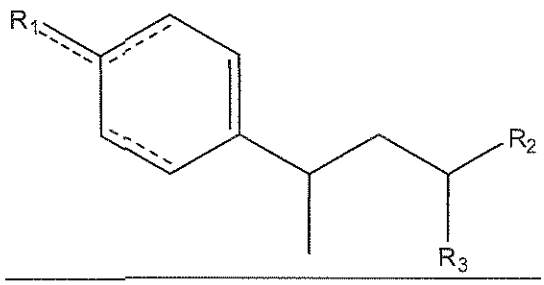
ISOLATED COMPOUNDS FROM TURMERIC OIL AND METHODS OF USE

[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 ~~invention~~ 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 ~~invention~~ 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 ~~invention~~present disclosure, compounds derived from turmeric oil by the chemical conditioning process described herein are provided. In another embodiment, the ~~invention~~ 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:

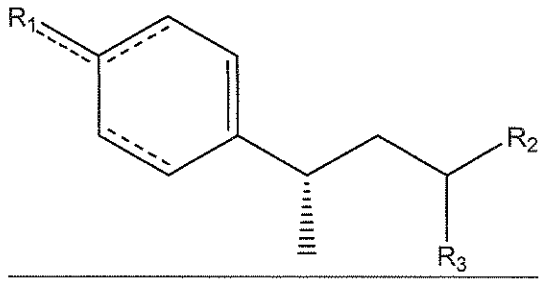
-------- is selected from a single bond and a double bond;

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:

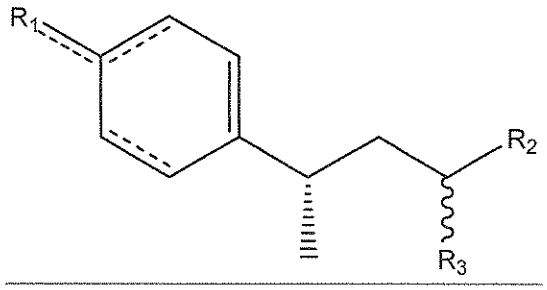
-------- is selected from a single bond and a double bond;

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:

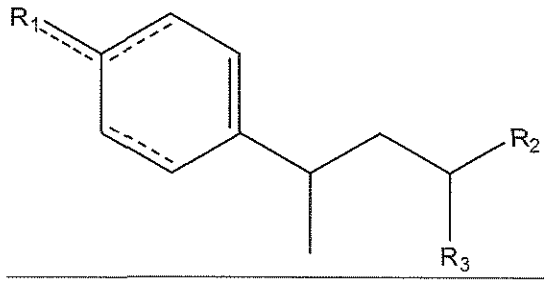
-------- is selected from a single bond and a double bond;

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:

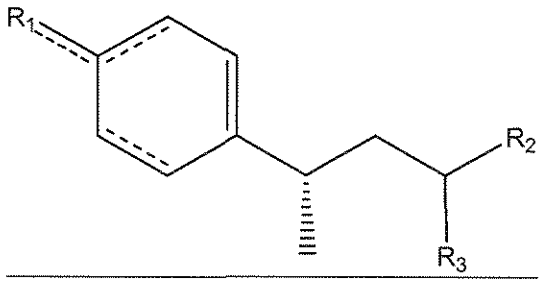
-------- is selected from a single bond and a double bond;

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:

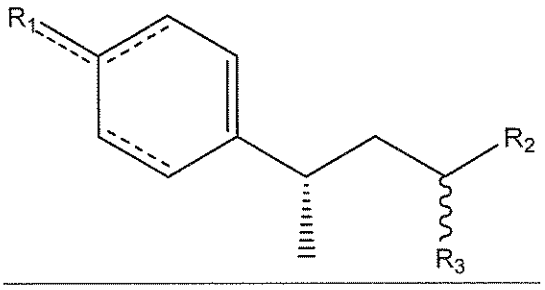
-------- is selected from a single bond and a double bond;

