Aspects of the invention pertain to chemical compounds, therapeutic compositions, and methods for treating neurodegenerative diseases, in particular, neurodegenerative diseases associated with abnormal accumulation of protein tau.
FIGURE 1

(A) Wild-type Tau

<table>
<thead>
<tr>
<th>Compounds (μM)</th>
<th>Palmadorin</th>
<th>Beauvericin</th>
</tr>
</thead>
<tbody>
<tr>
<td>pS199-202</td>
<td>0.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Tau H150</td>
<td>7.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Tau 46</td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>GAPDH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(B) P301L Tau

<table>
<thead>
<tr>
<th>Compounds (μM)</th>
<th>Palmadorin</th>
<th>Beauvericin</th>
</tr>
</thead>
<tbody>
<tr>
<td>pS199-202</td>
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<td>3.9</td>
</tr>
<tr>
<td>GAPDH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
COMPOUNDS AND RELATED METHODS FOR TREATMENT OF NEURODEGENERATIVE DISEASES

CROSS-REFERENCE TO RELATED APPLICATIONS

0001. This application is a divisional application of U.S. patent application Ser. No. 14/271,177, filed May 6, 2014, and now allowed, which claims the benefit of U.S. Provisional Application Ser. No. 61/819,701, filed May 6, 2013, which are hereby incorporated by reference in their entireties.

BACKGROUND

0002. Intracellular aggregation of abnormal species of phosphorylated tau (protein tau) is a major pathologic feature of a family of neurodegenerative diseases collectively referred to as the tauopathies. Tau normally functions to stabilize microtubules in neurons; however, it pathologically aggregates in AD and Parkinson’s disease. The most common tauopathy is Alzheimer’s disease, in which paired helical filaments (PHFs) of mis-folded protein tau aggregates in neurofibrillary tangles, in dystrophic neuritis of senile plaques, and in cell processes in the neuropil. Abnormal accumulation of protein tau is closely linked with post-symptomatic progression in Alzheimer’s disease. Abnormal accumulation of protein tau in the cytoplasm of neuronal and glial cells also represents major structural hallmarks in Pick’s disease, corticobasal degeneration, and progressive supranuclear palsy.

0003. At present, researchers on the development of therapeutics for tauopathies focus primarily on agents that prevent abnormal phosphorylation or aggregation of tau proteins. However, it has been discovered that while aggregation of hyperphosphorylated protein tau is visible evidence of tauopathies, these neurofibrillary tangles appear to be less toxic than soluble intermediates of protein tau. High levels of tau intermediates, particularly aberrant tau species failed to be cleared from cells, cause cognitive dysfunction in AD and tauopathies. Therefore, agents that degrade or destabilize tau intermediates, clear aberrant tau species from cells, or otherwise reduce intracellular tau levels, are promising therapeutics for AD and tauopathies.

0004. Existing therapeutics for the treatment of tauopathies (such as AD) only demonstrate limited efficacy; as such, additional therapeutics for the treatment of tauopathies are needed.

BRIEF SUMMARY

0005. Aspects of the invention provide chemical compounds for treating neurodegenerative diseases, in particular, neurodegenerative diseases associated with abnormal accumulation of protein tau.

0006. One aspect of the invention provides a method of reducing intracellular tau levels comprising administering, to cells comprising protein tau, an effective amount of compound A:

[0007] In another aspect, the invention provides a method of reducing intracellular tau levels comprising administering, to cells comprising protein tau, an effective amount of compound B:

0008. In some embodiments of aspects of the invention, the cells are in a subject, such as a human, in need of treatment for a neurodegenerative disease. The neurodegenerative disease may be a tauopathy. In some embodiments, the neurodegenerative disease is selected from Alzheimer’s disease, Parkinson’s disease, frontotemporal dementia, frontotemporal dementia with Parkinsonism, frontotemporal lobe dementia, pallidodopontinal degeneration, progressive supranuclear palsy, multiple system tauopathy, multiple system tauopathy with presenile dementia, William-Lynch disease, Pick’s disease, or Pick’s disease-like dementia. In one embodiment, the neurodegenerative disease is Alzheimer’s disease.

0009. In additional aspects, the invention provides pharmaceutical compositions comprising any of compounds A, B, and combinations thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

0010. FIG. 1 shows a western blot analysis of phosphorylated tau following Palmaranin M and Beauvericin treatment in HeLa cells transfected with (A) wild type human tau and (B) mutant P301L human tau.

BRIEF DESCRIPTION OF THE SEQUENCES

0011. SEQ ID NO:1 is an amino acid sequence of a tau protein isoform (tau 352) useful according to aspects of the invention.

0012. SEQ ID NO:2 is an amino acid sequence of a tau protein isoform (tau 441) useful according to aspects of the invention.

0013. SEQ ID NO:3 is an amino acid sequence of a tau protein isoform (tau 383) useful according to aspects of the invention.

0014. SEQ ID NO:4 is an amino acid sequence of a tau protein isoform (tau 776) useful according to aspects of the invention.

0015. SEQ ID NO:5 is an amino acid sequence of a tau protein isoform (tau 776) useful according to aspects of the invention.
SEQ ID NO:6 is an amino acid sequence of a tau protein isoform (tau 412) useful according to aspects of the invention.

DETAILED DESCRIPTION

Aspects of the invention provide chemical compounds and compositions for treating neurodegenerative diseases, in particular, neurodegenerative diseases associated with abnormal accumulation of protein tau.

