A61K 31/365 (2006.01)  A61P 25/28 (2006.01)
A61K 36/19 (2006.01)

(21) International Application Number:
PCT/US2014/034758

(22) International Filing Date:
21 April 2014 (21.04.2014)

(25) Filing Language: English

(26) Publication Language: English

(27) Priority Data:
61/814,445  22 April 2013 (22.04.2013)  US

(30) Designated States (unless otherwise indicated, for every kind of national protection available):


(84) Declarations under Rule 4.17:
— as to the identity of the inventor (Rule 4.17(i))
— as to applicant’s entitlement to apply for and be granted a patent (Rule 4.17(ii))
— as to the applicant’s entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:
— with international search report (Art. 21(3))
— with amended claims and statement (Art. 19(1))

Date of publication of the amended claims and statement: 4 December 2014

(51) International Patent Classification:
A61K 31/365 (2006.01)  A61P 25/28 (2006.01)
A61K 36/19 (2006.01)

(54) Title: TREATMENT OF ALZHEIMER’S AND COGNITIVE IMPAIRMENT WITH ANDROGRAPHOLIDES

(57) Abstract: Andrographolide binds to GSK-3Beta, preventing changes in neuropathology in an Alzheimer’s model, reducing Amyloid-Beta peptide levels, changing the ontology of hippocampus and cortex amyloid plaques, and reducing tau phosphorylation around Amyloid-Beta. Andrographolide recovers spatial memory functions in an Alzheimer’s model. Andrographolide and its derivatives may be used to treat Alzheimer’s disease.
AMENDED CLAIMS
received by the International Bureau on 03 November 2014 (03.11.2014)

We claim:

1. Administering to human diagnosed with dementia, a therapeutically effective amount of a compound of Formula (I):

![Formula Image]

wherein

- $R_1$ is selected from the group consisting of hydrogen, alkyl or hydroxyl,
- $R_2$ is selected from the group consisting of hydroxyalkyl or alkyl-O-$L_1$, wherein $L_1$ is a carbohydrate moiety,
- $R_3$ is selected from the group consisting of hydrogen or hydroxyl,
- $X$ is selected from the group consisting of $C(=CH_2)$, $CH(OH)$, or a spirooxirane-2 moiety,
- $Z$ is selected from the group consisting of $CH_2$, $CH(OH)$ or $C(=0)$, and
- $R_4$ is selected from the group consisting of an optionally substituted $L_2$-alkyl or $L_2$-alkenyl, wherein $L_2$ is an optionally substituted 3-furanyl or 3-fur-3-enyl moiety, or a pharmaceutically acceptable salt, ester, ether or prodrug thereof,
2. A method comprising: administering to a human diagnosed with dementia a therapeutically effective amount of a compound of the formula:

![Chemical structure](image)

wherein X1-X3 and X5-X7 are each individually selected from the group consisting of: H, OH, CH and COHn, where n = 0-3, and where X4 is selected from the group consisting of: H, OH, and optionally-substituted hydrocarbon.

3. The method of claim 2, where said compound comprises a therapeutically effective amount of a compound selected from the group consisting of: andrographolide, 14-deoxyandrographolide, neoandrographolide and a combination thereof.

4. The method of claim 3, where said compound comprises a therapeutically effective amount of andrographolide.

5. The method of claim 2, where said dementia is selected from the group consisting of: non-progressive dementia, slowly progressive dementia and rapidly progressive dementia.

6. The method of claim 5, wherein said dementia is slowly progressive dementia.

7. The method of claim 6, wherein said slowly progressive dementia is suspected of being caused by a condition selected from the group consisting of: Alzheimers-type dementia, senile dementia of Lewy type and vascular dementia.

8. The method of claim 2, where said dementia is associated with a chronic inflammatory condition of the brain.
9. The method of claim 8, wherein said chronic inflammatory condition of the brain is selected from the group consisting of: Behçet's Disease, multiple sclerosis, sarcoidosis, Sjögren's syndrome and systemic lupus erythematosus.

10. The method of claim 2, wherein said therapeutically effective amount comprises a daily oral dosage of from about 1 to about 4 milligrams of said compound per kilogram of body weight for said human.

11. The method of claim 6, wherein said therapeutically effective amount comprises a daily oral dosage of from about 1 to about 4 milligrams of said compound per kilogram of body weight for said human.

12. A method comprising:
   
a) Administering to a human a test selected from the group consisting of: the Mini Mental Status Exam (MMSE), the Alzheimer Disease Assessment Scale (ADAS), the Boston Naming Test (BNT) and the Token Test (TT); and then
   
b) Administering to said human, for at least about 30 days, a daily dosage effective to preserve or improve cognitive function, of a compound of claim 1.

13. The method of claim 12, where said compound comprises a therapeutically effective amount of a compound selected from the group consisting of: andrographolide, 14-deoxyandrographolide, neoandrographolide and a combination thereof.

14. The method of claim 13, where said compound comprises a therapeutically effective amount of andrographolide.

15. The method of claim 12, wherein said daily dosage comprises a daily dosage of from about 1 to about 4 milligrams of said compound per kilogram of body weight for said human.

16. The method of claim 3; wherein said compound(s) is provided as an extract of *Andrographispaniculata*, standardized to contain not less than about 50% (w/w) of said compound(s).

17. The method of claim 13, wherein said compound(s) is provided as an extract of *Andrographispaniculata*, standardized to contain not less than about 50% (w/w) of said compound(s).
Sirs:

Perhaps ten years ago, Professor J.L. HANCKE filed a patent application presenting claims to the use of the claimed compounds to treat Alzheimer's. That application was published as US 2006/0063831. The '831 application, however, provided no data to support its Alzheimer's claims. Given the unpredictability of the pharmaceutical arts, The United States Patent Office concluded that the '831 application failed to enable the artisan to treat Alzheimer's with a reasonable expectation of success. Professor HANCKE thus returned to the laboratory and invested his resources, and several years of his time, to collect the data the Office said is needed for an enabling disclosure. He presents that new data in the instant application.

The Examiner now correctly recognizes that the '831 application teaches andrographolide. The Examiner correctly recognizes the '831 application provides a prophetic Example 16 for Alzheimer's disease treatment.
The Office's own prior fact finding, however, is binding on future agency proceedings. See e.g., United States v. Utah Const. & Mining Co., 384 U.S. 394, 422 (1966); see also MAN. PAT. EXAM. PROC. § 706.04 ("Full faith and credit should be given to the search and action of a previous examiner .... In general, an examiner should not take an entirely new approach or attempt to reorient the point of view of a previous examiner."). § 704.01 (same); § 713.04 (same). The Office has already found that the '831 application fails to enable the instantly-claimed invention. Because the '831 application does not enable, it cannot be used to reject the claims. See In re Hoeksema, 399 F.2d 269 (CCPA 1968). All rejections relying on the '831 application must therefore be withdrawn.

This outcome is fair because Professor HANCKE has taken the time and resources to do exactly what the Office ten years ago demanded of him.

Thanking you for your continued help on this application, I remain yours truly,

PHARMACEUTICAL PATENT ATTORNEYS, LLC

Mark POHL, USPTO Reg. No. 35,325