amyloid deposition; and (v) inhibition, treatment, and/or abatement of the activity/effect of one or more of Abeta oligomers on a neuron cell.

[0034] In some embodiments, treating comprises one or more of inhibition of amyloid production, inhibition of amyloid assembly, inhibition of the activity of one or more of Abeta oligomers on a neuron cell, inhibition of amyloid aggregation, inhibition of amyloid binding, and inhibition of amyloid deposition.

[0035] In yet other embodiments, treating comprises inhibition of the activity of one or more of Abeta oligomers on a neuron cell, inhibition of amyloid aggregation, inhibition of amyloid binding, and inhibition of amyloid deposition.

[0036] In some embodiments, said compound is in a pharmaceutical composition comprising a pharmaceutically acceptable excipient.

[0037] In some embodiments, the present invention provides for a method for treating cognitive decline and/or Alzheimer's disease in a patient comprising administrating to the patient a pharmaceutical composition comprising a mixture of a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol and a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof.

[0038] In some embodiments, one or more symptoms of cognitive decline selected from the group consisting of memory loss, confusion, impaired judgment, personality changes, disorientation, and loss of language skills is treated.

[0039] In yet other embodiments, treating comprises one or more of: (i) restoration of long term potentiation; (ii) inhibition, treatment, and/or abatement of neurodegeneration; (iii) inhibition, treatment, and/or abatement of general amyloidosis; (iv) inhibition, treatment, and/or abatement of one or more of amyloid production, amyloid assembly, amyloid aggregation, amyloid oligomer binding, and amyloid deposition; and (v) inhibition, treatment, and/or abatement of the activity/effect of one or more of Abeta oligomers on a neuron cell.

[0040] In some embodiments, treating comprises one or more of inhibition of amyloid production, inhibition of amyloid assembly, inhibition of the activity of one or more of Abeta oligomers on a neuron cell, inhibition of amyloid aggregation, inhibition of amyloid binding, and inhibition of amyloid deposition.

[0041] In some embodiments, treating comprises inhibition of the activity of one or more of Abeta oligomers on a neuron cell, inhibition of amyloid aggregation, inhibition of amyloid binding, and inhibition of amyloid deposition.

[0042] In some embodiments said compound is in a pharmaceutical composition comprising a pharmaceutically acceptable excipient.

DESCRIPTION OF DRAWINGS

[0043] Figure 1 shows results of an MTT assay in the presence and absence of a processed product of amyloid precursor protein.

[0044] Figure 2 shows inhibition of processed product of amyloid precursor protein-mediated membrane trafficking effect by CT0109.

[0045] Figure 3 shows CT0109 and CT0093 inhibiting the memory loss effects of a processed product of amyloid precursor protein.

[0046] Figure 4 shows inhibition of processed product of amyloid precursor protein-mediated membrane trafficking effect by CT0093 and purified fractions CT01296, CT01297, CT01298.

[0047] Figure 5 shows inhibition of processed product of amyloid precursor protein-mediated synapse loss by CT0093 and CT0109

[0048] Figure 6 shows inhibition of processed product of amyloid precursor protein binding to brain cells in vitro by CT0093.

[0049] Figure 7 shows pharmacological competition between processed product of amyloid precursor protein and CT0093 for targets that mediate membrane trafficking and that compound CT0093 and CT0109 exhibit pharmacological competition with both synthetic (A, B) and human Alzheimer's patient-derived (C, D) oligomers and reduce toxicity of abeta oligomers.

[0050] Figure 8 shows that compound CT0093 and CT0109 effectively inhibit processed product of amyloid precursor protein inhibition of membrane trafficking whether they are added before or after.

[0051] Figure 9 shows that compound CT0093 and CT0109 improve memory deficits in a transgenic mouse model of Alzheimer's disease.

[0052] Figure 10 shows that compound CT0093 and CT0109 are effective in both prevention and treatment protocols.

DETAILED DESCRIPTION

[0053] Cognitive decline, such as memory loss, confusion, impaired judgment, personality changes, disorientation, and loss of language skills occurs in much of the

population as they age, in varying degree. The most common, severe and irreversible form of cognitive decline is Alzheimer's disease, which, at present, is always fatal.

[0054] : The symptoms of cognitive decline and Alzheimer's disease are thought to stem from the effect of amyloid beta and its higher order oligomeric forms on the brain, which contributes to the degradation of neuronal (nerve cell) performance and the subsequent onset of symptoms. Amyloid is a general term for protein fragments that the body produces normally. Beta-amyloid is a fragment of a protein that is snipped from another protein called amyloid precursor protein (APP). In a healthy brain, beta-amyloid protein fragments are broken down and eliminated. In individuals with Alzheimer's disease and other forms of cognitive decline, the fragments accumulate to form hard, insoluble plaques. Neurofibrillary tangles are insoluble twisted fibers that are found inside of the brain's cells. The protein contained in neurofibrillary tangles, i.e., the tau protein, forms a microtubule, which helps transport nutrients and other important substances from one part of the nerve cell to another. In Alzheimer's disease the tau protein is abnormal and the microtubule structures collapse.

[0055] Beta-secretase is the enzyme in the human brain responsible for the production of Beta-amyloid, the pathogenic substance responsible for the formation of brain plaques and tangles in the Alzheimer's diseased brain. Beta-amyloid and its oligomers (beta-amyloid oligomers or Abeta oligomers) are also believed to be responsible for early cognitive decline in the pre-Alzheimer's diseased brain. Inhibition of beta-secretase would be expected to lessen beta-amyloid burden in the brain and thus slow cognitive decline, block the formation of amyloid oligomers, the production of plaques and tangles, halt neurodegeneration, and to potentially treat mild cognitive impairment and more serious forms of cognitive impairment such as Alzheimer's disease. However, the effect of lowering beta-amyloid monomer levels is unknown. Recent clinical trials suggest that targeting secretases may not represent a viable therapeutic option.

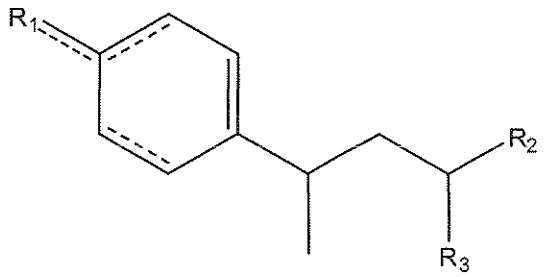
[0056] Millions of people worldwide are affected by cognitive decline and Alzheimer's disease. Accordingly, there is strong need to discover inhibitors of cognitive decline, and in particular, compounds that are useful in the treatment and abatement of cognitive decline and Alzheimer's disease, by methods such as inhibiting amyloid (including Abeta oligomers) production, amyloid (including Abeta oligomers) aggregation, and/or amyloid (including Abeta oligomers) deposition (*i.e.*, plaquing), inhibiting neuorodegeneration, and/or restoring long term potentiation, and/or inhibiting the activity/effect of Abeta oligomers on neurons. There is also a need for inhibitors of cognitive decline that are chemically and biologically stable.

[0057] Plants have attracted relatively little attention as potentially valuable resources for drug discovery in the area of cognitive decline and Alzheimer's disease. The use of plant extracts to produce unnatural derivatives of compounds of medicinal interest is not generally used. Accordingly, there is also a need for a method of producing compounds of medicinal interest from plant extracts and extracts from other biological sources. In particular, there is also a need to produce and identify compounds derived from plant extracts that are useful in the treatment and abatement of cognitive decline and Alzheimer's disease.

[0058] Turmeric, an herb with highly reputed medicinal properties in the Indian system of medicine, Ayurveda, is the rhizome of *Curcuma longa* L. Syn. *Curcuma domestica Valeton* (Fam. Zingiberaceae), which grows abundantly in India. It has long been used as a spice and a coloring agent in food. Its powder or extracts are recommended to treat wounds and inflammation. Lipid soluble extracts of rhizomes and leaves of *Curcuma* species of Zingiberaceae family are reported to be useful for the treatment of neurocerebrovascular disorders. *See* WO 2003051380. Turmeric oil can be isolated from turmeric (*Curcuma longa*) by supercritical fluid extraction with carbon dioxide. *See e.g.* B. Gopalan, et. al, "Supercritical Carbon Dioxide Extraction of Turmeric (*Curcuma longa*)",*J. Agric. Food Chem.*, 2000, 48 (6), pp 2189–2192; *see also* L-H Chang, et. al, "Supercritical carbon dioxide extraction of turmeric oil from *Curcuma longa* Linn and purification of turmerones", *Separation and Purification Technology* Volume 47, Issue 3, January 2006, Pages 119-125. The present invention, in part, relates to producing and identifying compounds derived from Turmeric oil (i.e. Turmeric oil derivatives) that are useful in the treatment and abatement of cognitive decline and Alzheimer's disease. The present invention also, in part, relates to chemically synthesizing compounds that are useful in the treatment and abatement of cognitive decline and Alzheimer's disease.

[0059] The compounds, compositions, and methods described herein are directed toward these needs and other ends.

[0060] Embodiments of the present invention provide, *inter alia*, a compound of Formula I-0:

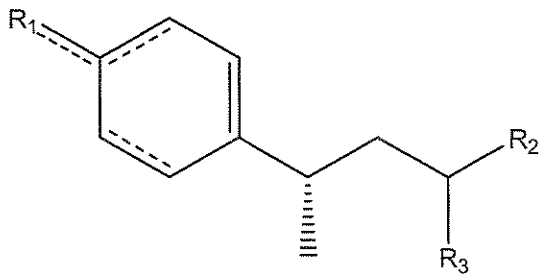


I-0

or a pharmaceutically acceptable salt thereof, wherein: ⎯⎯⎯ is a single bond or a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$. In some embodiments, R_1 is selected from CH_3 and CH_2.

[0061] In some embodiments, the compound is selected from: 2-methyl-6-p-tolylhept-2-en-4-ol; 2-methyl-6-(4-methylcyclohexa-1,3-dienyl)hept-2-en-4-ol; 2-methyl-6-p-tolylheptane-2,4-diol; N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine; 4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol; 4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol and pharmaceutically acceptable salts thereof.

[0062] Embodiments of the present invention provide, *inter alia*, a compound of Formula I-1:

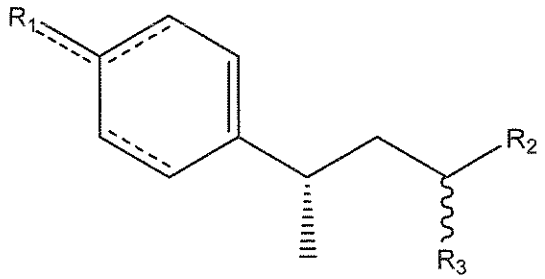


I-1

or a pharmaceutically acceptable salt thereof, wherein: ⎯⎯⎯ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$. In some embodiments, R_1 is selected from CH_3 and CH_2.

[0063] In some embodiments compounds are selected from: (6S)-2-methyl-6-p-tolylhept-2-en-4-ol; (6S)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)hept-2-en-4-ol; (6S)-2-methyl-6-p-tolylheptane-2,4-diol; (6S)-N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine; (6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol;(6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol and pharmaceutically acceptable salts thereof.

[0064] Embodiments of the present invention provide, *inter alia*, a compound of Formula I-2:



I-2

or a pharmaceutically acceptable salt thereof, wherein: ⁻⁻⁻⁻⁻⁻⁻⁻ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$. In some embodiments, R_1 is selected from CH_3 and CH_2.

[0065] In some embodiments, compounds are selected from: (4S,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine; (4R,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine and pharmaceutically acceptable salts thereof.

[0066] At various places in the present specification, substituents of compounds of the invention are disclosed in groups or in ranges. It is specifically intended that embodiments the invention include each and every individual subcombination of the members of such groups and ranges.

[0067] For compounds of the invention in which a variable appears more than once, each variable can be a different moiety selected from the Markush group defining the variable. For example, where a structure is described having two R groups that are simultaneously present on the same compound, then the two R groups can represent different moieties selected from the Markush group defined for R.

[0068] It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

[0069] The term "n-membered" where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example,

pyridine is an example of a 6-membered heteroaryl ring and thiophene is an example of a 5-membered heteroaryl group.

[0070] As used herein, the term "alkyl" is meant to refer to a saturated hydrocarbon group which is straight-chained or branched. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, t-butyl), pentyl (e.g., n-pentyl, isopentyl, neopentyl), and the like. An alkyl group can contain from 1 to about 20, from 2 to about 20, from 1 to about 10, from 1 to about 8, from 1 to about 6, from 1 to about 4, or from 1 to about 3 carbon atoms.

[0071] As used herein, "aryl" refers to monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings) aromatic hydrocarbons such as, for example, phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like. In some embodiments, aryl groups have from 6 to about 20 carbon atoms. In some embodiments, aryl groups have from 6 to about 10 carbon atoms.

[0072] As used herein, "cycloalkyl" refers to non-aromatic cyclic hydrocarbons including cyclized alkyl, alkenyl, and alkynyl groups that contain up to 20 ring-forming carbon atoms. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) ring systems as well as spiro ring systems. A cycloalkyl group can contain from 3 to about 15, from 3 to about 10, from 3 to about 8, from 3 to about 6, from 4 to about 6, from 3 to about 5, or from 5 to about 6 ring-forming carbon atoms. Ring-forming carbon atoms of a cycloalkyl group can be optionally substituted by oxo or sulfido. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, adamantyl, and the like. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo or thienyl derivatives of pentane, pentene, hexane, and the like (e.g., 2,3-dihydro-1H-indene-1-yl, or 1H-inden-2(3H)-one-1-yl). Preferably, "cycloalkyl" refers to cyclized alkyl groups that contain up to 20 ring-forming carbon atoms. Examples of cycloalkyl preferably include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, and the like.

[0073] As used herein, "heteroaryl" groups refer to an aromatic heterocycle having up to 20 ring-forming atoms and having at least one heteroatom ring member (ring-forming atom) such as sulfur, oxygen, or nitrogen. In some embodiments, the heteroaryl group has at least one or more heteroatom ring-forming atoms each independently selected from sulfur, oxygen,

and nitrogen. Heteroaryl groups include monocyclic and polycyclic (e.g., having 2, 3 or 4 fused rings) systems. Examples of heteroaryl groups include without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrryl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, benzothienyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, and the like. In some embodiments, the heteroaryl group has from 1 to about 20 carbon atoms, and in further embodiments from about 1 to about 5, from about 1 to about 4, from about 1 to about 3, from about 1 to about 2, carbon atoms as ring-forming atoms. In some embodiments, the heteroaryl group contains 3 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heteroaryl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms.

[0074] As used herein, "heterocycloalkyl" refers to non-aromatic heterocycles having up to 20 ring-forming atoms including cyclized alkyl, alkenyl, and alkynyl groups where one or more of the ring-forming carbon atoms is replaced by a heteroatom such as an O, N, or S atom. Hetercycloalkyl groups can be mono or polycyclic (e.g., both fused and spiro systems). Example "heterocycloalkyl" groups include morpholino, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, 2,3-dihydrobenzofuryl, 1,3-benzodioxole, benzo-1,4-dioxane, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, pyrrolidin-2-one-3-yl, and the like. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally substituted by oxo or sulfido. For example, a ring-forming S atom can be substituted by 1 or 2 oxo [i.e., form an S(O) or $S(O)_2$]. For another example, a ring-forming C atom can be substituted by oxo (i.e., form carbonyl). Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the nonaromatic heterocyclic ring, for example pyridinyl, thiophenyl, phthalimidyl, naphthalimidyl, and benzo derivatives of heterocycles such as indolene, isoindolene, isoindolin-1-one-3-yl, 4,5,6,7-tetrahydrothieno[2,3-c]pyridine-5-yl, 5,6-dihydrothieno[2,3-c]pyridin-7(4H)-one-5-yl, and 3,4-dihydroisoquinolin-1(2H)-one-3yl groups. Ring-forming carbon atoms and heteroatoms of the heterocycloalkyl group can be optionally substituted by oxo or sulfido. In some embodiments, the heterocycloalkyl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heterocycloalkyl group contains 3 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heterocycloalkyl group has 1 to about 4, 1 to about 3, or 1 to 2

heteroatoms. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 triple bonds.