In one aspect, the invention provides compounds A and B, or salts thereof:

- **B (Palmadorin M)**
  - Chemical Formula: C$_2$H$_{38}$O$_4$
  - Molecular Weight: 378.5454
  - Chemical Structure:

- **B (Beauvericin)**
  - Chemical Formula: C$_{45}$H$_{5}$N$_3$O$_o$
  - Molecular Weight: 783.9488
  - Chemical Structure:

In one embodiment, the invention provides an isolated or substantially pure compound A, or a salt thereof, and/or compound B, or a salt thereof:

- **B (Palmadorin M)**
  - Chemical Structure:

- **B (Beauvericin)**
  - Chemical Structure:

In certain embodiments, the invention pertains to the uses of compound A (palmadorin M) and/or compound B (beauvericin), or salts thereof, for treating neurodegenerative diseases, in particular, neurodegenerative diseases associated with abnormal accumulation of protein tau.

In some embodiments, the compounds of the present invention are at least 75% pure, preferably at least 90% pure, more preferably are more than 95% pure, and most preferably are more than 99% pure (substantially pure). The compounds of the present invention can also be synthesized.

The compounds and compositions of the present invention, through administration to a subject, are useful for treating or ameliorating neurodegenerative diseases or conditions, in particular, neurodegenerative diseases or conditions associated with abnormally high levels of protein tau and/or abnormal accumulation of protein tau in neurons. In some embodiments, the compounds and compositions are useful to treat or ameliorate Alzheimer’s disease or Parkinson’s disease.

In one aspect, the invention provides methods for treating or ameliorating a neurodegenerative disease or condition, particularly a disease or condition associated with abnormally high levels of protein tau and/or abnormal accumulation of protein tau in neurons, wherein the method comprises administering, to a subject in need of such treatment, an effective amount of a composition comprising a compound selected from compound A and compound B, or salts thereof.

Another aspect of the invention provides a method of reducing intracellular tau levels comprising administering, to cells comprising protein tau, an effective amount of compound A:
In another aspect, the invention provides a method of reducing intracellular tau levels comprising administering, to cells comprising protein tau, an effective amount of compound B:

![Diagram of compound B]

In yet another aspect, the invention provides a method of reducing intracellular tau levels comprising administering, to cells comprising protein tau, an effective amount of compounds selected from compound A (Palmarin M) and compound B (Beuvaricin), and combinations thereof.

The term “subject,” as used herein, describes an organism, including mammals, to which treatment with the compositions and compounds according to the subject invention can be administered. Mammalian species that can benefit from the disclosed methods include but are not limited to, apes, chimpanzees, orangutans, humans, monkeys; and other animals such as dogs, cats, horses, cattle, pigs, sheep, goats, chickens, mice, rats, guinea pigs, and hamsters. Typically, the subject is a human.

The term “tau protein” or any grammatical variation thereof (e.g., protein tau and tau etc.), as used herein, refers generally to any protein of the microtubule-associated tau protein family. Members of the tau family share the common features of a characteristic N-terminal segment, sequences of approximately 50 amino acids inserted in the N-terminal segment, a characteristic tandem repeat region consisting of 3 or 4 tandem repeats of 31-32 amino acids, and a C-terminal tail. Tau proteins of the present invention may be in a form of soluble tau intermediates, functional, aberrant, abnormally-truncated, mis-folded or mis-processed tau, and phosphorylated tau.

In some embodiments, tau protein of the invention is of mammalian origin, and more preferably, of human origin. Specifically, tau proteins of the subject invention include microtubule-associated protein translated from the human chromosomal sequence of GenBank Accession No. AH008595 and naturally-occurring mammalian variants or isoforms thereof. Six human brain tau isoforms are currently known, including tau52 (GenBank Accession No. NP_058525) (SEQ ID NO:1), tau441 (GenBank Accession No. NP_005901) (SEQ ID NO:2), tau383 (GenBank Accession No. NP_058518) (SEQ ID NO:3), tau758 (GenBank Accession No. NP_058519) (SEQ ID NO:4), tau776 (GenBank Accession No. NP_001116538) (SEQ ID NO:5), and tau412 (GenBank Accession No. NP_001116539) (SEQ ID NO:6).

The term “treatment” or any grammatical variation thereof (e.g., treat, treating and treatment etc.), as used herein, includes but is not limited to, ameliorating or alleviating a symptom of a disease or condition, reducing, suppressing, inhibiting, lessening, or affecting the progression, severity, and/or scope of a condition, chance of re-occurrence or returning of a disease after a remission. For instance, the term “treatment” includes (i) alleviating a symptom associated with a neurodegenerative disease in a patient diagnosed with the neurodegenerative disease; and/or (ii) relieving (such as attenuating the progress of) or remediating a neurodegenerative disease in a patient diagnosed with the neurodegenerative disease.

In some embodiments, the treatment methods of the present invention reduce tau levels and/or improve tau clearance. Normal, functional tau is less affected by clearance pathways in the cell than aberrant tau. In one embodiment, the treatment methods of the present invention modulate tau clearance by selectively targeting normal tau.