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;

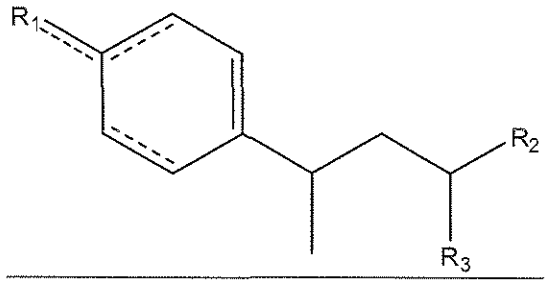
R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH=C(CH_3)_2$; and

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:

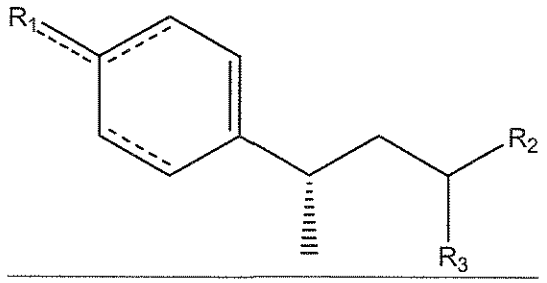
-------- is selected from a single bond and a double bond;

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:

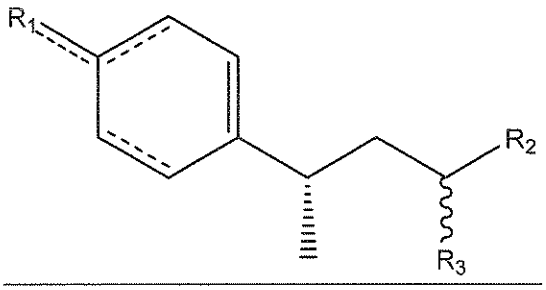
-------- is selected from a single bond and a double bond;

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;

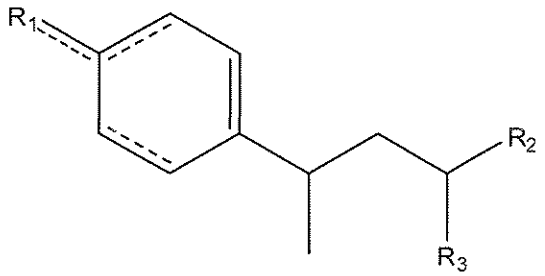
R_2 is selected from $CH_2C(CH_3)_2OH$ and $CH=C(CH_3)_2$; and

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 ~~invention~~ provides compounds of Formula I-0:



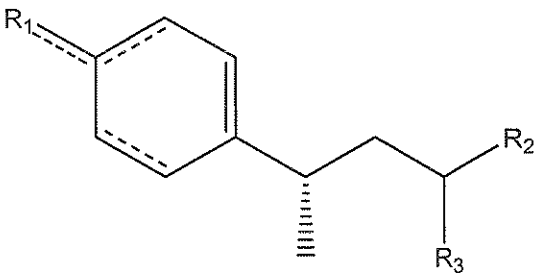
I-0

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 ~~invention~~ provides compounds of Formula I-1:

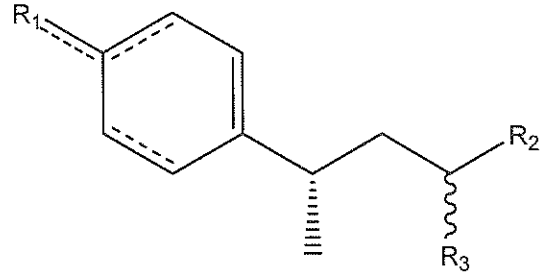


I-1

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.