[0075] As used herein, "alkoxy" refers to an -O-alkyl group. Example alkoxy groups include methoxy, ethoxy, propoxy (*e.g.*, n-propoxy and isopropoxy), t-butoxy, and the like.

[0076] As used herein, "arylalkyl" refers to a C_{1-6} alkyl substituted by aryl. Example arylalkyl groups include, but are not limited to, C_{1-6} alkyl substituted by C_{6-10} aryl (e.g. benzyl).

[0077] As used herein, "cycloalkylalkyl" refers to C_{1-6} alkyl substituted by cycloalkyl. Example cycloalkylalkyl groups include, but are not limited to, C_{1-6} alkyl substituted by C_{3-10} cycloalkyl or C_{3-7} cycloalkyl (e.g. cyclopropylmethyl).

[0078] As used herein, "amino" refers to NH_2.

[0079] As used herein, the term "optionally substituted" means that substitution is optional and therefore includes both unsubstituted and substituted atoms and moieties. A "substituted" atom or moiety indicates that any hydrogen on the designated atom or moiety can be replaced with a selection from the indicated substituent group, provided that the normal valency of the designated atom or moiety is not exceeded, and that the substitution results in a stable compound. For example, if a methyl group (i.e., CH_3) is optionally substituted, then 3 hydrogen atoms on the carbon atom can be replaced with substituent groups.

[0080] The compounds described in the embodiments herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. *Cis* and *trans* geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. Where a compound capable of stereoisomerism or geometric isomerism is designated in its structure or name without reference to specific R/S or cis/trans configurations, it is intended that all such isomers are contemplated.

[0081] Resolution of racemic mixtures (or mixture of diastereoisomers) of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallizaion using a chiral resolving acid which is an optically active, salt-

forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as α-camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α-methyl-benzyl-amine (*e.g.*, *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like.

[0082] Resolution of racemic mixtures (or mixture of diastereoisomers) can also be carried out by elution on a column packed with an optically active resolving agent (*e.g.*, dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

[0083] Compounds of embodiments the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide - imidic acid pairs, lactam – lactim pairs, amide - imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

[0084] Compounds of embodiments the invention further include hydrates and solvates, as well as anhydrous and non-solvated forms.

[0085] The term, "compound," as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted.

[0086] All compounds and pharmaceutically acceptable salts thereof, can be prepared or present together with other substances such as water and solvents (e.g. hydrates and solvates) or can be isolated.

[0087] Compounds of embodiments the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

[0088] In some embodiments, the compounds of the invention, or salts thereof, are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it is formed or detected. Partial separation can include, for example, a composition enriched in the compound of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound of the invention, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

[0089] Compounds of embodiments the invention are intended to include compounds with stable structures. As used herein, "stable compound" and "stable structure" are meant to indicate 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.

[0090] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0091] The expressions, "ambient temperature" and "room temperature," as used herein, are understood in the art, and refer generally to a temperature, *e.g.* a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

[0092] embodiments of the present invention also include pharmaceutically acceptable salts of the compounds described herein. as used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. the pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. the pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an

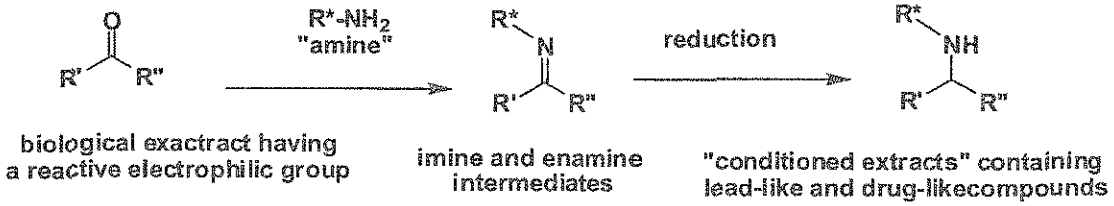
organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile (acn) are preferred. lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack publishing company, Easton, pa., 1985, p. 1418 and journal of pharmaceutical science, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

[0093] In some embodiments, a method of preparing an array of chemical compounds from a biological extract such as Turmeric oil is provided.

[0094] The method of the invention, termed "chemical conditioning" is generally applicable to all biological extracts, in particular, natural plant extracts, common or medicinal. *See e.g.* US20080193574 and WO2008042755, each of which is incorporated herein by reference in its entirety. Chemical conditioning is a method which produces novel unnatural drug-like compounds from readily available natural materials. In general, the "chemical conditioning" of natural extracts coupled with pre-fractionation of the chemically conditioned extracts facilitates successful biochemical screening of extracts by destroying reactive natural compounds that generate false positive results in biochemical assays. Chemical conditioning produces novel lead-like and drug-like compounds and, the reductive amination protocol and reduction protocol described here can produce structurally diverse nitrogen-containing products and alcohol products that are particularly lead-like and drug-like.

[0095] In certain embodiments of the present invention, a method of preparing chemical compounds from a biological extract is exemplified in Scheme 1 below. According to the method, a biological extract, *e.g.*, a plant extract is provided, the biological extract has one or more biological compounds, each biological compound having one or more reactive electrophilic groups. The biological compounds in the biological extract are reacted with an amine to incorporate the amine into the biological compounds. The biological compounds having the incorporated amine are reacted with a reducing agent to reduce any potential intermediate imine and enamine compounds and form one or more nitrogen-containing chemical compounds. Thus, the resultant nitrogen-containing chemical compounds are derivatives of the biological compounds in the biological extract.

SCHEME 1

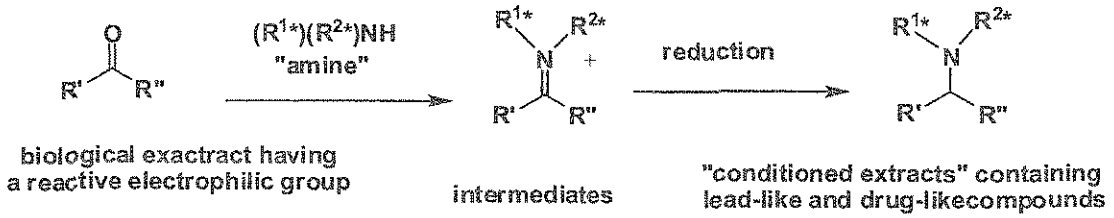


R' and R" represent a variety of substituents that make up a biological compound; and

R* represents a variety of substituent(s) that, together with the nitrogen, make up an amine compound.

[0096] Similarly, in certain other embodiments of the present invention, a method of preparing chemical compounds from a biological extract is exemplified in Scheme 1a below. A secondary amine (wherein each of R^{1*} and R^{2*} can be alkyl or the like; or R^{1*} and R^{2*}, together with the N atom to which they are attached, form a cyclic amine such as pyrollidine) is used in the conditioned extracts.

SCHEME 1a



R' and R" represent a variety of substituents that make up a biological compound; and

each of R^{1*} and R^{2*} represents a variety of substituent(s) that, together with the nitrogen, make up an amine compound.

[0097] In some embodiments, the compounds in the conditioned extraction are reaction products of compounds having ketones and aldehydes with various amines. This reaction is followed by reduction such as hydride reduction of the intermediate imines and enamines to provide secondary and tertiary amines. The reaction of ketones and aldehydes with amines, followed by reduction of the formed imines and enamines to provide amines, is known in the art.

[0098] In some embodiments, the compounds in the conditioned extraction are reaction products of compounds having ketones and aldehydes with a reducing reagent such as a hydride reducing reagent (e.g. sodium borohydride, lithium aluminum hydride, sodium triacetoxy borohydride). In some embodiments, the ketones and aldehydes are reduced to

alcohols. In some embodiments, the compounds in the conditioned extract are compounds having other reactive functional groups that can be reduced in the presence of a reducing reagent such as a hydride reducing reagent (e.g. sodium borohydride, lithium aluminum hydride, sodium triacetoxy borohydride).

[0099] In some embodiments, the chemical conditioning method described herein employs a biological extract (such as Turmeric oil), using many different reagents, to efficiently produce an array of nitrogen-containing chemical compounds. The ready commercial availability of many low molecular weight amines for use as inputs in the reductive amination sequence enables the development of many different and structurally diverse central nervous system drug-like mixtures from the same natural extract. Suitable amines for use in the present method are selected from the group consisting of primary amines, secondary amines, cyclic amines, pyrollidine, and amino acids. Suitable reducing agents for use in the present method are selected from the group of hydride reducing agents including but not limited to sodium borohydride, sodium triacetoxyborohydride, and lithium aluminum hydride.

[00100] In some embodiments, the chemical conditioning method described herein employs a biological extract (such as Turmeric oil), using one or more reducing reagents, to efficiently produce an array of alcohol-containing chemical compounds (alcohol derivatives). Suitable reducing agents for use in the present method are selected from the group of hydride reducing agents including but not limited to sodium borohydride, sodium triacetoxyborohydride, and lithium aluminum hydride.

[00101] The method may further comprise quenching the reaction by using a quenching agent, wherein the quenching agent is selected from but not limited to the group consisting of sodium bicarbonate, sodium carbonate, sodium sulfate, sodium sulfate decahydrate. The method may also further comprise isolating one or more of the nitrogen-containing chemical compounds, in a purified or unpurified form. The resultant nitrogen-containing chemical may then be screened or tested for biological activity.

[00102] The process of chemical conditioning by reduction or reductive amination described herein destroys reactive electrophiles in the natural extract, including ketones, as in the Turmeric oils, and converts them to chemically stable compounds such as amines or alcohols. The resulting conditioned extracts contain both natural compounds and novel unnatural nitrogen-containing amine products or alcohol products that are potential drug candidates. In some embodiments, in the process of chemical conditioning by reductive

amination described herein, reactive electrophiles in the natural extract, including ketones, as in the Turmeric oils, are destroyed and the ketone compounds are converted to other chemical compounds such as amines. In some other embodiments, in the process of chemical conditioning by reduction described herein, reactive electrophiles in the natural extract, including ketones, as in the Turmeric oils, are destroyed and the ketone compounds are converted to other chemical compounds such as alcohols.

[00103] In the case of the extracts of Turmeric oil, the nitrogen-containing amine derivatives and alcohol derivatives may be used to treat central nervous system disorders.

[00104] For the purpose of this disclosure, the following terms have the following meanings.

[00105] The term "biological compound" as used herein refers to a chemical compound that occurs in nature.

[00106] The term "biological extract" as used herein refers to an extract from a biological sample, such as a plant extract, or other extract from organic matter, containing chemical compounds that occur in nature.

[00107] The term "reactive electrophilic group" as used herein refers to an atom or group of atoms that has the ability to react with a nucleophile.

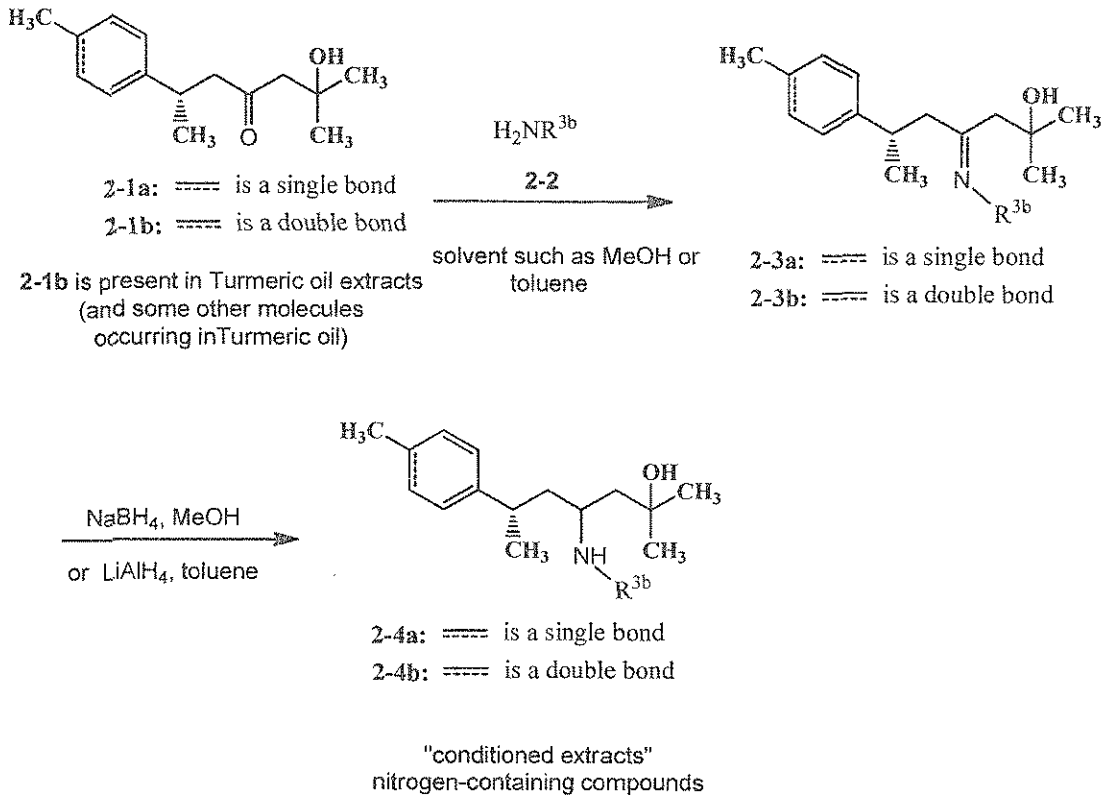
[00108] The term "nitrogen-containing derivative" as used herein represents those derivatives containing a nitrogen atom, where the nitrogen atom is a substitution another atom, such as oxygen in the parent compound.

[00109] The term "alcohol derivative" as used herein represents those derivatives containing a hydroxyl group, where the hydroxyl group is reduced from a carbonyl group in the parent compound (such as a ketone or aldehyde parent compound).

[00110] In one embodiment, a specific example of a chemical conditioning process is shown in Scheme 2 below. Scheme 2 shows the two-step reductive amination chemical conditioning protocol performed on Turmeric oil in accordance with one embodiment of the method, wherein Turmeric oil comprising ketones **2-1a** and **2-1b** are converted to amines **2-4a** and **2-4b** respectively. According to the method shown in Scheme 2, Turmeric oil (containing ketones **2-1a** and **2-1b** and other molecules occurring in Turmeric) is reacted with amine **2-2** [wherein R^{3b} can be C1-6 alkyl (e.g. isobutyl) or the like] to form compounds **2-3a** and **2-3b** respectively. The resultant compounds **2-3a** and **2-3b** are reduced, with a reducing agent such

as a borohydride, to from the nitrogen-containing compounds **2-4a** and **2-4b** respectively (the reaction crude product also includes other chemical compounds).

SCHEME 2

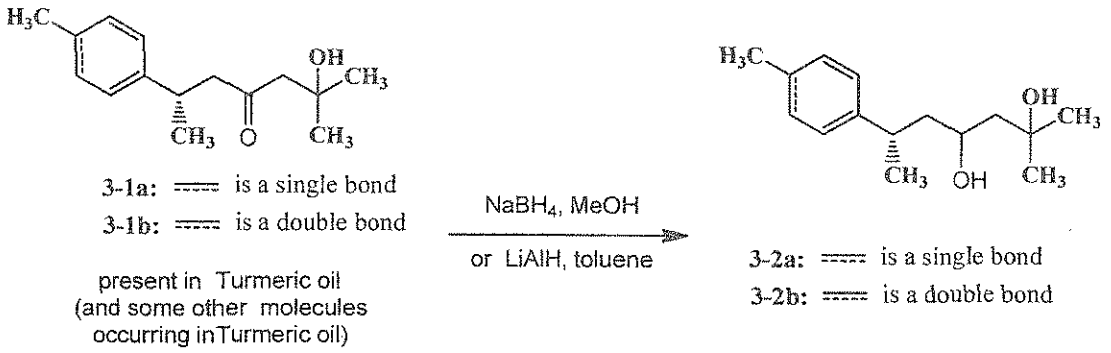


[00111] In the next step of the method, amines **2-4a** and **2-4b** are isolated/purified from the extract (the crude reaction product of the 2-step reductive amination process). The conditioned extracts can be fractionated by flash chromatography. The fractions that contain amines **2-4a** or **2-4b** can undergo further purification/isolation according to the methods known to those in the art. Further isolation and characterization of the fraction that contains amines **2-4a** or **2-4b** may follow. In some embodiments, amine **2-4a** can be subject to further separation (such as using column chromatography) to isolate each of the diastereoisomers. In some embodiments, amine **2-4b** can be subject to further separation (such as using column chromatography) to isolate each of the diastereoisomers. The isolated amines **2-4a** and **2-4b** are tested for their biological activities such as by those methods described herein with.