In an embodiment, the therapeutic composition is administered to a human subject who has symptoms of, or is diagnosed with, a neurodegenerative disease. In some embodiments, the therapeutic composition is administered to a human subject who has symptoms of, or is diagnosed with, a neurodegenerative disease associated with abnormal accumulation of protein tau. For instance, the therapeutic composition is administered to a human subject who has elevated levels of soluble protein tau and/or hyperphosphorylated protein tau in the nervous system, such as in the brain or cytoplasm of neuronal and glial cells. In addition, the therapeutic composition is administered to a human subject who exhibits pathologic features such as neurofibrillary tangles or senile plaques in neuronal cells and/or cell processes. In a specific embodiment, the therapeutic composition is administered to a human subject who has symptoms of, or is diagnosed with, Alzheimer’s disease.

The identification of subjects who are in need of treatment for a neurodegenerative disease is well within the knowledge and ability of one skilled in the art. By way of example, a clinician skilled in the art can readily identify, by the use of clinical tests, neurologic and physical examination, and medical/family history, those patients who are suffering from a neurodegenerative disease as well as those who are predisposed to developing a neurodegenerative disease and thus readily determine if an individual is in need of treatment. For instance, neurofibrillary tangles or senile plaques present in neuronal cells and/or cell processes can be determined using electron microscopy (EM) or other clinical techniques known in the art. In addition, spinal fluid or cerebral fluid samples or tissues samples from hippocampal tissue or frontal cortex tissue samples may be obtained from a subject and levels of protein tau present in the samples can be determined using routine techniques such as enzyme-linked immunosorbent assay (ELISA), western blot, and immunological assays.

The compounds and compositions of the present invention can be administered to the subject being treated by standard routes, including oral, inhalation, or parenteral administration including intravenous, subcutaneous, topical, transdermal, intradermal, transmucosal, intraperitoneal, intramuscular, intracapsular, intraorbital, intracardiac, transstrachial, subcutaneous, subcuticular, intraarticular, subcap-
The term “effective amount” or “therapeutically effective amount,” as used herein, refers to an amount that is capable of treating or ameliorating a disease or condition or otherwise capable of producing an intended therapeutic effect. For instance, the effective amount of the compounds and compositions of the present invention is an amount capable of reducing levels of protein tau in a subject. In certain embodiments, the effective amount enables a 5%, 25%, 50%, 75%, 90%, 95%, 99% and 100% reduction of levels of protein tau (e.g., soluble protein tau intermediates and/or aberrant protein tau) in a subject.

The amount of the therapeutic or pharmaceutical composition which is effective in treatment of a neurodegenerative disease will depend on the nature of the disease, condition or disorder and can be determined by standard clinical techniques. Illustratively, dosage levels of the administered active ingredients can be: intravenous, 0.01 to about 20 mg/kg; intraperitoneal, 0.01 to about 100 mg/kg; subcutaneous, 0.01 to about 100 mg/kg; intramuscular, 0.01 to about 100 mg/kg; orally 0.01 to about 200 mg/kg and preferably about 1 to 100 mg/kg; intranasal instillation, 0.01 to about 20 mg/kg; and aerosol, 0.01 to about 20 mg/kg of animal (body) weight.

Once improvement of the subject’s condition has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, may be reduced as a function of the symptoms to a level at which the improved condition is retained. When the symptoms have been alleviated to the desired level, treatment should cease. Subjects may however require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation/composition will also depend on the route of administration, and the seriousness of the disease, condition or disorder, and should be decided according to the judgment of the practitioner and each patient’s circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

The compounds and compositions of the present invention can be used to treat or ameliorate neurodegenerative diseases including, but not limited to, Alzheimer’s disease, Parkinson’s disease, Amyotrophic lateral sclerosis (ALS), Huntington’s disease, multiple sclerosis, Pick’s disease, fronto temporal dementia, cortico-basal degeneration, progressive supranuclear palsy, Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, and Kuru.

The compounds and compositions of the present invention can also be used to treat or ameliorate neurodegenerative diseases including, but not limited to, Down’s syndrome, Aryogrophic grain disease, parkinsonism dementia complex of Guam, non-Guamanian motor neurone disease with NFT, Niemann-Pick disease type C, subacute sclerosing panencephalitis, postencephalitic parkinsonism, dementia pugilistica, myotonic dystrophy, prion protein amyloid antipathy, and Hallervorden-Spatz disease.

The compounds and compositions of the present invention are particularly useful to treat or ameliorate a neurodegenerative disease involving tau pathologies (i.e., tauopathies) including, but not limited to, Alzheimer’s disease, Parkinson’s disease, frontotemporal dementia, frontotemporal dementia with parkinsonism, frontotemporal lobe dementia, pallidopontonigral degeneration, progressive supranuclear palsy, multiple system atrophy, multiple system atrophy with parkinsonism, and Hallervorden-Spatz disease.

Specifically, the compounds and compositions of the present invention are particularly useful to treat or ameliorate a disease or condition arising, at least in part, from abnormally high levels of protein tau in the nervous system, such as in cytoplasm of neuronal and glial cells and in neuronal and glial cell processes. Thus, the subject invention is particularly useful for treatment of neurodegenerative diseases and disorders, in which reduction of levels of protein tau in the nervous system would be beneficial.

In addition, the compounds and compositions of the subject invention are useful for alleviating or attenuating symptoms arising from or associated with neurodegenerative diseases, including cognitive dysfunction, impaired memory, impaired mental capacities, emotional disturbances, speech dysfunction, incontinence, tremor, postural instability, rigidity or stiff movement, muscle paralyisis, and pain.