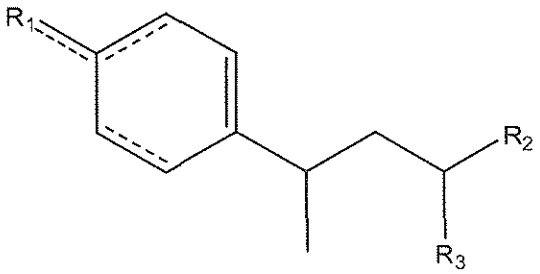
[0007] In some embodiments, the present disclosure ~~invention~~ provides compounds of formula I-2:



I-2

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 ~~selected from OH and~~ $NHCH_2CH(CH_3)_2$.

2. The compound of claim 1 selected from:

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

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

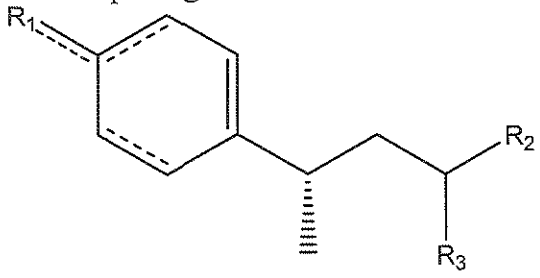
~~2-methyl-6-p-tolylheptane-2,4-diol;~~

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.

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 ~~selected from OH and~~ $NHCH_2CH(CH_3)_2$.

4. The compound of claim 3 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;~~

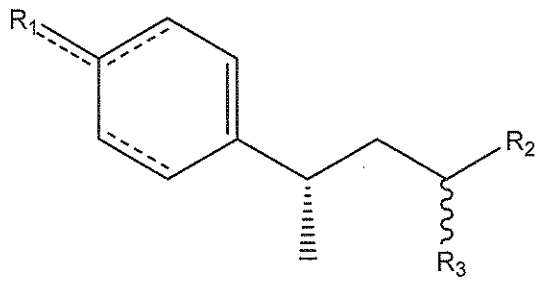
~~(6S)-2-methyl-6-p-tolylheptane-2,4-diol;~~

(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.

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

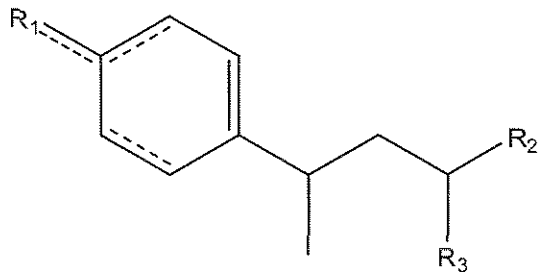
R_3 is ~~selected from OH and~~ $NHCH_2CH(CH_3)_2$.

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 ~~selected from OH and~~ $NHCH_2CH(CH_3)_2$ or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

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

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

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

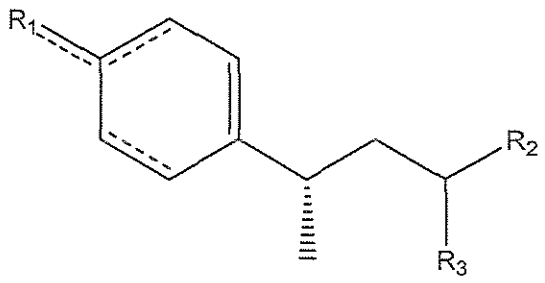
~~2-methyl-6-p-tolylheptane-2,4-diol;~~

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.

9. 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.

10. The pharmaceutical composition of claim 9, 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;~~

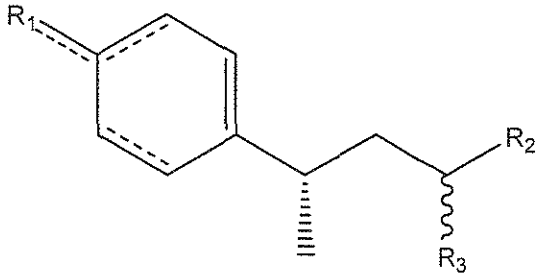
~~(6S)-2-methyl-6-p-tolylheptane-2,4-diol;~~

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

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

(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:

-------- 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.

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.