[00112] Some examples of amine **2-2** used in the chemical conditioning process of the invention shown in Scheme 2 include akylamines such as methylamine, ethylamine, n-propylamine, isopropylamine, n-butylamine, 2-butylamine, isobutylamine, and *tert*-butylamine; phenylamine, and benzylamine.

[00113] In another embodiment, a specific example of a chemical conditioning process is shown in Scheme 3 below. Scheme 3 shows a reductive chemical conditioning protocol (or a chemical conditioning protocol of reduction) performed on Turmeric oil in accordance with one embodiment of the method, wherein Turmeric oil comprising ketones **3-1a** and **3-1b** are reduced/converted to alcohols **3-2a** and **3-2b** respectively. In some embodiments, alcohol **3-2a** can be subject to further separation (such as using column chromatography) to isolate each of the diastereoisomers. In some embodiments, alcohol **3-2b** can be subject to further separation (such as using column chromatography) to isolate each of the diastereoisomers. The alcohol derivatives **3-2a** and **3-2b** are tested for their biological activities such as by those methods described herein with.

SCHEME 3



[00114] In some embodiments, the derivatives of Turmeric oil such as amine derivatives **2-4a** and **2-4b** and alcohol derivatives **3-2a** and **3-2b** possess beta-secretase inhibitory activity, and/or inhibit amyloid production, amyloid assembly, the activity/effect of Abeta oligomers on neurons (such as neurons in the brain), amyloid aggregation, amyloid (including amyloid oligomer) binding, or amyloid deposition. These compounds are useful therapeutic agents for the treatment and prevention of cognitive decline, amyloid production, neurodegeneration, and Alzheimer's disease.

[00115] New lead compounds generated by this chemical conditioning method can also be prepared by the synthetic methods described herein.

[00116] Compounds of embodiments the invention, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes.

[00117] The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis.

Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, *e.g.*, temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

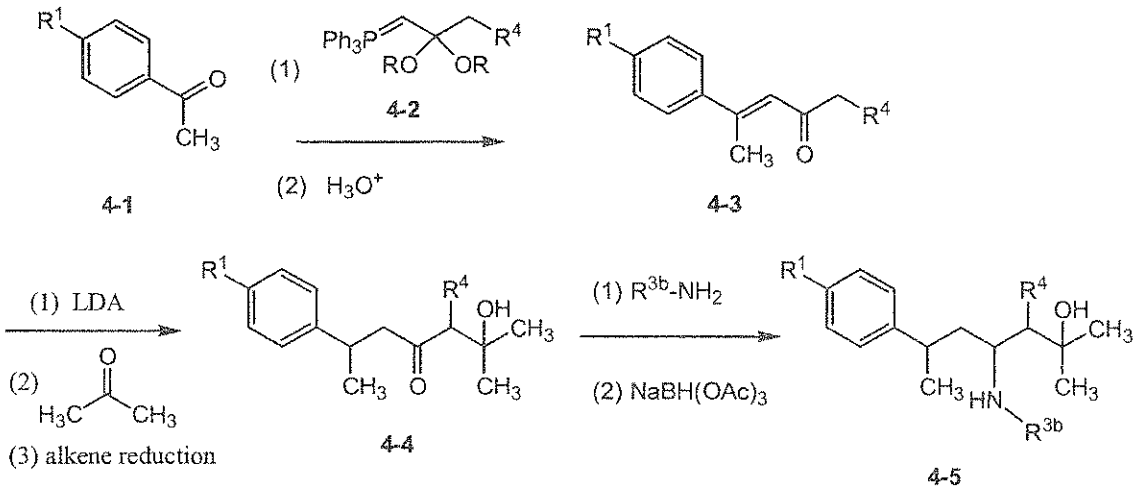
[00118] Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., Wiley & Sons, Inc., New York (1999), which is incorporated herein by reference in its entirety.

[00119] Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C), infrared spectroscopy, spectrophotometry (*e.g.*, UV-visible), mass spectrometry, or by chromatographic methods such as high performance liquid chromatography (HPLC) or thin layer chromatography (TLC).

[00120] The compounds of embodiments of the invention can be prepared, for example, according to the reaction pathways, synthetic procedures, and techniques described below.

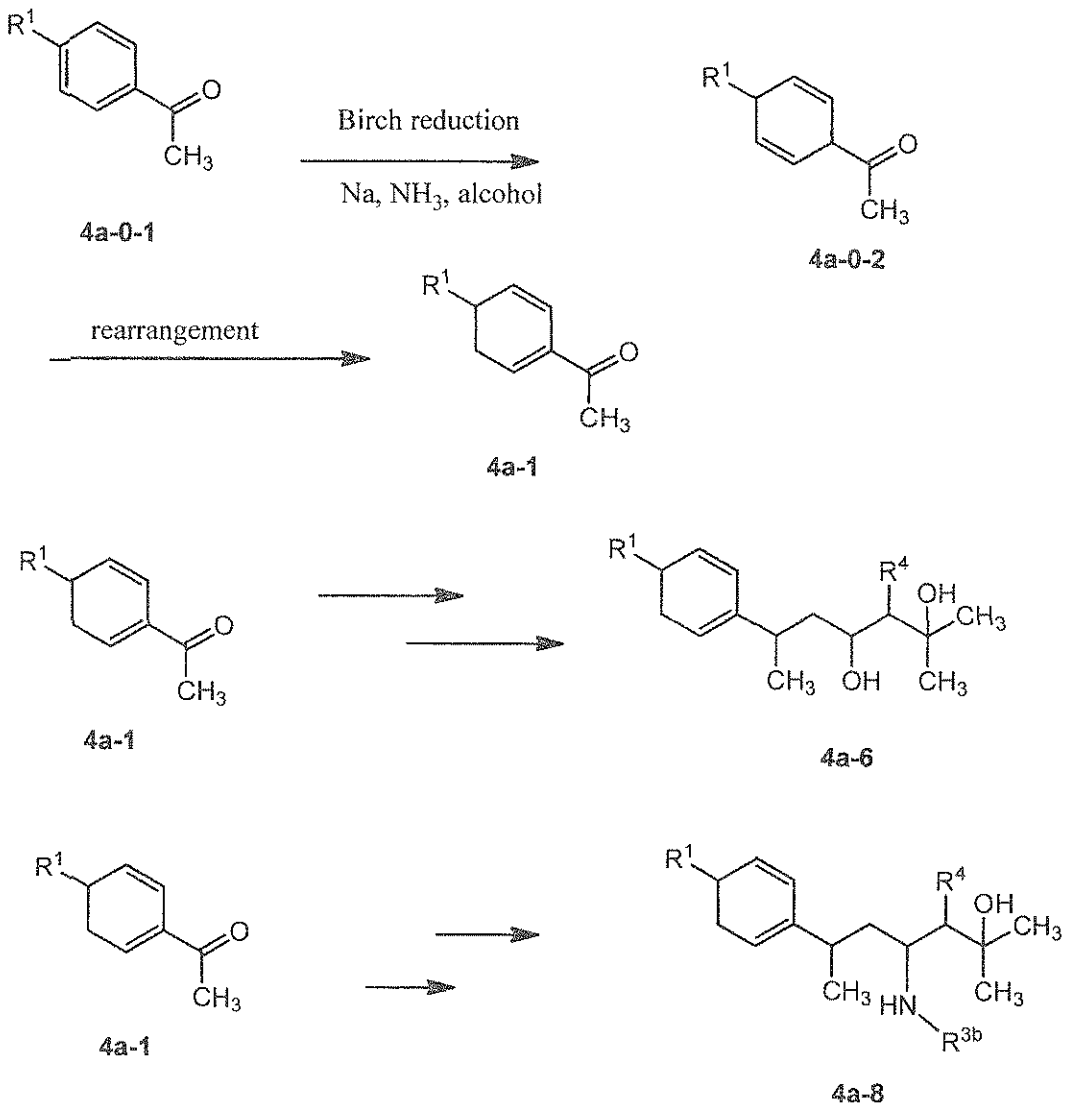
[00121] As shown in Scheme 4, wherein R^1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; and R^4 is H, ketone **4-1** can be reacted with Wittig reagents such as **4-2**, followed by hydrolysis (for example under acidic condition) to afford ketone **4-3**. The enolate of ketone **4-3** with a reagent such as LDA, and condensed with acetone followed by conjugate reduction of the alkene toto form ketone **4-4**. Reductive amination of ketone **4-5** with a suitable amine $R^{3b}NH_2$ wherein R^{3b} can be C1-6 alkyl (e.g. isobutyl) or the like in the presence of a suitable hydride such as sodium borohydride can afford amine **4-6**. Different diastereomers of amine **4-6** can be separated by methods known to those skilled in the art such as column chromatography.

SCHEME 4



[00122] As shown in Scheme 4a, wherein R^1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R^{3b} is C1-6 alkyl and R^4 is H, aromatic compound **4a-0-1** can be reduced to cyclohexa-1,4-diene **4a-02** under Birch reduction conditions. *See e.g.* Rabideau, P. W., "The metal-ammonia reduction of aromatic compounds", *Tetrahedron*, Volume 45, Issue 6, 1989, pages 1579-1603. Under acidic conditions (such as in the presence of catalytic amount of HCl or acetic acid), cyclohexa-1,4-diene **4a-02** can rearrange to the thermodynamically more stable cyclohexa-1,3-diene **4a-1**. Cyclohexa-1,3-diene **4a-1** can be converted to alcohol **4a-6** or amine **4a-8** according to methods similar to those described in Scheme 4.

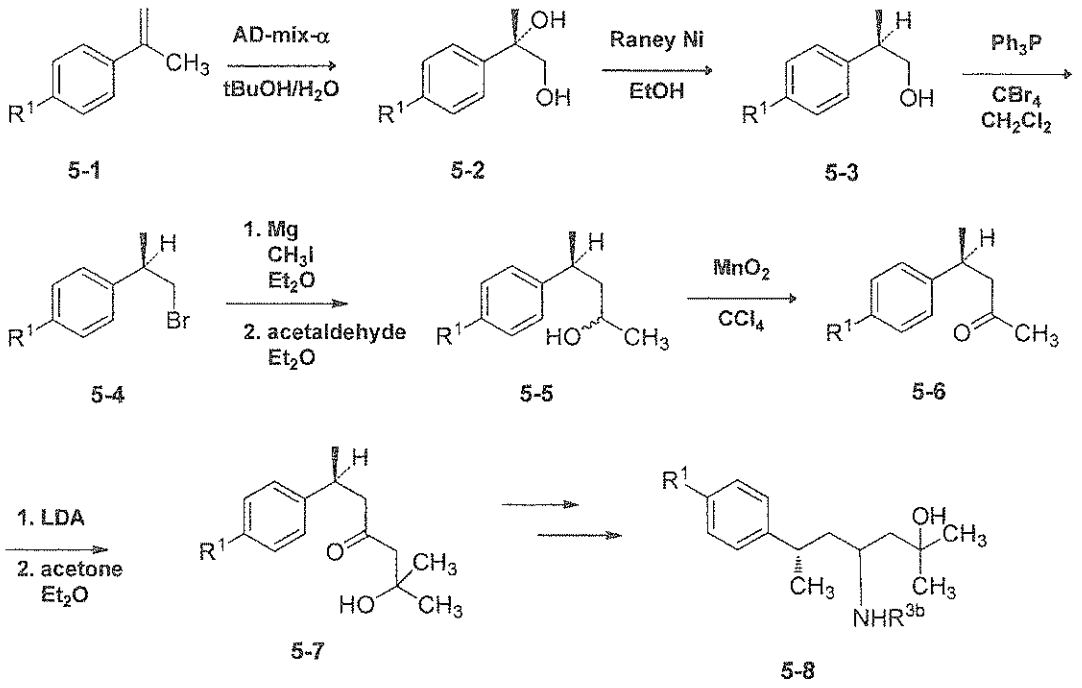
SCHEME 4a



[00123] As shown Scheme 5, wherein R^1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; and R^{3b} is C1-6 alkyl, treatment of styrene derivative **5-1** with AD-mix-α (*See e.g.* Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; et al. *J. Org. Chem.* **1992**, 57, 2771) affords diol **5-2**. *See* A. Li, et. al, "Total asymmetric synthesis of (7S,9R)-(+)-bisacumol", Tetrahedron: Asymmetry (2003), 14(1), 75-78. Stereo-selective reduction of the benzylic OH of diol **5-2** with Raney nickel gives alcohol **5-3**. *See id.* Both the isomer of **5-2** can be obtained based on selection of the Sharpless catalyst. Treatment of alcohol **5-3** with PPh_3 and CBr_4 in a suitable solvent such as methylene chloride affords bromide **5-4**.

Conversion of bromide **5-4** to the corresponding Grignard reagent in the presence of magnesium powder and CH_3I (by metal-halogen exchange), followed by reaction with acetaldehyde, provides alcohol **5-5**. Different diastereomers of alcohol **5-5** can be separated by methods known to those skilled in the art such as column chromatography. *See id.* Alcohol **5-5** can be transformed into its corresponding amine compound **5-6** using similar methods to those outlined in Scheme 4. The isomers of the amine compound **5-8** can be obtained by stereoselective immine reduction.

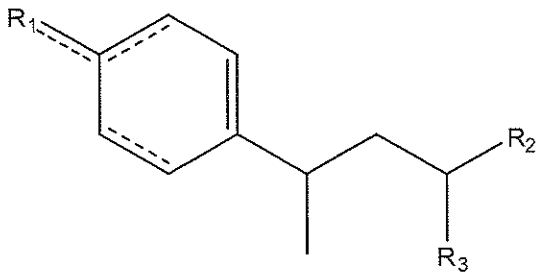
SCHEME 5



[00124] Those skilled in the art can recognize that in all of the schemes described herein, if there are functional (reactive) groups present on a substituent group such as R^1, R^2, R^3, and R^4, etc., further modification can be made if appropriate and/or desired. For example, an OH group can be converted into a better leaving group such as mesylate, which in turn is suitable for nucleophilic substitution, such as by Br. Thus, a compound of Formula I (such as compound 4-8 of Scheme 4) having a substituent which contains a functional group can be converted to another compound of Formula I having a different substituent group.

[00125] As used herein, the term "reacting" refers to the bringing together of designated chemical reactants such that a chemical transformation takes place generating a compound different from any initially introduced into the system. Reacting can take place in the presence or absence of solvent.

[00126] Some embodiments are a method for treating cognitive decline and/or Alzheimer's disease in a patient comprising administrating to the patient a therapeutically effective amount of a compound of formula I-0:

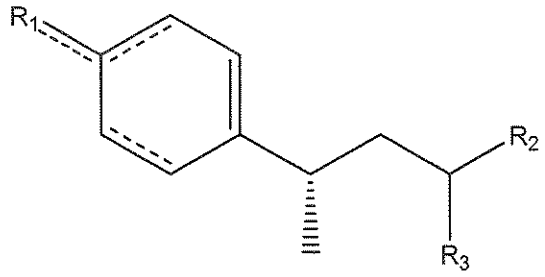


I-0

wherein: ⎓ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In some embodiments, R_1 is selected from CH_3 and CH_2.

[00127] In some embodiments the compound is selected from: 2-methyl-6-p-tolylhept-2-en-4-ol; 2-methyl-6-(4-methylcyclohexa-1,3-dienyl)hept-2-en-4-ol; 2-methyl-6-p-tolylheptane-2,4-diol; N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine; 4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol; and 4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof. In some embodiments said compound is in a pharmaceutical composition comprising a pharmaceutically acceptable excipient.