In additional aspects, the invention provides pharmaceutical compositions comprising a therapeutically effective amount of any of compounds A and/or B and a pharmaceutically acceptable carrier or adjuvant.

The terms “pharmaceutically acceptable”, “physiologically tolerable” and grammatical variations thereof, as used herein, include compositions, carriers, diluents and reagents, are used interchangeably, and represent that the materials are capable of administration to or upon a subject such as mammal.

The term “carrier” refers to an adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum oil such as mineral oil, vegetable oil such as peanut oil, soybean oil, and sesame oil, animal oil, or oil of synthetic origin. Particularly preferred pharmaceutical carriers for treatment of or amelioration of a neurodegenerative disease are carriers that can penetrate the blood/brain barrier.

Suitable carriers also include ethanol, dimethyl sulfoxide, glycerol, silica, alumina, starch, sorbitol, inositol, xylitol, D-xylene, mannitol, powdered cellulose, microcrystalline cellulose, talc, colloidal silicon dioxide, calcium carbonate, calcium phosphate, calcium aluminium silicate, aluminium hydroxide, sodium starch phosphate, lecithin, and equivalent carriers and diluents. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions.

Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol and the like. The therapeutic composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

The amount of active ingredient (i.e., one or more of compounds A or B) that may be combined with the carrier materials to produce a single dosage form will vary, depend-
In general, a therapeutic composition contains from about 5% to about 95% active ingredient (w/w). More specifically, a therapeutic composition contains from about 20% (w/w) to about 80% or about 30% to about 70% active ingredient (w/w).

[0051] The compounds and compositions can be formulated according to known methods for preparing pharmaceutically useful compositions. Formulations are described in detail in a number of sources which are well known and readily available to those skilled in the art. For example, Remington’s Pharmaceutical Science by E. W. Martin describes formulations which can be used in connection with the present invention. In general, the compositions of the present invention will be formulated such that an effective amount of the bioactive compound(s) is/are combined with a suitable carrier in order to facilitate effective administration of the composition.

[0052] The therapeutic or pharmaceutical compositions of the invention can also be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, ethylenediamine, histidine, procaine, etc.

[0053] The preparation of a pharmacological composition that contains active ingredients dissolved or dispersed therein is well understood in the art and need not be limited based on formulation. Typically such compositions are prepared as injectables, either as liquid solutions or suspensions; however, solid forms suitable for solution, or suspensions, in liquid prior to use also can be prepared. The preparation also can be emulsified, such as oil-in-water emulsion.

[0054] The compounds and compositions of the present invention in prescription amounts can be readily made into any form of drug, suitable for administering to humans or other animals. Suitable forms include, for example, tinctures, decoctions, and dry extracts. These can be taken orally, applied through venous injection, mucous membranes or inhalation. The active ingredient(s) can also be formulated into capsules, powder, pellets, pastille, suppositories, oral solutions, pasteurized gastroenteric suspension injections, small or large amounts of injection, frozen powder injections, pasteurized powder injections and the like.

EXAMPLES

[0055] All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

[0056] Following are examples that illustrate procedures for practicing the invention. These examples should not be construed as limiting. All percentages are by weight and all solvent mixture proportions are by volume unless otherwise noted.

Example 1
Palmadorin M Extraction and Characterization

[0057] 600 g of freeze-dried Antarctic nudibranchs, Astrodoris kerguilenensis, collected by hand via SCUBA off the Palmer Station in the Western Antarctic Peninsula (3-40 m depth range), were first extracted by DCM/MeOH (1:1) then EtOAc/CH₂O⁻H (1:1). Both resulting extracts were combined and fractionated by normal phase MPLC using gradient conditions from 100% hexanes to 100% ethyl acetate to 100% methanol. The separation provided 10 MPLC fractions. The last 8 fractions were combined and purified by reversed-phase semi-preparative HPLC (40-100% MeOH/H₂O over 70 minutes) to provide 16 fractions. Frac tion 13 (47 min) yielded 10.1 mg of palmadorin M (Maschek J. A., 2011 et Maschek J. A. et al., 2012).

![Palmadorin M Chemical Formula: C_{23}H_{38}O_4](image)

Colorless oil; [α]_D^20-18 (c 0.1, CHCl₃); UV (MeOH) λmax (ε) 230 (4.38) nm; IR (thin film) 3429 (br), 2935, 1696, 1645, 1214 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 5.72 (H, s, H-14), 4.93 (H, s, H-2'), 4.71 (H, t, H-17b), 4.52 (H, t, H-17a), 3.83 (2H, m, H-1'), 3.83 (2H, m, H-3'), 2.18 (1H, m, H-7b), 2.15 (3H, s, H₂-16), 2.04 (1H, m, H-7a), 2.04 (1H, m, H-12b), 1.87 (1H, m, H-12a), 1.70 (1H, m, H-11b), 1.63 (1H, m, H-2b), 1.62 (1H, m, H-6b), 1.53 (1H, m, H-1b), 1.51 (1H, m, H-9), 1.47 (1H, m, H-11a), 1.44 (1H, m, H-2a), 1.42 (1H, m, H-3b), 1.29 (1H, m, H-5a), 1.28 (1H, m, H-5), 1.18 (1H, m, H-3a), 1.16 (1H, m, H-1a), 0.92 (3H, s, H₂-20), 0.88 (3H, s, H₂-19), 0.81 (3H, s, H₁-18); ¹³C NMR (125 MHz, CDCl₃) 166.8 (C-15), 163.2 (C-13), 148.7 (C-8), 114.5 (C-14), 109.9 (C-17), 74.2 (C-2'), 62.3 (C-1'), 62.3 (C-3'), 57.8 (C-9), 45.8 (C-5), 42.6 (C-3), 39.8 (C-12), 38.0 (C-10), 36.7 (C-1), 33.4 (C-19), 33.2 (C-4), 31.5 (C-7), 24.7 (C-11), 23.5 (C-6), 22.3 (C-20), 22.1 (C-18), 19.4 (C-16), 19.1 (C-2), HRMS m/z 401.2648 [M+Na]^+ (C_{23}H_{38}O_4Na requires 401.2668).