[00128] Some embodiments are a method for treating cognitive decline and/or Alzheimer's disease in a patient comprising administrating to the patient a therapeutically effective amount of a compound of formula I-1:

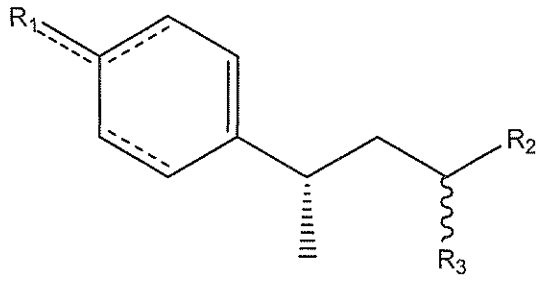


I-1

wherein: ⎓ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In some embodiments, R_1 is selected from CH_3 and CH_2.

[00129] In some embodiments the compound is selected from: (6S)-2-methyl-6-p-tolylhept-2-en-4-ol; (6S)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)hept-2-en-4-ol; (6S)-2-methyl-6-p-tolylheptane-2,4-diol; (6S)-N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine; (6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol; and (6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

[00130] Some embodiments are a method for treating cognitive decline and/or Alzheimer's disease in a patient comprising administrating to the patient a therapeutically effective amount of a compound of formula I-2:



I-2

or pharmaceutically acceptable salt thereof, wherein: ⎓ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In some embodiments, R_1 is selected from CH_3 and CH_2.

[00131] In some embodiments, the compound is selected from: (4S,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine; (4R,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine and pharmaceutically acceptable salts thereof.

[00132] In some embodiments, one or more symptoms of cognitive decline selected from the group consisting of memory loss, confusion, impaired judgment, personality changes, disorientation, and loss of language skills is treated.

[00133] In some embodiments, treating comprises one or more of: (i) restoration of long term potentiation; (ii) inhibition, treatment, and/or abatement of neurodegeneration; (iii) inhibition, treatment, and/or abatement of general amyloidosis; (iv) inhibition, treatment, and/or abatement of one or more of amyloid production, amyloid assembly, amyloid aggregation, amyloid oligomer binding, and amyloid deposition; and (v) inhibition, treatment, and/or abatement of the activity/effect of one or more of Abeta oligomers on a neuron cell.

[00134] In yet other embodiments, treating comprises one or more of inhibition of amyloid production, inhibition of amyloid assembly, inhibition of the activity of one or more of Abeta oligomers on a neuron cell, inhibition of amyloid aggregation, inhibition of amyloid binding, and inhibition of amyloid deposition.

[00135] In other embodiments, treating comprises inhibition of the activity of one or more of Abeta oligomers on a neuron cell, inhibition of amyloid aggregation, inhibition of amyloid binding, and inhibition of amyloid deposition.

[00136] Some embodiments are a method for treating cognitive decline and/or Alzheimer's disease in a patient comprising administrating to the patient a pharmaceutical composition comprising a mixture of a therapeutically effective amount of 4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol and a therapeutically effective amount of 4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof. In some embodiments, said compound is in a pharmaceutical composition comprising a pharmaceutically acceptable excipient.

[00137] Some embodiments are a method for treating cognitive decline and/or Alzheimer's disease in a patient comprising administrating to the patient a pharmaceutical composition comprising a mixture of a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol and a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof. In some embodiments, said compound is in a pharmaceutical composition comprising a pharmaceutically acceptable excipient.

[00138] In yet other embodiments, one or more symptoms of cognitive decline selected from the group consisting of memory loss, confusion, impaired judgment, personality changes, disorientation, and loss of language skills is treated.

[00139] In some embodiments, treating comprises one or more of: (i) restoration of long term potentiation; (ii) inhibition, treatment, and/or abatement of neurodegeneration; (iii) inhibition, treatment, and/or abatement of general amyloidosis; (iv) inhibition, treatment,

and/or abatement of one or more of amyloid production, amyloid assembly, amyloid aggregation, amyloid oligomer binding, and amyloid deposition; and (v) inhibition, treatment, and/or abatement of the activity/effect of one or more of Abeta oligomers on a neuron cell.

[00140] In further embodiments, treating comprises one or more of inhibition of amyloid production, inhibition of amyloid assembly, inhibition of the activity of one or more of Abeta oligomers on a neuron cell, inhibition of amyloid aggregation, inhibition of amyloid binding, and inhibition of amyloid deposition.

[00141] In some embodiments, treating comprises inhibition of the activity of one or more of Abeta oligomers on a neuron cell, inhibition of amyloid aggregation, inhibition of amyloid binding, and inhibition of amyloid deposition.

[00142] In some embodiments, the compounds of the present invention inhibit, treat, or abate (partially inhibit) binding of amyloid (including Abeta oligomers) to neurons (such as neurons in the brain) and are useful for the inhibition, treatment, and abatement of cognitive decline and/or Alzheimer's disease. In some embodiments, the compounds of the present invention inhibit, treat, or abate (partially inhibit) one or more of amyloid aggregation, amyloid oligomer binding, and amyloid deposition. In some embodiments, the compounds of the present invention inhibit, treat, or abate (partially inhibit) amyloid deposition. In some embodiments, the compounds of the present invention inhibit, treat, or abate (partially inhibit) the activity/effect of Abeta oligomers on neurons (such as neurons in the brain) and are useful for the inhibition, treatment, and abatement of cognitive decline and/or Alzheimer's disease. In some embodiments, the compounds of the present invention inhibit, treat, or abate (partially inhibit) the activity/effect of Abeta oligomers on neurons (such as neurons in the brain) via disruption of Abeta oligomers, inhibition of Abeta oligomer binding to neurons, and/or counteraction of signal transduction mechanisms of action initiated by Abeta oligomer binding.

[00143] In some embodiments, the compounds show activity in a beta-secretase assay and are useful for the inhibition, treatment, and abatement of cognitive decline and Alzheimer's disease. In some embodiments the derivative of turmeric oil is a compound in purified and isolated form (for example, with a purity of greater than 80%, 85%, 90%, 95%, 98%, or 99% by weight). The compounds and methods described herein may be used to treat one or more symptoms of cognitive decline and/or Alzheimer's disease such as memory loss, confusion, impaired judgment, personality changes, disorientation, and loss of language skills. Further, the compounds and methods described herein may be useful in inhibition, treatment, and/or abatement of cognitive decline and/or Alzheimer's disease by restoring long term

potentiation, and/or inhibition, treatment, and/or abatement of one or both of neurodegeneration and general amyloidosis, more specifically, by the inhibition, treatment, and/or abatement of one or more of amyloid production, amyloid assembly, amyloid aggregation, amyloid (including amyloid oligomer) binding, and amyloid deposition.

[00144] In some embodiments, compounds of the invention can inhibit, treat, or abate one or more of amyloid production, amyloid assembly, amyloid aggregation, amyloid oligomer binding, and amyloid deposition. In some embodiments, compounds of the invention can restore long term potentiation, inhibit, treat, or abate one or both of neurodegeneration and general amyloidosis.

[00145] In some embodiments, compounds of present invention inhibit, treat, or abate (partially inhibit) one or more of amyloid aggregation, amyloid oligomer binding, and amyloid deposition. In some embodiments, the compounds of present invention inhibit (or partially inhibit) amyloid deposition. In some embodiments, the compounds of present invention inhibit, treat, or abate (partially inhibit) binding of amyloid (including Abeta oligomers) to neurons (such as neurons in the brain). In some embodiments, the compounds of present invention are useful for the inhibition, treatment, and abatement of cognitive decline and/or Alzheimer's disease.

[00146] In some embodiments, compounds of the invention can inhibit activity of beta-secretase. In some embodiments, compounds of the invention can be used in methods of inhibiting activity of beta-secretase by contacting the beta-secretase with any one or more of the compounds or compositions described herein.

[00147] Another aspect of the present invention pertains to methods of treating cognitive decline and/or Alzheimer's disease in an individual (*e.g.*, patient) by administering to the individual a therapeutically effective amount or dose of a compound of the present invention or a pharmaceutical composition thereof.

[00148] Treatment of the diseases/disorders herein includes treating one or more symptoms associated with the diseases/disorders, for example, symptoms of cognitive decline and/or Alzheimer's disease.

[00149] As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" a beta-secretase or a neuron cell (or a neuron cell in the presence of one or more of beta-amyloid oligomers) with a compound of the invention includes the administration of a compound of the present invention to an individual or patient, such as a human, having a beta-secretase or a

neuron cell, as well as, for example, introducing a compound of the invention into a sample containing a cellular or purified preparation containing the a beta-secretase or a neuron cell (or a neuron cell in the presence of one or more of beta-amyloid oligomers).

[00150] As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

[00151] As used herein, the term "treating" or "treatment" refers to one or more of inhibition, treatment, and/or abatement of cognitive decline and/or Alzheimer's disease in a patient and comprises the inhibition, treatment, and/or abatement of one or more symptoms of cognitive decline selected from the group consisting of memory loss, confusion, impaired judgment, personality changes, disorientation, and loss of language skills.

[00152] As used herein, "treating" or "treatment" includes the inhibition, treatment and/or abatement of one or more symptoms associated with the disease. As used herein, the inhibition, treatment and/or abatement of cognitive decline and/or Alzheimer's disease further includes one or more of: (i) restoration of long term potentiation; and/or (ii) inhibition, treatment, and/or abatement of neurodegeneration; and/or (iii) inhibition, treatment, and/or abatement of general amyloidosis; and/or (iv) inhibition, treatment, and/or abatement of one or more of amyloid production, amyloid assembly, amyloid aggregation, amyloid oligomer binding, and amyloid deposition; and/or (v) inhibition, treatment, and/or abatement of the activity/effect of one or more of Abeta oligomers on a neuron cell.

[00153] The term "treating" or "treatment" also comprises inhibition, treatment, and/or abatement of one or more of amyloid production, amyloid assembly, the activity/effect of one or more of Abeta oligomers on a neuron cell, amyloid aggregation, amyloid binding, and amyloid deposition.

[00154] The term "treating" or "treatment" also comprises disease comprises inhibition, treatment, and/or abatement of one or more of the activity/effect of one or more of Abeta oligomers on a neuron cell, amyloid aggregation, amyloid binding, and amyloid deposition.

[00155] The term "pharmaceutical composition" shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for

determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

[00156] The term "Therapeutically effective amount" as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology). As used herein, the term "therapeutically effective amount" may also refer to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician.

[00157] In certain embodiments, one or more additional pharmaceutical agents for treatment of cognitive decline and/or Alzheimer's disease can be used in combination with the compounds of the present invention for treatment of cognitive decline and/or Alzheimer's disease. The one or more additional pharmaceutical agents can be administered to a patient simultaneously or sequentially with the compounds of the present invention.

[00158] In some embodiments, the one or more additional pharmaceutical agents include but are not limited to donepezil, galantamine, memantine, rivastigmine and tacrine

[00159] Some embodiments are a pharmaceutical composition comprising a mixture of a therapeutically effective amount of 4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol and a therapeutically effective amount of 4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

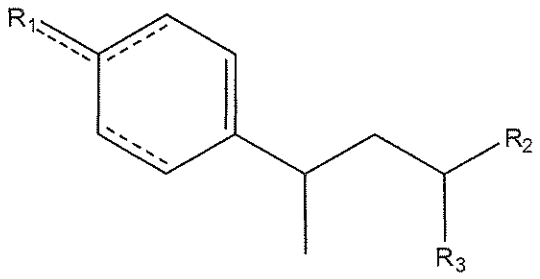
[00160] Some embodiments are a pharmaceutical composition comprising a mixture of a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol

and a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

[00161] In certain embodiments, the compounds of the invention can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (*e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, *e.g.*, intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Some embodiments may comprise a sustained release pharmaceutical composition suitable for enteral administration, including, but not limited to, oral, rectal or intranasal administration. In an embodiment, the pharmaceutical composition is one that is suitable for oral administration, such as, a tablet, a capsule, and a liquid. In other embodiments, the sustained release pharmaceutical composition may be a bilayer tablet or modified capsule. The sustained release pharmaceutical composition may also be suitable for parenteral administration, including, but not limited to, intravascular administration, subcutaneous injection, and intramuscular administration. In some embodiments, a pharmaceutical composition is suitable for oral administration, and may be formulated into a tablet, a capsule, or a liquid, preferably a tablet or capsule. In one embodiment, the pharmaceutical composition may be a multi-layer tablet, such as a bilayer tablet. In another embodiment, the pharmaceutical composition may be a multicomponent capsule, such as a divided capsule or a capsule contained within another capsule. Pharmaceutical compositions may also comprise immediate release formulations, sustained release formulations or a combination thereof. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful.

[00162] Embodiments of this invention also include pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of the invention above

in combination with one or more pharmaceutically acceptable carriers (excipients). Some embodiments are a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I-0:

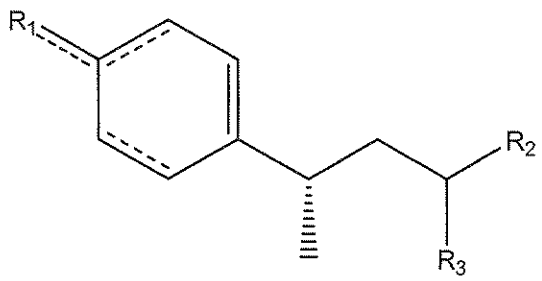


I-0

wherein: ⎓ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In some embodiments, R_1 is selected from CH_3 and CH_2.

[00163] In some embodiments a pharmaceutical composition selected from a therapeutically effective amount of: 2-methyl-6-p-tolylhept-2-en-4-ol; 2-methyl-6-(4-methylcyclohexa-1,3-dienyl)hept-2-en-4-ol; 2-methyl-6-p-tolylheptane-2,4-diol; N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine; 4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol; and 4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

[00164] Embodiments of this invention also include pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of the invention above in combination with one or more pharmaceutically acceptable carriers (excipients). Some embodiments are a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I-1:

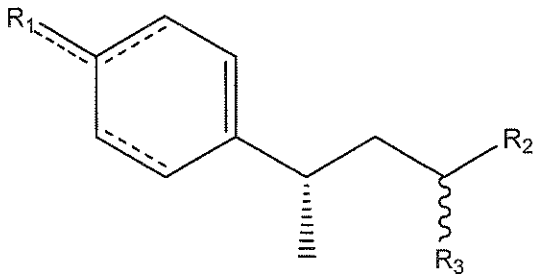


I-1

wherein: ⎓ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In some embodiments, R_1 is selected from CH_3 and CH_2.

[00165] In some embodiments compounds are selected from: (6S)-2-methyl-6-p-tolylhept-2-en-4-ol; (6S)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)hept-2-en-4-ol; (6S)-2-methyl-6-p-tolylheptane-2,4-diol; (6S)-N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine; (6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol;(6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol and pharmaceutically acceptable salts thereof.

[00166] Embodiments of this invention also include pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of the invention above in combination with one or more pharmaceutically acceptable carriers (excipients). Some embodiments are a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I-2:



I-2

wherein: ⎓ is selected from a single bond and a double bond; R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3; R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and R_3 is selected from OH and $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In some embodiments, R_1 is selected from CH_3 and CH_2.

[00167] In some embodiments, pharmaceutical compositions are selected from: (4S,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine; (4R,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine and pharmaceutically acceptable salts thereof.

[00168] Some embodiments are a pharmaceutical composition comprising a mixture of a therapeutically effective amount of 4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol and a therapeutically effective amount of 4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-

dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

[00169] Some embodiments are a pharmaceutical composition comprising a mixture of a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol and a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

[00170] In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

[00171] In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, *e.g.* about 40 mesh.

[00172] The compounds of the invention may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nano particulate) preparations of the compounds of the invention can be prepared by processes known in the art, for example see International Patent Application No. WO 2002/000196.

[00173] Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick,

sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

[00174] The compositions can be formulated in a unit dosage form, each dosage containing from about 0.1 mg to about 1000 mg (1 g), more usually about 100 to about 500 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

[00175] The active compound can be effective over a wide dosage range and can be generally administered in a pharmaceutically effective amount. For example, the dosage of the active compounds of the invention as employed for the treatment of a patient in need thereof (such as an adult human) may range from 0.1 to 3000 mg per day, depending on the route and frequency of administration. Such a dosage corresponds to 0.001 to 50 mg/kg per day. In some embodiments, the dosage of the active compounds of the invention as employed for the treatment of a patient in need thereof (such as an adult human) may range from 1 to 2000 mg per day, from 1 to 1000 mg per day, from 10 to 1000 mg per day, or from 10 to 500 mg per day. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[00176] For preparing solid compositions such as tablets, the principal active ingredient can be mixed with a pharmaceutical excipient to form a solid pre-formulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these pre-formulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid pre-formulation is then subdivided into unit dosage forms of the type described above containing from, for example, about 0.1 to about 1000 mg of the active ingredient of the present invention.

[00177] The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the

latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[00178] The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

[00179] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

[00180] The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

[00181] The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be

between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

[00182] The therapeutic dosage of the compounds of the present invention can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 μg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[00183] The compositions of the invention can further include one or more additional pharmaceutical agents such as a chemotherapeutic, steroid, anti-inflammatory compound, or immunosuppressant, examples of which are listed herein.

[00184] Another aspect of the present invention relates to labeled compounds of the invention (radio-labeled, fluorescent-labeled, etc.) that would be useful not only in radio-imaging but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating the enzyme in tissue samples, including human, and for identifying ligands by inhibition binding of a labeled compound. Accordingly, the present invention includes enzyme assays that contain such labeled compounds.

[00185] Embodiments of the present invention further include isotopically-labeled compounds of the invention. An "isotopically" or "radio-labeled" compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^{2}H (also written as D for

deuterium), ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I and ^{131}I. The radionuclide that is incorporated in the radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* receptor labeling and competition assays, compounds that incorporate ^{3}H, ^{14}C, ^{82}Br, ^{125}I , ^{131}I, ^{35}S or will generally be most useful. For radio-imaging applications ^{11}C, ^{18}F, ^{125}I, ^{123}I, ^{124}I, ^{131}I, ^{75}Br, ^{76}Br or ^{77}Br will generally be most useful.

[00186] It is understood that a "radio-labeled compound" is a compound that has incorporated at least one radionuclide. In some embodiments the radionuclide is selected from ^{3}H, ^{14}C, ^{125}I , ^{35}S and ^{82}Br.

[00187] In some embodiments, the labeled compounds of the present invention contain a fluorescent label.

[00188] Synthetic methods for incorporating radio-isotopes and fluorescent labels into organic compounds are well known in the art.

[00189] A labeled compound of the invention (radio-labeled, fluorescent-labeled, etc.) can be used in a screening assay to identify/evaluate compounds. For example, a newly synthesized or identified compound (i.e., test compound) which is labeled can be evaluated for its ability to bind a beta-secretase or a neuron cell (or a neuron cell in the presence of one or more of beta-amyloid oligomers) by monitoring its concentration variation when contacting with the beta-secretase or the neuron cell (or the neuron cell in the presence of one or more of beta-amyloid oligomers), through tracking the labeling. For another example, a test compound (labeled) can be evaluated for its ability to reduce binding of another compound which is known to bind to beta-secretase or neuron cell (i.e., standard compound). Accordingly, the ability of a test compound to compete with the standard compound for binding to the beta-secretase or the neuron cell directly correlates to its binding affinity. Conversely, in some other screening assays, the standard compound is labeled and test compounds are unlabeled. Accordingly, the concentration of the labeled standard compound is monitored in order to evaluate the competition between the standard compound and the test compound, and the relative binding affinity of the test compound is thus ascertained.

[00190] Embodiments of the present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of cognitive decline and/or Alzheimer's disease which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components,

such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

[00191] The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results. Certain compounds of the Examples were found to be inhibit, treat, or abate one or more of amyloid production, amyloid assembly, the activity/effect of Abeta oligomers on neurons (such as neurons in the brain), amyloid aggregation, amyloid oligomer binding, and amyloid deposition according to one or more of the assays provided herein. In some further embodiments, certain compounds of the Examples were found to be inhibit, treat, or abate one or more of the activity/effect of Abeta oligomers on neurons (such as neurons in the brain), amyloid aggregation, amyloid (including amyloid oligomer) binding, and amyloid deposition according to one or more of the assays provided herein.

[00192] In some embodiments, the compound of invention has an IC_{50} value of less than 100μM, 50 μM, 20 μM, 15 μM, 10 μM, 5 μM, 1 μM, 500 nM, 100 nM, 50 nM, or 10 nM with respect to inhibition of one or more of the activity/effect of Abeta oligomers on neurons (such as neurons in the brain), amyloid aggregation, amyloid (including amyloid oligomer) binding, and amyloid deposition. In some embodiments, the compound of invention has an IC_{50} value of less than 100μM, 50 μM, 20 μM, 15 μM, 10 μM, 5 μM, 1 μM, 500 nM, 100 nM, 50 nM, or 10 nM with respect to inhibition the activity/effect of Abeta oligomers on neurons (such as neurons in the brain).

[00193] In some embodiments, percentage inhibition of the compound of invention to one or more of the activity/effect of Abeta oligomers on neurons (such as neurons in the brain), amyloid aggregation, amyloid (including amyloid oligomer) binding, and amyloid deposition was measured at a concentration of from 10 nM to 10 μM. In some embodiments, the percentage inhibition measured is about 1% to about 20%, about 20% to about 50%, about 1% to about 50%, or about 1% to about 80%.

[00194] The invention may be appreciated in certain aspects with reference to the following examples, offered by way of illustration, not by way of limitation. Materials,

reagents and the like to which reference is made in the following examples are obtainable from commercial sources, unless otherwise noted.

EXAMPLES

Example 1 - Conditioned extraction of turmeric oil (reductive amination): reaction of turmeric oil with isobutylamine followed by reduction with sodium borohydride in methanol and by fractioning using column chromatography

[00195] In the present example, the light oil extract from turmeric was obtained by supercritical CO_2 extraction. Turmeric oil (10 g) was dissolved in methanol (250 mL) and isobutylamine (4.0 mL) was added. The mixture was maintained at room temperature for 16 hours. At this time the reaction mixture was cooled to 0°C on an ice bath. A solution of sodium borohydride (5 g) in methanol (50 mL) was added portion-wise over 30 minutes with vigorous stirring. After the addition was complete the resultant mixture was maintained at reflux for 16 hours. At this time the reaction mixture was cooled to room temperature and poured into saturated aqueous sodium bicarbonate solution (300 mL). The resulting mixture was concentrated by rotary evaporation and the aqueous residue was partitioned between water and chloroform. The chloroform layer was dried over anhydrous sodium sulfate and then filtered and concentrated. The crude product was then fractionated using silica gel column chromatography employing a gradient from 100% chloroform to chloroform:methanol (4:1). Twenty combined fractions from relatively non-polar to polar were collected and concentrated. Each fraction was submitted for biological testing. The active product-containing fractions were the relatively polar fractions.

[00196] An active product-containing fraction (Fraction 1A) was subject to further separation by column chromatography and two major components were isolated: Component 1A-1 and Component 1A-2.

[00197] The weight ratio of Turmeric oil to isobutylamine used in the reductive amination is about 3:1 (from 2 to 4: 1).The purity of 1A was measured by HPLC. Only two major peaks (two components) were present. The HPLC conditions used are as follows.

[00198] HPLC conditions were as follows: Mobile Phase A: 13.3 mM ammonium formate/6.7 mM formic acid in water; Mobile Phase B: 6 mM ammonium formate/3 mM formic acid in water/CH_3CN (1/9, v/v);Column 1: Synergi Fusion-RP 100A Mercury, 2 x 20 mm, 2.5 micron (Phenomenex Part No 00M-4423-B0_CE); Column 2: Synergi Max-RP 80, 2 x 50 mm, 4 micron zPhenomenex Part No 00B-4337-B0).

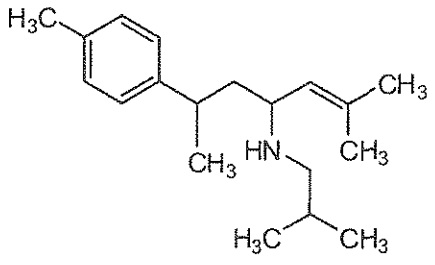
Table 1 Gradient Program: (the same for both column I and II)

Time, minute	% Phase B	Flow rate, ml/min
0	20	0.5
1	20	0.5
2.5	100	0.5
3.4	100	0.5
3.5	20	0.5
4.5	20	0.5

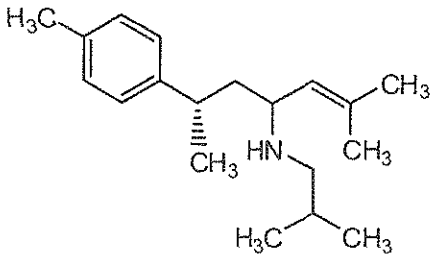
Component Number	RT on Column I (minute)	RT on Column I (minute)
1A-1	2.15	2.46
1A-2	2.24	2.55

[00199] *Component 1A-1*: ^{1}H NMR (500 MHz, CDCl3) δ 7.11, 7.09, 5.23, 3.72, 2.94, 2.51, 2.34, 2.31, 1.92, 1.72, 1.71, 1.58, 1.29, 1.27, 0.92. ^{13}C NMR (125 MHz, CDCl3) 144.50, 135.37, 135.03, 129.03, 126.89, 126.70, 66.97, 49.25, 46.39, 35.05, 32.46, 25.83, 20.96, 20.67, and 18.36.- MS ($M+H^{+}$) *m/z* 274.3.

[00200] The structure of Fraction 1A, Component 1A-1 was determined to be as follows.

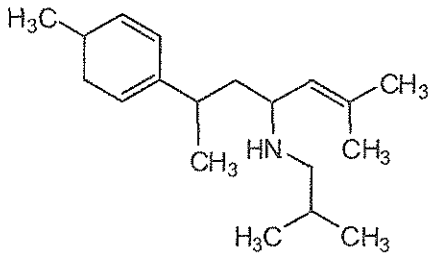


or

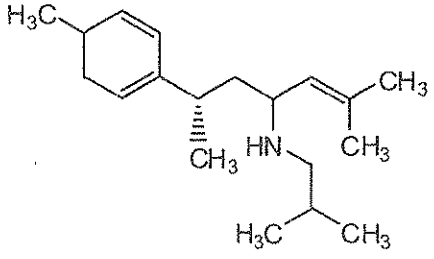


[00201] *Component 1A-2*: **^{1}H NMR (500 MHz, CDCl3)** δ 5.77, 5.65, 5.45, 5.23, 3.96, 2.94, 2.93, 2.51, 2.31, 2.30, 2.05, 1.92, 1.72, 1.71, 1.58, 1.29, 1.27, 0.92. **^{13}C NMR (125 MHz, CDCl3)** δ 144.50, 135.37, 130.96, 127.86, 126.70 120.80, 66.72, 49.25, 46.39, 35.05, 32.46, 25.83, 21.79, 21.79, 20.67, and 18.36. **MS** ($M+H^+$) *m/z* 276.3.

[00202] The structure of Fraction 1A, Component 1A-2 was determined to be as follows.



or



[00203] The chemical shift measure by ^{1}H NMR may vary, for example, up to 0.3 ppm. The chemical shift measure by ^{13}H NMR may vary, for example, up to 0.6 ppm. The analytical Mass Spectrum may have an experimental error of +/- 0.4.

Example 2 - Conditioned extraction of turmeric oil (reduction): reduction of turmeric oil with sodium borohydride in methanol and by fractioning using column chromatography

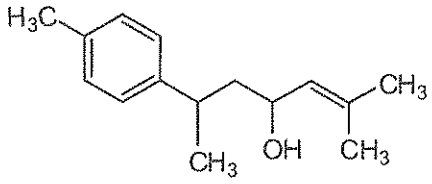
[00204] In the present example, the light oil extract from turmeric was obtained by supercritical CO_2 extraction. Turmeric oil (10 g) was dissolved in methanol (250 mL). The reaction mixture was cooled to 0°C on an ice bath. A solution of sodium borohydride (5 g) in methanol (50 mL) was added portion-wise over 30 minutes with vigorous stirring. When the addition was complete the mixture was maintained at reflux for 16 hr. At this time the reaction mixture was cooled to room temperature and poured into saturated aqueous sodium bicarbonate (300 mL). The resulting mixture was concentrated by rotary evaporation and the aqueous residue was partitioned between water and chloroform. The chloroform layer was dried over anhydrous sodium sulfate and then filtered and concentrated. The product was then fractionated using silica gel column chromatography employing a gradient from 100% chloroform to chloroform: methanol (4:1). Twenty combined fractions from relatively non-polar to polar were collected and concentrated. Each fraction was submitted for biological testing. The active product-containing fractions were the relatively polar fractions.

[00205] The molar ratio of sodium borohydride to Turmeric oil (the ketones and aldehydes therein) is greater than 1:1, 2:1, 3:1, 4:1, 5:1, or 6:1 to ensure that reduction of ketones and aldehydes to alcohols. In some embodiments, the weight ratio of sodium borohydride to Turmeric oil is about 0.5:1 (from 0.3:1 to about 0.8:1).

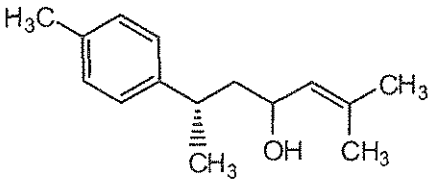
[00206] An active product-containing fraction (Fraction 2A) was subject to further separation by column chromatography and two major components were isolated: Component 2A-1 and Component 2A-2.

[00207] *Component 2A-1*: ^{1}H NMR (500 MHz, CDCl3) δ 7.11, 7.09, 5.17, 4.45, 2.32, 2.76 1.75, 1.58, 1.52, and 1.26. ^{13}C NMR (125 MHz, CDCl3) δ 144.3, 135.37, 135.03, 129.11, 128.32, 126.90, 67.10, 42.05, 39.64, 25.81, 23.00, 21.01, and 18.12. MS ($M+H^{+}$) *m/z* 219.2.

[00208] The structure of Fraction 2A, Component 2A-1 is determined to be as follows.

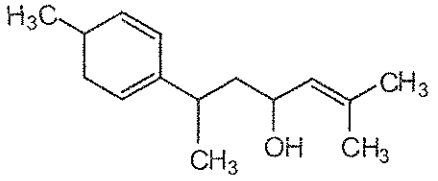


or

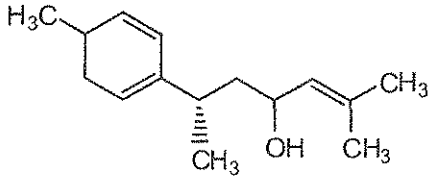


[00209] *Component 2A-2*: ^{1}H NMR (500 MHz, CDCl3) δ 6.18, 5.70, 5.56, 5.17, 4.24, 2.32, 2.80, 2.29, 2.15, 1.95, 1.68, 1.75, 1.58, 1.42, 1.27. ^{13}C NMR δ 144.10, 135.00, 134.10, 129.58, 128.32, 125.3, 66.90, 46.18, 41.17, 39.55, 37.14, 25.81, 24.50, 23.00, and 18.12. MS ($M+H^{+}$) *m/z* 221.1.

[00210] The structure of Fraction 2A, Component 2A-2 was determined to be as follows.



or



[00211] The chemical shift measure by ^{1}H NMR may vary, for example, up to 0.3 ppm. The chemical shift measure by ^{13}H NMR may vary, for example, up to 0.6 ppm. The analytical Mass Spectrum may have an experimental error of +/- 0.4.The purity of Fraction 2A was measure by HPLC. Only two major peaks (two components) were present.

Example 3 - Exocytosis assay/MTT assay

[00212] Primary neurons from E18 Sprague-Dawley rat embryos are plated at optimized concentrations in 384 well plates in NB media (Invitrogen). Neurons are maintained in cultures for 3 weeks, with twice weekly feeding of NB media with N_2 supplement (Invitrogen). A test compound is added to cells, followed by addition of Vehicle or Abeta oligomer preparations (1.5 μM), and incubated for 1 to 24 hr. at 37 °C in 5% CO_2. MTT

reagent (3-(4, 5-dimethylthizaol-2yl)-2,5diphenyl tetrazolium bromide) (Roche Molecular Biochemicals) is reconstituted in phosphate buffered saline to 5mg/mL. 10 μL of MTT labeling reagent is added to each well and incubated at 37 °C for 1h, then imaged.