Example 2
Beauvericin Extraction and Characterization

[0058] Fungi Collection, Culture Preparation, Isolation and Scale Up:

[0059] Segments of approximately 1-2 mm² of mangrove samples were plated on malt extract freshwater agar. Fungal growth was examined every day for two weeks and then twice a week for at least one month for isolation of pure fungal strain. Pure fungal cultures were grown for scale up to 2 L total volume in liquid medium which contained 1% w/v glucose, 0.1% w/v yeast extract and 0.2% w/v peptone (3 weeks) for extraction, separation and pure metabolite identification (Calcule et al. 2013).

[0060] Beauvericin:

[0061] 2.3 g from a freeze-dried scale up of fungus strain collection # EGO9-15D-2, isolated from the Florida Everglades bark of Coccoloba uvifera, was extracted by MeOH. The methanolic extract was separated by reverse phase
MPLC using gradient from H₂O/10% MeOH to 100% MeOH to give 6 fractions. Fraction 5 was selected to be further chromatographed by normal phase MPLC using a gradient from 100% hexane to 100% EtOAc and provided 6 fractions. Fraction 4 was purified on reverse phase semi-preparative HPLC using isocratic H₂O/55% ACN yielding 206.2 mg of Beauvericin (trimer). (Beau J. 2012)

Colorless film; ¹H NMR (500 MHz, CDC13) 7.26-7.14 (3H, m, H-12), 7.26-7.14 (6H, m, H-11), 7.26-7.14 (6H, m, H-10), 5.62 (3H, s, H-6), 4.81 (3H, d, H-3), 3.39 (3H, dd, H-8a), 3.03 (9H, s, H-7), 2.93 (3H, dd, H-8b), 1.93 (3H, dq, H-13), 0.78 (9H, d, H-14), 0.35 (9H, d, H-15); ¹³C NMR (125 MHz, CDCl3) 170.0 (C-1), 169.9 (C-4), 136.4 (C-9), 128.7 (C-11), 128.5 (C-10), 126.8 (C-12), 75.7 (C-6), 56.8 (C-3), 34.7 (C-7), 31.9 (C-8), 29.7 (C-13), 18.4 (C-14), 17.1 (C-15); LRESIMS m/z 784.4 [M+H]+—Note: the ¹H and ¹³C NMR data matched to the data from the literature (Gupta, S. et al. 1991);

Example 3
Palmadorin M and Beauvericin Preferentially Reduce Phosphorylated Tau

[0062] Compounds effects on tau activity/level were determined by a previously described method (Jinwal et al J. Neurosci. 2009 Sep. 30, 29(39):12079-88). In brief, human tau transfected HeLa Cells were treated with Compounds for 24 hours. Cells were harvested using MPER reagent containing protease inhibitor and phosphatase inhibitor. Samples were analyzed by western blot. pS199-202 antibody was used to detect phospho tau level. Total tau levels were detected by tau H-150 and/or tau 46 antibodies.

HeLa cells were transfected with wild-type human tau (A) and mutant P301L human tau (B) (FIG. 1). After 24 hours, cells were treated with either palmadorin M or beauvericin for 24 hours. Western blot analysis of samples showed potent reduction in phosphorylated (pS199-202) wild type and mutant P301L tau at various doses of palmadorin M and beauvericin. Tau H-150 antibody tested for N-terminal tau showed increase in tau level. Tau 46 antibody tested for C-terminal tau showed moderate change in tau level.

[0066] It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims. In addition, any elements or limitations of any invention or embodiment thereof disclosed herein can be combined with any and/or all other elements or limitations (individually or in any combination) or any other invention or embodiment thereof disclosed herein, and all such combinations are contemplated with the scope of the invention without limitation thereeto.

REFERENCES


-continued

Gln Asp Gln Glu Gly Asp Thr Asp Ala Gln Ala Leu Lys Ala Glu Glu Ala 35 40 45
Gly Ile Gly Asp Thr Pro Ser Leu Asp Glu Ala Ala Gly His Val 50 55 60
Thr Gln Ala Arg Met Val Ser Lys Ser Lys Asp Gly Thr Gly Ser Asp 65 70 75 80
Asp Lys Lys Ala Lys Gly Ala Asp Gly Lys Thr Lys Ile Ala Thr Pro 85 90 95
Arg Gly Ala Ala Pro Pro Gly Gin Gly Gin Ala Asn Ala Thr Arg 100 105 110
Ile Pro Ala Lys Thr Pro Pro Ala Pro Lys Thr Pro Pro Ser Ser Gly 115 120 125
Glu Pro Pro Lys Ser Gly Asp Arg Ser Gly Tyr Ser Pro Gly Ser 130 135 140
Pro Gly Thr Pro Gly Ser Arg Ser Arg Thr Pro Ser Leu Pro Thr Pro 145 150 155 160
Pro Thr Arg Glu Pro Lys Lys Val Ala Val Val Arg Thr Pro Lys 165 170 175
Ser Pro Ser Ser Ala Lys Ser Arg Leu Gin Thr Ala Pro Val Pro Met 180 185 190
Pro Asp Leu Lys Asn Val Lys Ser Lys Ile Gly Ser Thr Glu Asn Leu 195 200 205
Lys His Gln Pro Gly Gly Gly Lys Val Gin Ile Val Tyr Lys Pro Val 210 215 220
Amp Leu Ser Lys Val Thr Ser Lys Cys Gly Ser Leu Gly Asn Ile His 225 230 235 240
His Lys Pro Gly Gly Gly Gin Val Glu Val Lys Ser Glu Lys Leu Asp 245 250 255
Phe Lys Asp Arg Val Gin Ser Lys Ile Gly Ser Leu Asp Asn Ile Thr 260 265 270
His Val Pro Gly Gly Gin Lys Val Ile Gly Thr His Lys Leu Thr 275 280 285
Phe Arg Glu Asn Ala Lys Ala Lys Thr Asp His Gly Ala Glu Ile Val 290 295 300
Tyr Lys Ser Pro Val Val Ser Gly Asp Thr Ser Pro Arg His Leu Ser 305 310 315 320
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Ala Thr Leu Ala Asp Glu Val Ser Ala Ser Leu Ala Lys Gin Gly Leu 340 345 350

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&lt;212&gt; TYPE: PRT
&lt;213&gt; ORGANISM: Homo sapiens

&lt;400&gt; SEQUENCE: 2

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Gln Thr Pro Thr Glu Asp Gly Ser Gly Glu Pro Gly Ser Gly Thr Ser
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Asp Arg Ser Gly Tyr Ser Ser Pro Gly Ser Pro Gly Thr Pro Gly Ser
 195 200 205
Arg Ser Arg Thr Pro Ser Leu Pro Thr Pro Pro Thr Arg Glu Pro Lys
 210 215 220
Lys Val Ala Val Val Arg Thr Pro Ser Pro Ser Ser Ala Lys
 225 230 235 240
Ser Arg Leu Gln Thr Ala Pro Val Pro Met Pro Ser Leu Lys Asn Val
 245 250 255
Lys Ser Lys Ile Gly Ser Thr Glu Asn Leu Lys His Gln Pro Gly Gly
 260 265 270
Gly Lys Val Gln Ile Ile Asn Lys Leu Asp Leu Ser Asn Val Gln
 275 280 285
Ser Lys Cys Gly Ser Lys Asp Asn Ile Lys His Val Pro Gly Gly Gly
 290 295 300
Ser Val Gln Ile Val Tyr Lys Pro Val Asp Leu Ser Lys Val Thr Ser
 305 310 315 320
Lys Cys Gly Ser Leu Gly Asn Ile His His Lys Pro Gly Gly Gly Gln
 325 330 335
Val Glu Val Lys Ser Glu Leu Asp Phe Lys Asp Val Gln Ser
 340 345 350
Lys Ile Gly Ser Leu Asp Asn Ile Thr His Val Pro Gly Gly Gly Asn
 355 360 365
Lys Lys Ile Glu Thr His Lys Leu Thr Phe Arg Glu Asn Ala Lys Ala
 370 375 380
Lys Thr Asp His Gly Ala Glu Ile Val Tyr Lys Ser Pro Val Val Ser
 385 390 395 400
Gly Asp Thr Ser Pro Arg His Leu Ser Asn Val Ser Ser Thr Glu Ser
 405 410 415
Ile Asp Met Val Asp Ser Pro Gln Leu Ala Thr Leu Ala Asp Glu Val
 420 425 430
Ser Ala Ser Leu Ala Lys Gin Gly Leu
 435 440
<210> SEQ ID NO 3
<211> LENGTH: 383
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