[00213] Each assay plate is formatted so that compounds are tested with and without Abeta on each plate. This design eliminates toxic or metabolically active compounds early on in the screening cascade (at the level of the primary screen).

[00214] Similar procedures for exocytosis assays/MTT assays can be found in the literature. *See e.g.*, Liu Y, et. al., Detecting bioactive amyloid beta peptide species in Alzheimer's disease. J Neurochem. 2004 Nov; 91(3):648-56; Liu Y, and Schubert D. "Cytotoxic amyloid peptides inhibit cellular 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) reduction by enhancing MTT formazan exocytosis." J Neurochem. 1997 Dec; 69(6):2285-93; and Liu Y, and Schubert D. "Treating Alzheimer's disease by inactivating bioactive amyloid beta peptide" Curr. Alzheimer Res. 2006 Apr; 3(2):129-35.Abeta 1-42 oligomers made according to published methods [*See e.g.* Dahlgren et al., "Oligomeric and fibrillar species of amyloid-beta peptides differentially affect neuronal viability" J Biol Chem. 2002 Aug 30; 277(35):32046-53. Epub 2002 Jun 10. LeVine H 3rd. "Alzheimer's beta-peptide oligomer formation at physiologic concentrations" Anal Biochem. 2004 Dec 1; 335(1):81-90; Shrestha et.al,"Amyloid beta peptide adversely affects spine number and motility in hippocampal neurons" Mol Cell Neurosci. 2006 Nov; 33(3):274-82. Epub 2006 Sep 8; Puzzo et al., "Amyloid-beta peptide inhibits activation of the nitric oxide/cGMP/cAMP-responsive element-binding protein pathway during hippocampal synaptic plasticity" J Neurosci. 2005 Jul 20; 25(29):6887-97; Barghorn et al., "Globular amyloid beta-peptide oligomer - a homogenous and stable neuropathological protein in Alzheimer's disease" J Neurochem. 2005 Nov; 95(3):834-47. Epub 2005 Aug 31; Johansson et al., Physiochemical characterization of the Alzheimer's disease-related peptides A beta 1-42 Arctic and A beta 1-42wt. FEBS J. 2006 Jun;2 73(12):2618-30] as well as brain-derived Abeta oligomers (*See e.g.* Walsh et al., Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature (2002). 416, 535-539; Lesne et al., A specific amyloid-beta protein assembly in the brain impairs memory. Nature. 2006 Mar 16; 440(7082):352-7; Shankar et al, Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. Nat Med. 2008 Aug; 14(8):837-42. Epub 2008 Jun 22) constitute the positive controls. Negative controls include vehicle-treated neurons as well as neurons treated with 28 μM concentrations of memantine. Memantine produces 50%

inhibition of oligomer effects at this dose. These controls, on each plate, serve as normalization tools to calibrate assay performance on a plate-by-plate basis.

[00215] Primary neuronal cultures are prepared as follows: Optimal cell density of primary neuronal cultures is determined based on cellular response to Abeta oligomers using the exocytosis assay as a readout, and immunohistochemical analysis of the relative proportion of glia to neurons in the cultures. Cultures are monitored on a weekly basis with immunohistochemistry and image processing-based quantification to monitor the percentage of the cultures that are neurons vs. glia (Glial cells). Cultures containing more than 20% glia (positive for GFAP) vs. neurons (staining positively with antibodies directed against MAP2) at the screening age of 21 days in vitro (21 DIV) are rejected.

[00216] Abeta oligomer preparations are prepared as follows: Human amyloid peptide 1-42 is obtained from California Peptide, with lot-choice contingent upon quality control analysis. Quality controls of oligomer preparations consist of Westerns to determine oligomer size ranges and relative concentrations, and the MTT assay to confirm exocytosis acceleration without toxicity. Toxicity is monitored in each image-based assay via quantification of nuclear morphology visualized with the DNA binding dye DAPI (Invitrogen). Nuclei that are fragmented are considered to be in late stage apoptosis (Majno and Joris '95). Peptide lots producing unusual peptide size ranges or significant toxicity at a standard 1.5 uM concentration on neurons are rejected. Plate-based controls –The assay optimization will be complete when reformatted plates achieve a minimum of statistically significant two-fold separation between vehicle and Abeta oligomer-treated neurons ($p<0.01$, Student's t-test, unequal variance) on a routine basis, with no more than 10% CV between plates, equivalent to its current performance.

[00217] Data handling and analysis are accomplished by Cellomics VTI image analysis software and STORE automated database software. Because of the low dynamic range and neuronal well-to-well variability after three weeks in culture, statistical comparisons are made via pairwise Tukey-Kramer analysis to determine the significance of the separation between compound + Abeta oligomers from Abeta alone, and between compound alone from vehicle. These statistics are more akin to what is seen in animal behavioral testing than the z' statistic that has been used for the past two decades in high throughput screening. The ability of mature primary neurons to more closely approximate the electrophysiologically mediated signal transduction network of the adult brain justifies this screening strategy. Power analysis will be set for a number of replicate screening wells that will minimize false negatives (e.g. N=4) and shift the burden of distinguishing false positives from actual hits to dose-response

confirmation screening. Rank ordering of compounds is done on the basis of secondary assay mechanism of action and physicochemical properties of the compound structures. Certain test compounds significantly reverse the effects of Abeta oligomers but not affect neuronal metabolism.

[00218] Fraction 1A was dosed in the MTT assay and was shown to block the Abeta oligomer-induced acceleration of exocytosis with an EC_{50} of 10.5 μM, indicating that one or both of Component 1A-1 and Component 1A-2 block/abate the activity/effect of Abeta oligomer on neuron cells.

[00219] Fraction 2A was dosed in the MTT assay and was shown to block the Abeta oligomer-induced acceleration of exocytosis with an EC_{50} of 25.4 μM, indicating that one or both of Component 2A-1 and Component 2A-2 block/abate the activity/effect of Abeta oligomer on neuron cells.

Example 4 - Binding assay

[00220] Each test compound was added to a plate followed by an addition of one or more of Abeta 1-42 Oligomers. The plates were fixed with 3.7 % paraformaldehyde in phosphate buffered saline (PBS) for 15 min. The plate was then washed 3x with PBS for 5 min each. The plates were blocked at room temperature for 1 hour in 5 % goat serum and 0.5% Triton X-100 (CAS number: 9002-93-1) in PBS. Primary antibodies (anti-MAP 2 polyclonal, Millipore #AB5622 and anti-Beta Amyloid 6E10 monoclonal, Convance #SIG-39300) were diluted 1:1000 in 5 % goat serum with PBS. Primary antibodies were incubated either overnight at 4 °C or 1 hour at RT. The plate was then washed 3x with PBS for 5 min each. Secondary antibodies (Alex Flor 488 polyclonal, Invitrogen # A11008 and Alexa Flor 647 monoclonal, Invitrogen #A21235) were diluted 1:1000 in 5 % goat serum with PBS. Secondary antibodies were incubated at RT for 1 hr. The plates were washed once with PBS. DAPI (4', 6-diamidino-2-phenylindole, Invitrogen) was then applied at 0.03 μg/μL and incubated at RT for 5 min, then washed with PBS. Image process was carried out for analysis.

[00221] Similar procedures for binding assays can be found in the literature. *See e.g.*, Look GC, et. al. Discovery of ADDL--targeting small molecule drugs for Alzheimer's disease. Curr Alzheimer Res. 2007 Dec;4(5):562-7. Review.

[00222] The EC_{50} of Fraction 2A was determined to be 14.5 μM according the binding assay.

[00223] Abeta oligomer preparations Human amyloid peptide 1-42 is obtained from California Peptide, with lot-choice contingent upon quality control analysis. Abeta 1-42 oligomers made according to published methods [*See e.g.* Dahlgren et al., "Oligomeric and fibrillar species of amyloid-beta peptides differentially affect neuronal viability" J Biol Chem. 2002 Aug 30;277(35):32046-53. Epub 2002 Jun 10.; LeVine H 3rd. "Alzheimer's beta-peptide oligomer formation at physiologic concentrations" Anal Biochem. 2004 Dec 1;335(1):81-90; Shrestha et.al, "Amyloid beta peptide adversely affects spine number and motility in hippocampal neurons" Mol Cell Neurosci. 2006 Nov;33(3):274-82. Epub 2006 Sep 8; Puzzo et al., "Amyloid-beta peptide inhibits activation of the nitric oxide/cGMP/cAMP-responsive element-binding protein pathway during hippocampal synaptic plasticity" J Neurosci. 2005 Jul 20;25(29):6887-97; Barghorn et al., "Globular amyloid beta-peptide oligomer - a homogenous and stable neuropathological protein in Alzheimer's disease" J Neurochem. 2005 Nov;95(3):834-47. Epub 2005 Aug 31; Johansson et al., Physiochemical characterization of the Alzheimer's disease-related peptides A beta 1-42 Arctic and A beta 1-42wt. FEBS J. 2006 Jun;2 73(12):2618-30] as well as brain-derived Abeta oligomers (*See e.g.* Walsh et al., Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature (2002). 416, 535-539; Lesne et al., A specific amyloid-beta protein assembly in the brain impairs memory. Nature. 2006 Mar 16;440(7082):352-7; Shankar et al, Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. Nat Med. 2008 Aug;14(8):837-42. Epub 2008 Jun 22) will serve as positive controls. Quality controls of oligomer preparations consist of Westerns to determine oligomer size ranges and relative concentrations, and the MTT assay to confirm exocytosis acceleration without toxicity. Toxicity is monitored in each image-based assay via quantification of nuclear morphology visualized with the DNA binding dye DAPI (Invitrogen). Nuclei that are fragmented are considered to be in late stage apoptosis (Majno and Joris Apoptosis, oncosis, and necrosis. An overview of cell death. Am J Pathol 1995;146:3–16). Peptide lots producing unusual peptide size ranges or significant toxicity at standard concentrations on neurons are rejected. Images were captured and analyzed with the Cellomics VTI automated microscope platform, using the Neuronal Profiling algorithm. For statistical analysis, a Tukey-Kramer pair-wise comparison with unequal variance was used.

[00224] Western blotting was carried as follows: Samples containing Abeta 1-42 were diluted (1:5) in non-reducing lane marker sample buffer (Pierce #1859594). A 30 microliter (μL) sample was loaded onto an eighteen well precast 4-15% Tris-HCl gel (BIORAD #345-0028). Electrophoresis was performed in a BIO-RAD Criterian precast gel system using Tris-

Glycine buffer at 125 volt (V) for 90 minutes. The gels were blotted onto 0.2 μM nitrocellulose membranes in Tris-Glycine/10% methanol buffer at 30V for 120 minutes. The membranes were boiled for 5 minutes in a PBS solution and blocked over night with TBS/5% milk solution at 4 °C. The membrane was probed with 6E10-HRP (Covance #SIG-39345) diluted to 10 μg/mL in TBS/1% milk solution for one hour at room temperature. Membrane was washed three times for 40 minutes each with a solution of TBS/0.05% tween-20 and developed with ECL reagent (BIO-RAD #162-0112) for 5 minutes. Image acquisition was performed on an Alpha Innotech FluorChem Q quantitative imaging system and analyzed with AlphaView Q software.

[00225] Fraction 1A was shown to partially block binding of the Abeta oligomer ligand to neurons by 33% according to the binding assay (using imaging processing algorithm).

[00226] Fraction 2A was shown to partially block binding of the Abeta oligomer ligand to neurons by 35% according to the binding assay (using imaging processing algorithm).PK studies are performed at CEREP Inc. of Redmond WA, according to their standard protocols: The plasma samples were processed using acetonitrile precipitation and analyzed by HPLC-MS or HPLC-MS/MS. Peak areas were recorded, and the concentrations of the test compound in the unknown plasma samples were determined using the respective calibration curve. The reportable linear range of the assay was determined, along with the lower limit of quantitation (LLQ).Active fractions were analyzed by 1H NMR spectroscopy (Varian 500 MHz NMR spectrometer) and purified compounds were characterized using a combination 1D and 2D 1H NMR experiments and 13C NMR experiments. Structure proof was obtained using these NMR techniques in combination with low resolution mass spectrometry to determine molecular weight and high resolution mass spectrometry (Thermo Finnigan LCQ Ion trap) to determine composition-of-matter.

Example 5 - Pharmacokinetic studies

[00227] Pharmacokinetic studies were performed according to the following protocols: The plasma samples were processed using acetonitrile precipitation and analyzed by HPLC-MS or HPLC-MS/MS. Peak areas were recorded, and the concentrations of the test compound in the unknown plasma samples were determined using the respective calibration curve. The reportable linear range of the assay was determined, along with the lower limit of quantitation (LLQ). For example, Component 1A-1 was determined to have a half life of 50 minutes in the plasma of rats when injected intravenously at 1 mg/Kg; Component 1A-2 was determined to have a half life of 70 minutes in the plasma of rats when injected intravenously at 1 mg/Kg;

and Component 2A-1 was determined to have a half life of 180 minutes in the plasma of rats when injected intravenously at 1 mg/Kg. However, the experimental condition used did not give a detectable half lift for Component 2A-2.

Example 6 - Abeta oligomer formation inhibition assay

[00228] Abeta 42 oligomer formation can be readily assayed in a multiwell format and used to determine the ability of a test compound to block the formation of soluble high-molecular weight (>20kDa) oligomers. *See e.g.* assays described in Harry LeVine III, "Biotin-avidin interaction-based screening assay for Alzheimer's β-peptide oligomer inhibitors", Analytical Biochemistry 356 (2006) 265-272.

[00229] 100 µL of different concentrations of a test compound in 50 mM NaP_i, 150 mM NaCl, and 0.02% (w/v) NaN_3 pH 7.5 was added to wells of a 96-well plate containing 2 µL of freshly HFIP (1,1,1,3,3,3-Hexafluoro-2-propanol)-depolymerized 2.5 µg/ml bio-Abeta42 in DMSO, giving a total concentration of 50 ng/ml (11 nM) peptide and 2% (v/v) DMSO. After 30 min at room temperature, 50-µL aliquots were transferred to an NA/SA–HRP (NeutrAvidin/ secondary antibody and streptavidin–Horseradish peroxidase) single-site assay plate. 100 µL of tetramethylbenzidine/H_2O_2 substrate solution is added, and the plate is incubated at room temperature for 2–30min, depending on the concentration of bio-Abeta 42 peptide in the assay. The OD_{450nm} is determined on a Biotech Synergy HT plate reader after stopping the reaction with 100 µL of 1% (v/v) H_2SO_4. The ability of a test compound to block the formation of soluble high-molecular weight (>20kDa) oligomers is determined by the concentration of the bio-Abeta 42 peptide formed. *See id.*

[00230] According to the assay, Fraction 1A does not inhibit the formation of Abeta oligomers. Therefore Fraction 1A likely inhibits Abeta oligomer binding to neurons by acting directly on neuronal receptors to prevent oligomer binding or by causing Abeta oligomers to disassemble.

Example 7 - A primary neuron-based functional screening assay to detect small molecule Abeta oligomer blockers

[00231] Primary rat neurons grown for at least 3 weeks *in vitro* were chosen as the basis for this screening assay. These neurons express the full complement of synaptic proteins characteristic of neurons in the mature brain, and exhibit a complex network of activity-dependent electrical signaling. Neurons and glia in such cultures have molecular signaling networks exhibiting excellent registration with intact brain circuitry, and for this reason have been used for over two decades as a model system for learning and memory (*See e.g.* Kaech S,

Banker G. Culturing hippocampal neurons. Nat Protoc. 2006;1(5):2406-15. Epub 2007 Jan 11; See also Craig AM, Graf ER, Linhoff MW. How to build a central synapse: clues from cell culture. Trends Neurosci. 2006 Jan;29(1):8-20. Epub 2005 Dec 7. Review). More complex systems such as acute or organotypic brain slices are very useful but not amenable to high throughput screening. Immortalized or transformed neuronal cell lines are amenable to high throughput screening, but do not replicate the electrophysiological state-dependent signaling of primary neuronal cultures and are unlikely to adequately model the subtle alterations in this signaling that are caused by oligomers during the earliest manifestations of the disease state (*See e.g.* Görtz P, Fleischer W, Rosenbaum C, Otto F, Siebler M. Neuronal network properties of human teratocarcinoma cell line-derived neurons. Brain Res. 2004 Aug 20;1018(1):18-25). For this reason, primary neuronal cultures were chosen because of their ability to be used in high throughput screens and fidelity to what occurs *in vivo*.