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Gln Asp Gln Glu Gly Asp Thr Ala Gly Leu Ala Glu Glu Ala
35 40 45
Gly Ile Gly Asp Thr Pro Ser Leu Glu Asp Ala Ala Gly His Val
50 55 60
Thr Gln Ala Arg Met Val Ser Lys Ser Lys Asp Gly Thr Gly Ser Asp
65 70 75 80
Asp Lys Lys Ala Lys Gly Ala Asp Gly Lys Thr Lys Ile Ala Thr Pro
85 90 95
Arg Gly Ala Ala Pro Pro Gly Glu Gly Glu Ala Asn Ala Thr Arg
100 105 110
Ile Pro Ala Lys Thr Pro Ala Pro Lys Thr Pro Pro Ser Ser Gly
115 120 125
Glu Pro Pro Lys Ser Gly Asp Arg Ser Gly Tyr Ser Ser Pro Gly Ser
130 135 140
Pro Gly Thr Pro Gly Ser Arg Ser Arg Thr Pro Ser Leu Pro Thr Pro
145 150 155 160
Pro Thr Arg Glu Pro Lys Lys Ala Val Val Arg Thr Pro Pro Lys
165 170 175
Ser Pro Ser Ser Ala Lys Ser Arg Leu Glu Thr Ala Pro Val Pro Met
180 185 190
Pro Asp Leu Lys Asn Val Lys Ser Lys Ile Gly Ser Thr Glu Asn Leu
195 200 205
Lys His Gln Pro Gly Gly Lys Val Gin Ile Ile Asn Lys Lys Leu
210 215 220
Asp Leu Ser Asn Val Gin Ser Lys Cyd Gly Ser Lys Asp Asn Ile Lys
225 230 235 240
His Val Pro Gly Gly Ser Val Gin Ile Val Tyr Lys Pro Val Asp
245 250 255
Leu Ser Lys Val Thr Ser Lys Cys Gly Ser Leu Gly Asn Ile His His
260 265 270
Lys Pro Gly Gly Gly Glu Val Gly Val Lys Ser Gly Lys Leu Asp Phe
275 280 285
Lys Asp Arg Val Gin Ser Lys Ile Gly Ser Asp Asn Ile Thr His
290 295 300
Val Pro Gly Gly Asn Lys Ser Glu Thr His Lys Leu Thr Phe
305 310 315 320
Arg Glu Asn Ala Lys Ala Lys Thr Asp His Gly Ala Glu Ile Val Tyr
325 330 335
Lys Ser Pro Val Val Ser Gly Asp Thr Ser Pro Arg His Leu Ser Asn
340 345 350
Val Ser Ser Thr Gly Ser Ile Asp Met Val Asp Ser Pro Glu Leu Ala
355 360 365
Thr Leu Ala Asp Glu Val Ser Ala Ser Leu Ala Lys Gln Gly Leu

<210> SEQ ID NO 4
<211> LENGTH: 758
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

Met Ala Glu Pro Arg Gln Glu Phe Glu Val Met Glu Asp His Ala Gly
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Thr Tyr Gly Leu Gly Asp Arg Lys Asp Gin Gly Gly Tyr Thr Met His
 20  25  30
Gln Asp Gin Glu Gly Asp Thr Asp Ala Gly Leu Lys Glu Ser Pro Leu
 35  40  45
Gln Thr Pro Thr Glu Asp Gly Ser Glu Glu Pro Gly Ser Glu Thr Ser
 50  55  60
Asp Ala Lys Ser Thr Pro Thr Ala Glu Asp Val Thr Ala Pro Leu Val
 65  70  75  80
Asp Glu Gly Ala Pro Gly Lys Gin Ala Ala Ala Asp Pro His Thr Glu
 85  90  95
Ile Pro Glu Gly Thr Thr Ala Glu Ala Gly Ile Gly Asp Thr Pro
100 105 110
Ser Leu Glu Asp Glu Ala Gly His Val Thr Gin Glu Pro Glu Ser
115 120 125
Gly Lys Val Val Gin Glu Gly Phe Leu Arg Glu Pro Gly Pro Gly
130 135 140
Leu Ser His Gin Leu Met Ser Gly Met Pro Gly Ala Pro Leu Leu Pro
145 150 155 160
Glu Gly Pro Arg Glu Ala Thr Arg Gin Pro Ser Gly Thr Gly Pro Glu
165 170 175
Asp Thr Glu Gly Arg Asp Ala Pro Glu Leu Leu Lys His Gin Leu
180 185 190
Leu Gly Asp Leu His Gin Glu Gly Pro Pro Leu Lys Gly Ala Gly Gly
195 200 205
Lys Glu Arg Pro Gly Ser Lys Glu Glu Val Asp Glu Asp Arg Asp Val
210 215 220
Asp Glu Ser Ser Pro Gin Asp Ser Pro Ser Lys Ala Ser Pro Ala
225 230 235 240
Gln Asp Gly Arg Pro Gin Thr Ala Ala Arg Ala Thr Ser Ile
245 250 255
Pro Gly Phe Pro Ala Glu Gly Ala Ile Pro Leu Pro Val Asp Phe Leu
260 265 270
Ser Lys Val Ser Thr Glu Ile Pro Ala Ser Glu Pro Asp Gly Pro Ser
275 280 285
Val Gly Arg Ala Lys Gin Asp Ala Pro Leu Gin Phe Thr Phe His
290 295 300
Val Glu Ile Thr Pro Asp Val Gin Lys Gin Ala His Ser Glu Glu
305 310 315 320
His Leu Gly Arg Ala Ala Phe Pro Gly Ala Pro Gly Glu Gly Pro Glu
325 330 335
Ala Arg Gly Pro Ser Leu Gly Glu Asp Thr Lys Glu Ala Asp Leu Pro
Glu Pro Ser Glu Lys Gln Pro Ala Ala Ala Pro Arg Gly Lys Pro Val 340 345 350
355 360 365
Ser Arg Val Pro Gln Leu Lys Ala Arg Met Val Ser Lys Ser Lys Asp 370 375 380
Gly Thr Gly Ser Asp Asp Lys Ala Lys Thr Ser Thr Arg Ser Ser 385 390 395 400
Ala Lys Thr Leu Lys Arg Pro Cys Leu Ser Pro Lys His Pro Thr 405 410 415
Pro Gly Ser Ser Asp Pro Leu Ile Gln Pro Ser Ser Pro Ala Val Cys 420 425 430
435 440 445
Thr Gly Ser Ser Gly Ala Lys Glu Met Lys Leu Lys Gly Ala Asp Gly 450 455 460
Lys Thr Lys Ile Ala Thr Pro Arg Gly Ala Ala Pro Pro Gly Gln Lys 465 470 475 480
Gly Gln Ala Asn Ala Thr Arg Ile Pro Ala Lys Thr Pro Pro Ala Pro 485 490 495
499 500 505 510
Gly Tyr Ser Ser Pro Gly Ser Pro Gly Thr Pro Gly Ser Arg Ser Arg 515 520 525
Thr Pro Ser Leu Pro Thr Pro Thr Arg Glu Pro Lys Val Ala 530 535 540
545 550 555 560
Val Val Arg Thr Pro Pro Lys Ser Pro Ser Ala Lys Ser Arg Leu 565 570 575 580
585 590 595 600
Gln Thr Ala Pro Val Pro Met Pro Asp Leu Lys Asn Val Lys Ser Lys 595 600 605
Ile Gly Ser Thr Glu Asn Leu Lys His Gin Pro Gly Gly Gly Lys Val 605 610 615 620
Gln Ile Ile Asn Lys Leu Asp Leu Ser Asn Val Gin Ser Lys Cys 625 630 635 640
645 650 655 660
Gly Ser Lys Asp Asn Ile His Val Pro Gly Gly Gly Ser Val Gln 665 670 675 680 685
Ile Val Tyr Lys Pro Val Asp Leu Ser Lys Val Thr Ser Lys Cys Gly 690 695 700 705 710 715 720
Ser Leu Gly Asn Ile His His Lys Pro Gly Gly Gly Gin Val Glu Val 725 730 735
Lys Ser Glu Lys Leu Asp Phe Lys Arg Val Gin Ser Lys Ile Gly 740 745 750
Leu Ala Lys Gln Gly Leu