[00232] Reduced formazan was first visible in intracellular vesicles (Figure 1A). Example of neurons filled with labeled vesicles following endocytosis of dye and reduction to an insoluble purple product. (Scale bar = 20 microns in Figure 1A). Eventual formazan exocytosis was accelerated via Abeta oligomers in mature hippocampal neurons *in vitro* (Figure 1B). Example photomicrograph of neurons covered with insoluble purple dye that has been extruded via exocytosis. The dye precipitated in the aqueous environment of the culture and formed needle-shaped crystals on the surface of the neuron. (Figure 1B). Endocytosis rate was altered in the presence of Abeta oligomers. (Figure 1C) Exocytosis rate was altered in the presence of Abeta oligomers (Figure 1D).

[00233] Since synaptic and memory deficits, and not widespread cell death, predominate at the earliest stages of Alzheimer's disease, assays that measure these changes can be used to discover small molecule inhibitors of oligomer activity. The MTT assay can be used as a measure of toxicity in cultures. Yellow tetrazolium salts were endocytosed by cells and reduced to insoluble purple formazan in the endosomal pathway. The level of purple formazan was a reflection of the number of actively metabolizing cells in culture, and reduction in the amount of formazan was taken as a measure of cell death or metabolic toxicity in culture. When observed through a microscope, the purple formazan was first visible in intracellular vesicles that fill the cell (Figure. 1A). Over time, the vesicles were exocytosed and the formazan precipitated as needle-shaped crystals on the outer surface of the plasma membrane as the insoluble formazan was exposed to the aqueous media environment (Figure 1B). Cells respond to sublethal levels of Abeta oligomers by selectively accelerating the exocytosis rate of reduced formazan, while leaving endocytosis rate unaffected, which can be

seen in mature primary neurons *in vitro* and quantified these morphological shifts via automated microscopy and image processing. At a given point in time following tetrazolium salt addition to the culture well, vehicle-treated cells had the appearance of those in Figure 1A, while Abeta oligomer-treated cells had the appearance of those in Figure 1B. Under these circumstances, there was no overall change in the total amount of reduced formazan, simply a shift in its morphology. This assay is sensitive to low levels of oligomers that do not cause cell death.

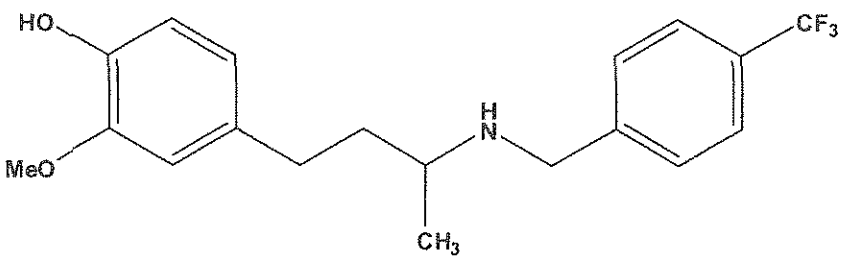
[00234] Evidence suggests that Abeta oligomer-mediated reduction in neuronal surface receptor expression mediated by membrane trafficking are the basis for oligomer inhibition of electrophysiological measures of synaptic plasticity (LTP) and thus learning and memory (See Kamenetz F, Tomita T, Hsieh H, Seabrook G, Borchelt D, Iwatsubo T, Sisodia S, Malinow R. APP processing and synaptic function. Neuron. 2003 Mar 27;37(6):925-37; and Hsieh H, Boehm J, Sato C, Iwatsubo T, Tomita T, Sisodia S, Malinow R. AMPAR removal underlies Abeta-induced synaptic depression and dendritic spine loss. Neuron. 2006 Dec 7;52(5):831-43). Measuring membrane trafficking rate changes induced by oligomers via formazan morphological shifts has been used in cell lines to discover Abeta oligomer-blocking drugs [Maezawa I, Hong HS, Wu HC, Battina SK, Rana S, Iwamoto T, Radke GA, Pettersson E, Martin GM, Hua DH, and Jin LW. A novel tricyclic pyrone compound ameliorates cell death associated with intracellular amyloid-beta oligomeric complexes. J Neurochem. 2006 Jul;98(1):57-67; Liu Y, Schubert D. Cytotoxic amyloid peptides inhibit cellular 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction by enhancing MTT formazan exocytosis. J Neurochem. 1997 Dec;69(6):2285-93; Liu Y, Dargusch R, Banh C, Miller CA, Schubert D. Detecting bioactive amyloid beta peptide species in Alzheimer's disease. J Neurochem. 2004 Nov;91(3):648-56; Liu Y, Schubert D. Treating Alzheimer's disease by inactivating bioactive amyloid beta peptide. Curr Alzheimer Res. 2006 Apr;3(2):129-35; Rana S, Hong HS, Barrigan L, Jin LW, Hua DH. Syntheses of tricyclic pyrones and pyridinones and protection of Abeta-peptide induced MC65 neuronal cell death. Bioorg Med Chem Lett. 2009 Feb 1;19(3):670-4. Epub 2008 Dec 24; and Hong HS, Maezawa I, Budamagunta M, Rana S, Shi A, Vassar R, Liu R, Lam KS, Cheng RH, Hua DH, Voss JC, Jin LW. Candidate anti-Abeta fluorene compounds selected from analogs of amyloid imaging agents. Neurobiol Aging. 2008 Nov 18. (Epub ahead of print)] that lower Abeta brain levels in rodents in vivo [Hong HS, Rana S, Barrigan L, Shi A, Zhang Y, Zhou F, Jin LW, and Hua DH. Inhibition of Alzheimer's amyloid toxicity with a tricyclic pyrone molecule in vitro and in vivo. J Neurochem. 2009 Feb; 108(4):1097-1108].

[00235] The exocytosis assay was adapted for use with mature primary neuronal cultures grown for 3 weeks *in vitro*. Abeta oligomers caused a dose-dependent decrease in the amount of intracellular vesicles (puncta) filled with reduced purple formazan (Figure. 2A, squares; 3μM dose corresponds to image in Figure 2C) as measured via image processing using a Cellomics VTI automated microscopy system. Increasing the amount of Abeta oligomers eventually resulted in overt toxicity. Thus, the concentration of neuroactive Abeta oligomers was much lower than that causing cell death. This decrease can be blocked by adding stoichiometric amounts of anti-Abeta monoclonal antibody 6E10 (IgG) to the cultures prior to oligomer addition (Figure 2A, circle; the circle corresponds to image in Figure 2D; antibody alone [down triangle] has no effect on the neurons). Several compounds were tested that have been reported to block the effects of Abeta oligomers, including the sugar alcohol scyllo-inositol (AZD-103), the nAChR antagonist hexamethonium bromide, and the NMDAR antagonists MK-801 and none were active (Fenili et al., '07, Calabrese et al., '06, LeCor et al., '07).

[00236] The assay was optimized for performance in 384-well microtiter plates with automated liquid handling robotics for compound formatting and assay plate stamping, routinely achieving statistically significant two-fold separation between vehicle and Abeta oligomer-treated neurons (Student's t-test, unequal variance). Compounds were added to neurons first, then oligomers were added. When configured in this manner the assay was able to detect compounds that act via disruption of oligomers, inhibition of oligomer binding to neurons, or counteraction of signal transduction mechanisms of action initiated by oligomer binding.

[00237] Compounds were considered active if they significantly block Abeta-mediated changes in membrane trafficking, but do not significantly affect membrane trafficking when dosed on their own. An example is shown in Figure 2B; CT0109 inhibits oligomer effects on membrane trafficking with an EC50 of 7μM.

[00238] CT0109 is 4-(3-(4-(trifluoromethyl)benzylamino)butyl)-2-methoxyphenol, the structure of which is:



[00239] Figure 2A shows dose-dependent decrease of intracellular formazan-filled vesicles (puncta) caused by Abeta 42 oligomer treatment acceleration of exocytosis (squares). Oligomer effects were blocked by anti Abeta IgG (circle and up triangle; circle refers to stoich amount of IgG, i.e., 3μM of Aβ and 1.5 μM of IgG; up triangle refers to substoich IgG, i.e., 3μM of Aβ and 0.5 μM of IgG). IgG itself (down triangle) has no effect. Figure 2B shows CT0109, which inhibits oligomer effects on membrane trafficking. Figure 2C shows representative micrographs of 21DIV hippocampal neurons *in vitro* showing oligomer effects membrane trafficking (corresponding to data point 3μM in Figure 2A); and Figure 2D shows blockade by anti-Abeta antibodies (corresponding to the circle in Figure 2A). Data were the average of 3 experiments. Scale bar = 20 micron in Figure 2D.

[00240] As shown in figure 10, Both CT0109 and CT0093 are effective in both prevention (Figure 10D) and treatment protocols (Figure 10E) where ascending doses of efficacious small molecules from two structurally distinct series (CT0109 and CT0093) stop oligomer effects and cultures look more like vehicle-treated cultures (upper panel of micrographs in Figure 10A-C). The molecules can also prevent oligomer effects on membrane trafficking whether they were present before or after oligomer addition, and the EC50's of both drug candidates appears to be similar regardless of order of addition as shown in the bottom left and right graphs respectively. This suggests that these drugs and their targets might be effective in both prevention and treatment of existing deficits

Example 8 - Fear Conditioning Assay

[00241] CT0109 and CT0093 were tested in an animal model of a memory-dependent behavioral task known as fear conditioning. The study protocol was designed based on published protocols (*See e.g.* Puzzo D, Privitera L, Leznik E, Fà M, Staniszewski A, Palmeri A, Arancio O. Picomolar amyloid-beta positively modulates synaptic plasticity and memory in hippocampus. J Neurosci. 2008 Dec 31;28(53):14537-45.). The formation of contextual memories is dependent upon the integrity of medial temporal lobe structures such as the hippocampus. In this assay mice were trained to remember that a particular salient context (conditioned stimulus; CS) is associated with an aversive event, in this case a mild foot shock (the unconditioned stimulus, US). Animals that show good learning will express an increase in freezing behavior when placed back into the same context. This freezing is absent in a novel context. Increased freezing in the context indicates strong hippocampal-dependent memory formation in animals. Memory tested in Fear Conditioning is sensitive to elevations of soluble Aβ. Figure 3 shows the results of administration of Abeta oligomers (bar labeled with "b") during training results in memory deficits when animals are tested 24 later, compared to

vehicle administration (bar labeled with "a"). Both CT0109 and CT0093 were effective at stopping Abeta oligomer mediated effects on membrane trafficking (Figure. 3). When administered to animals prior to Abeta oligomer administration, CT0109 and CT0093 blocked oligomer effects on memory at the 2 pmol dose (Figure 3, bar labeled with "c" and "d"). This behavioral efficacy demonstrates that the membrane trafficking assay is able to predict which compounds will be efficacious in treating the behavioral memory loss caused by oligomers. The fear condition model for memory was performed as described herein.

[00242] Figure 3 shows that Abeta produces significant deficits in memory formation vs. vehicle ($p<0.05$) in the contextual fear conditioning memory task. Figure 3 shows that the 2 pmol doses of CT0109 + Abeta (200nM) and CT0093 +Abeta (200 nM) completely blocked the effect of Abeta on memory ($p<0.05$, one way ANOVA, post hoc comparison with Bonferroni correction). No effect of compound alone was observed (data not shown). No adverse behavioral changes were observed at any dose.

Example 9 - Characterization of CT0093 active stereoisomers

[00243] Clinical data from trials of secretase inhibitors suggest that drugs that act to lower the total Abeta protein levels may not be clinically efficacious in Alzheimer's disease patients, perhaps because Abeta monomer may be required for normal cognition (See L. A. Hyde, R. A. Del Vecchio, et al. Merck Res. Labs, Kenilworth, NJ. Chronic administration of a novel γ-secretase inhibitor SCH 1375975 to post-plaque transgenic CRND8-APPswe/ind (TgCRND8) mice dramatically reduced Aβ, halted amyloid plaque progression and was well tolerated. 2010 Society for Neuroscience Abstracts 650.16). Development of drugs that block the effects of an exclusively pathological species, namely Abeta oligomers, may be a better therapeutic target.

[00244] CT0093 inhibits binding of Abeta 1-42 oligomers to synapses and completely blocks Abeta oligomer-induced membrane trafficking changes and synapse loss in vitro. CT0093 also completely blocks oligomer-induced memory deficits in an acute Alzheimer's disease mouse model in vivo.NMR spectra indicated that the original CT0093 parent compound was a mixture of four stereoisomers. To resolve these structures, CT0093 was subjected to reverse-phase preparative HPLC separation on gram scale and three purified compounds were collected. CT1296 (4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol) and CT1297 (4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol) were 98% pure isolates, each contained diastereomers of the same molecular weight. The third, CT1298 was 70% pure and contained a mixture of compounds. CT1296 and CT1297 represent close

analogs to the original CT0093 structure. High purity diastereoisomers can also be isolated by chiral chromatography methods using stationary phase columns. Isolated compounds were screened in our primary assay that measures oligomer-induced membrane trafficking deficits. Efficacious compounds block oligomer-induced deficits in the rate of membrane trafficking in mature primary neurons *in vitro* (21DIV), producing a high rate of inhibition. CT01296 had a similar EC50 as the parent CT0093 although was slightly less efficacious (Figure 4). Additive effects of CT1296 and CT1297 may account for the parent compound CT0093's high degree of efficacy. Both CT01297 and mixture CT01298 were significantly less potent than the parent CT0093.

Synthetic routes have been designed to access both the original CT0093 structures as well as the presumptive CT01296/CT01297 structures as separate diastereomers.

Table 2 HPLC and pharmacokinetic parameters of CT0093 compounds

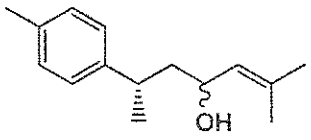
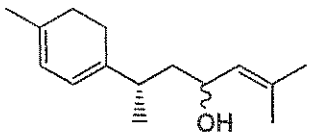
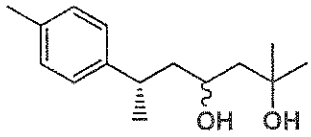
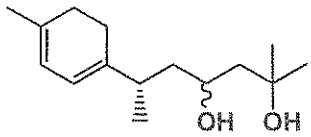
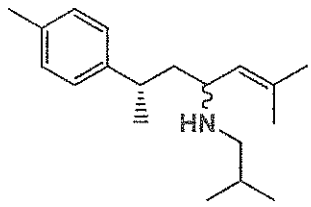
Compound ID	Dose (mg/kg)	$T_{1/2}$ (min)	Cl (mL/min/kg)
CT1296	1	69±5	120±13
CT1297	1	161±97	101±12
CT1298	n.s.	n.s.	n.s.

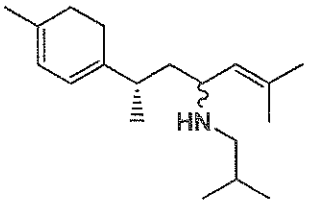
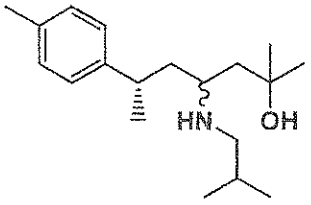
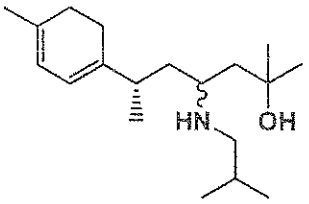
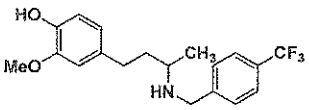
[00245] The oligomer hypothesis holds that compounds that inhibit the effects of oligomers should both immediately improve the tonic inhibition of synapses and improve cognitive function and result in a regrowth of spines as the oligomer effects are blocked (G.A Krafft and W.L. Klein. ADDLs and the signaling web that leads to Alzheimer's disease. Neuropharmacology (2010) 59: 230-42.). We compared compound activity for its effectiveness at blocking oligomer effects if added before or after oligomers were added to our cultures. The results show that CT0093 is equally effective whether added before (prevention format) or after (treatment format) the addition of Abeta oligomers and thus would be effective in treating Abeta induced defects in neuronal function.