<210> SEQ ID NO 5
<211> LENGTH: 776
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

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Ala Ser Leu Ala Lys Gln Gly Leu 790 795

<210> SEQ ID NO: 6
<211> LENGTH: 412
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6
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Gln Asp Gln Glu Gly Asp Thr Ala Gly Leu Lys Gly Ser Pro Leu 35  40  45
Gln Thr Pro Thr Glu Asp Gly Ser Glu Pro Gly Ser Glu Thr Ser 50  55  60
Asp Ala Lys Ser Thr Pro Thr Ala Glu Ala Ala Gly Ala Gly Ile Gly 65  70  75  80
Asp Thr Pro Ser Leu Glu Asp Glu Ala Ala Gly His Val Thr Gln Ala 85  90  95
Arg Met Val Ser Lys Ser Lys Gly Thr Gly Ser Asp Arg Lys Lys 100 105 110
Ala Lys Gly Ala Asp Gly Lys Thr Lys Ile Ala Thr Pro Arg Gly Ala 115 120 125
Ala Pro Pro Gly Gln Gly Gly Ala Asn Ala Thr Arg Ile Pro Ala 130 135 140
Lys Thr Pro Pro Ala Pro Lys Thr Pro Pro Ser Ser Gly Glu Pro Pro 145 150 155 160
Lys Ser Gly Asp Arg Ser Gly Tyr Ser Ser Pro Gly Ser Pro Gly Thr 165 170 175
Pro Gly Ser Arg Ser Arg Ser Pro Ser Leu Pro Thr Pro Pro Thr Arg 180 185 190
Glu Pro Lys Lys Val Ala Val Val Arg Thr Pro Pro Lys Ser Pro Ser 195 200 205
Ser Ala Lys Ser Arg Leu Glu Thr Ala Pro Val Pro Met Pro Asp Leu 210 215 220
Lys Asn Val Lys Ser Lys Ile Gly Ser Thr Glu Asn Leu Lys His Gin 225 230 235 240
Pro Gly Gln Gly Lys Val Gln Ile Asn Lys Lys Leu Asp Leu Ser 245 250 255
Asn Val Gln Ser Lys Cys Gly Ser Lys Asp Asn Ile Lys His Val Pro 260 265 270
Gly Gly Gln Ser Val Gly Val Ile Val Tyr Lys Pro Val Asp Leu Ser Lys 275 280 285
Val Thr Ser Lys Cys Gly Ser Lys Asn Ile His His Lys Pro Gly 290 295 300
Gly Gly Gln Val Glu Val Lys Ser Glu Leu Asp Phe Lys Asp Arg 305 310 315 320
Val Gln Ser Lys Ile Gly Ser Leu Asp Asn Ile Thr His Val Pro Gly
We claim:

1. A method of reducing intracellular tau phosphorylation levels, wherein the method comprises administering, to cells comprising phosphorylated protein tau, an effective amount of compound B:

![Compound B](image)

2. The method according to claim 1, wherein the cells are in a subject in need of treatment for a neurodegenerative disease.

3. The method of claim 2, wherein the neurodegenerative disease is a tauopathy.

4. The method of claim 3, wherein the subject is a human.

5. The method of claim 4, wherein the neurodegenerative disease is selected from Alzheimer’s disease, Parkinson’s disease, frontotemporal dementia, frontotemporal dementia with Parkinsonism, frontotemporal lobe dementia, pallidopontonigral degeneration, progressive supranuclear palsy, multiple system tauopathy, multiple system tauopathy with presenile dementia, Wilhelmsen-Lynch disease, Pick’s disease, or Pick’s disease-like dementia.

6. The method of claim 4, wherein the neurodegenerative disease is Alzheimer’s disease.

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound selected from compound A and combinations thereof; and a pharmaceutically acceptable carrier or adjuvant.