Table 3 CT0093 effectiveness administered in treatment or prevention mode

Membrane Trafficking Assay Format	EC50 (uM)	% Inhibition of Abeta
Prevention	4.2 ± 1.5	92 ± 12
Treatment	3.4 ± 1.0	89 ± 12

Table 4. Relative activity of compounds

Cmpd ID	Structure	Name[1]	Activity[2]
1		(6S)-2-methyl-6-p-tolylhept-2-en-4-ol	+
2		(6S)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)hept-2-en-4-ol	+
3		(6S)-2-methyl-6-p-tolylheptane-2,4-diol	+
4		(6S)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptane-2,4-diol	+
5		(6S)-N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine	++++

Cmpd ID	Structure	Name[1]	Activity[2]
6		(6S)-N-isobutyl-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)hept-2-en-4-amine	++
7		(6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol	+++
8		(6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol	+++
9		2-methoxy-4-(3-(4-(trifluoromethyl)benzylamino)butyl)phenol	++++

[1] as determined by ChemDraw® 2. Relative activity in membrane trafficking assay.

[00246] Dose response experiments were performed with Abeta in the presence of multiple concentrations of CT0093 resulting in a rightward shifting of the Abeta EC50 indicative of a competitive interaction between CT0093 and Abeta. A Schild analysis of the competition curves gives a linear relationship with a slope indistinguishable from unity and a calculated inhibition constant of 0.57 uM. This submicromolar potency is consistent with the value reported in our original application using a Chen-Prusoff relationship and the competitive mechanism support the idea that our compound class will be more potent against a more potent Abeta ligand, such as that found in human AD brains.

[00247] The relative effectiveness of isolated stereoisomers of CT0093 has been demonstrated in a primary screening assay and their pharmacokinetic properties in rats determined. CT1296 maintained the potency of the parent compound but was somewhat less efficacious while CT1297 and CT1298 were nearly 2-fold less potent than the parent. CT1297

has a longer half-life than CT1296 in plasma. The ability of these compounds to reverse the effects of Abeta oligomers on trafficking supports our therapeutic goal of disease modifying treatment of Alzheimer's Disease by restoring neuronal function.

Example 10 – Behavioral efficacy

[00248] CT0093 was tested for its ability to reverse deficits in 9 month old male Swe/Ldn mice in a pilot study at 1 and 10 mg/kg/day via the osmotic minipump method.

[00249] Transgenic mice (red) performed significantly worse than the non-Transgenic vehicle-treated animals (blue) on the third day of learning (by ANOVA) but not in the probe trial (Figure 9).

[00250] Subcutaneous administration of 10 mg/kg/day of CT0093 (shown in gray squares and solid gray line and solid bar) achieved brain concentrations of 540 nM (Figure 9). This concentration significantly improves transgenic performance on the second and fourth day of testing, and is trending that way in the probe test of memory (by t-test).

[00251] No adverse behavioral events were observed during the study. Like CT0109, CT0093 is capable of improving cognitive performance in the transgenic model of AD and reversing established cognitive deficits. this efficacy is seen at shorter treatment periods than any other published therapeutic. The ability of both CT0109 and CT0093 to rescue Abeta-induced memory deficits in these mouse models is a significant proof-of-concept milestone towards the development of viable clinical candidates.

Example 11 - Preparation of mixture of diastereomers

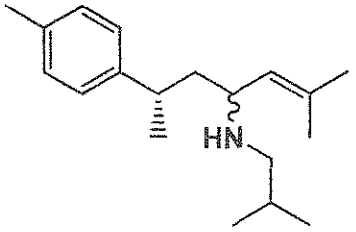


turmerone

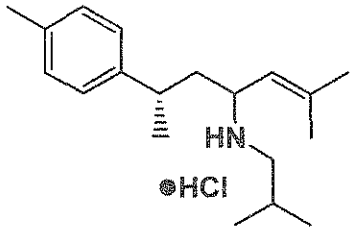
[00252] A solution of turmerone (217 mg, 1.00 mmol) and isobutyl amine (150 μL, 1.50 mmol) in DCM (4 mL) was treated with $TiCl_4$ (1 M in DCM, 2.00 mL, 2.0 mmol) at –78 °C. The mixture was stirred at –78 °C for 2h. To the reaction mixture was added NaBH4 (200 mg). The resulting mixture was warmed to 0 °C over 30 min. The reaction was diluted with ethyl acetate and washed with sat. $NaHCO_3$. The organic phase was separated, dried, and concentrated.

[00253] The residue was purified by prep-HPLC to afford the title compound (140 mg, 51%). LC-MS: 274 (M+1)^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.26–6.99 (m, 4H), 5.13–5.08 (m, 1H), 3.76–3.71 (m, 1/2H), 3.36–3.32 (m, 1/2H), 2.76–2.37 (m, 2H), 2.31–2.29 (m, 2H), 1.95–1.75 (m, 5H), 1.60–1.15 (m, 6H), 0.99–0.93 (m, 9H).

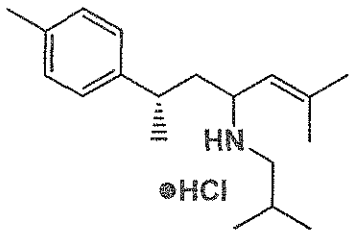
Example 12 – Separation of diastereoisomers



[00254] A mixture of diastereomers of the above compound (290mg) was separated on a ChiralCel OD-H column (CO_2 / Ethanol / DEA = 95 / 5 / 0.1 (v/v/v)) to give two fractions. Both fractions were treated with 1N HCl in ethyl acetate to give the corresponding salts: AB3494 and AB3495.



[00255] **Diastereomer 1** (Peak 1, 62 mg): LC-MS: 274 (M+1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (br s, 1H), 7.09 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 7.6 Hz, 2H), 5.26 (d, J = 10.4 Hz, 1H), 3.74 (br s, 1H), 2.84 (br m, 1H), 2.56 (m, 3H), 2.28 (s, 3H), 2.11-2.07 (m, 1H), 1.73 (s, 3H), 1.57 (d, J = 4.4 Hz, 3H), 1.17 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H).



[00256] **Diastereomer 2** (Peak 2, 101mg) LC-MS: 274 (M+1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19-9.17 (br m, 1 H), 7.11 (s, 4H), 5.30 (d, J= 10.8 Hz, 1 H), 3.40 (br s, 1H), 2.78 (t, J = 5.6 Hz, 1H), 2.64-2.48 (m, 3H), 2.33 (s, 3H), 1.30 (s, 3H), 1.19 (d, J = 6.4 Hz, 3H), 1.04 (d, J= 6.4, 1H), 0.97 (d, J = 6.0 Hz, 3H).

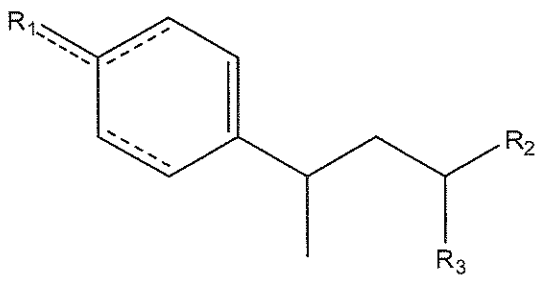
[00257] Although the present invention has been described in considerable detail with reference to certain preferred versions thereof, other versions are possible. Therefore, the spirit and scope of the invention should not be limited to the description of the preferred versions described herein.

[00258] All features disclosed in the specification, including the abstract and drawings, and all the steps in any method or process disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. Each feature disclosed in the specification, including abstract and drawings, can be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features. Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

[00259] Each reference cited in the present application is herein incorporated by reference in its entirety.

What is claimed:

1. A compound comprising formula I-0



I-0

or pharmaceutically acceptable salt thereof, wherein:

-------- is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and

R_3 is $NHCH_2CH(CH_3)_2$.

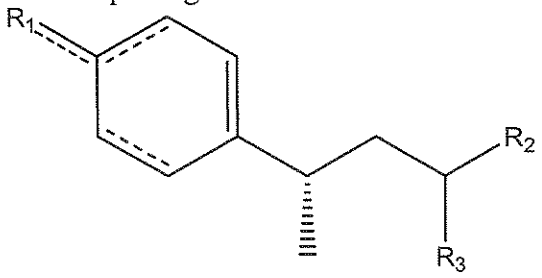
2. The compound of claim 1 selected from:

N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine;

4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol;

4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol and pharmaceutically acceptable salts thereof.

3. A compound comprising formula I-1



I-1

or pharmaceutically acceptable salt thereof, wherein:

-------- is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and

R_3 is $NHCH_2CH(CH_3)_2$.

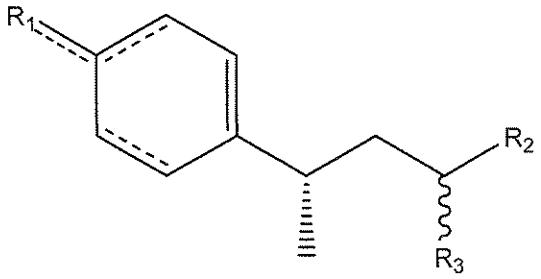
4. The compound of claim 3 selected from:

(6S)-N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine;

(6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol;

(6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol and pharmaceutically acceptable salts thereof.

5. A compound comprising formula I-2



I-2

or pharmaceutically acceptable salt thereof, wherein:

-------- is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and

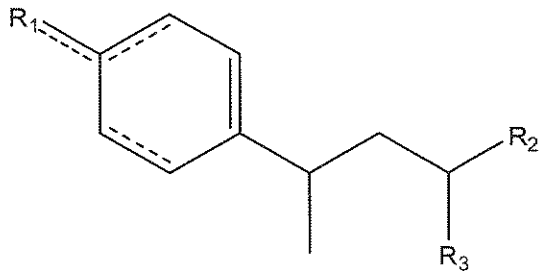
R_3 is $NHCH_2CH(CH_3)_2$.

6. The compound of claim 5, selected from:

(4S,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine;

(4R,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine and pharmaceutically acceptable salts thereof.

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I-0



I-0

wherein:

-------- is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$ and

R_3 is $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

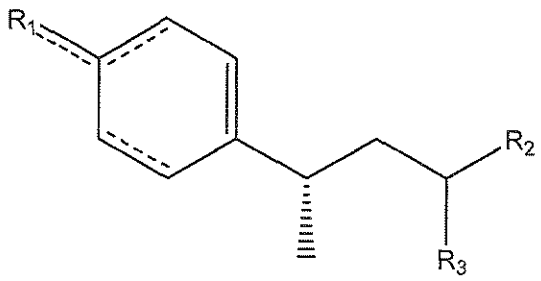
8. The pharmaceutical composition of claim 7, wherein the compound is selected from:

N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine;

4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol;

4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol and pharmaceutically acceptable salts thereof.

9. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I-1



I-1

wherein:

$\equiv\equiv\equiv$ is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and

R_3 is $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

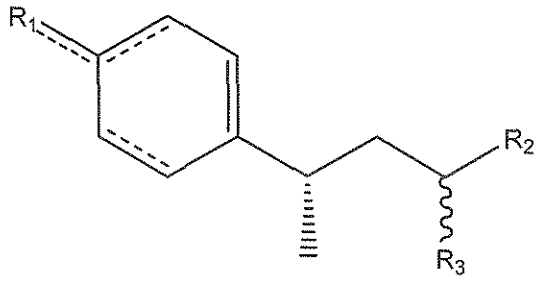
10. The pharmaceutical composition of claim 9, wherein the compound is selected from:

(6S)-N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine;

(6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol;

(6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol and pharmaceutically acceptable salts thereof.

11. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I-2



I-2

wherein:

$\overline{\text{--------}}$ is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and

R_3 is $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

12. The pharmaceutical composition of claim 11, wherein the compound is selected from:

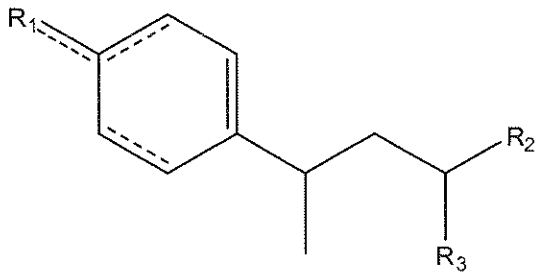
(4S,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine;

(4R,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine and pharmaceutically acceptable salts thereof.

13. A pharmaceutical composition comprising a mixture of a therapeutically effective amount of 4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol and a therapeutically effective amount of 4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

14. A pharmaceutical composition comprising a mixture of a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol and a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

15. Use of a compound of formula I-0



I-0

in the manufacture of a medicament for treating cognitive decline and/or Alzheimer's disease in a patient, wherein:

-------- is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and

R_3 is selected from OH and $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

16. The use of claim 15, wherein the compound is selected from:

2-methyl-6-p-tolylhept-2-en-4-ol;

2-methyl-6-(4-methylcyclohexa-1,3-dienyl)hept-2-en-4-ol;

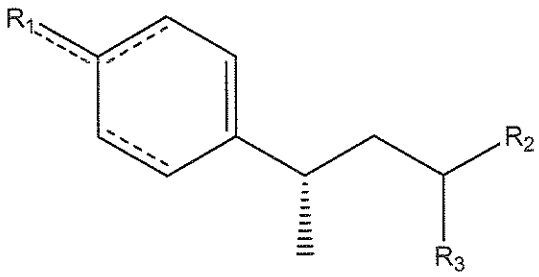
2-methyl-6-p-tolylheptane-2,4-diol;

N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine;

4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol; and

4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol and pharmaceutically acceptable salts thereof.

17. Use of a compound of formula I-1



I-1

in the manufacture of a medicament for treating cognitive decline and/or Alzheimer's disease in a patient, wherein:

-------- is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and

R_3 is selected from OH and $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

18. The use of claim 17, wherein the compound is selected from:

(6S)-2-methyl-6-p-tolylhept-2-en-4-ol;

(6S)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)hept-2-en-4-ol;

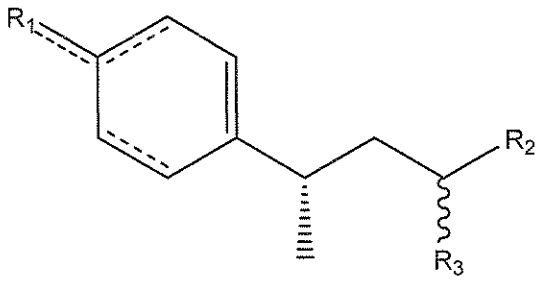
(6S)-2-methyl-6-p-tolylheptane-2,4-diol;

(6S)-N-isobutyl-2-methyl-6-(p-tolyl)hept-2-en-4-amine;

(6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol; and

(6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol and pharmaceutically acceptable salts thereof.

19. Use of a compound of formula I-2



I-2

or pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cognitive decline and/or Alzheimer's disease in a patient, wherein:

 is selected from a single bond and a double bond;

R_1 is selected from CH_3, CH_2, F, Cl, Br, CF_3, O-alkyl, and OCF_3;

R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH{=}C(CH_3)_2$; and

R_3 is selected from OH and $NHCH_2CH(CH_3)_2$.

20. The use of claim 19, wherein the compound is selected from:

(4S,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine;

(4S,6S)-N-isobutyl-2-methyl-6-p-tolylhept-2-en-4-amine and pharmaceutically acceptable salts thereof.

21. Use of a pharmaceutical composition comprising a mixture of a therapeutically effective amount of 4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol and a therapeutically effective amount of 4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof in the manufacture of a medicament for treating cognitive decline and/or Alzheimer's disease in a patient,.

22. Use of a pharmaceutical composition comprising a mixture of a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-p-tolylheptan-2-ol and a therapeutically effective amount of (6S)-4-(isobutylamino)-2-methyl-6-(4-methylcyclohexa-1,3-dienyl)heptan-2-ol or pharmaceutically acceptable salts thereof in the manufacture of a medicament for treating cognitive decline and/or Alzheimer's disease in a patient.