



(12) APPLICATION

(11) 20171941

(13) A1

NORWAY

(19) NO

(51) Int Cl.

A61K 31/496 (2006.01)

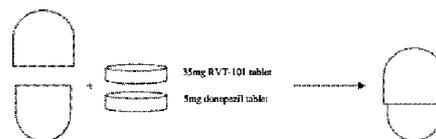
A61P 25/28 (2006.01)

Norwegian Industrial Property Office

(21)	Application nr	20171941	(86)	Int. application day and application nr	2016.05.06 PCT/US2016/031359
(22)	Application day	2017.12.05	(85)	Entry into national phase	2017.12.05
(24)	Date from which the industrial right has effect	2016.05.06	(30)	Priority	2015.05.07, US, 62/158,422 2015.05.15, US, 62/162,060 2015.05.15, US, 62/162,068 2015.05.15, US, 62/162,138 2015.05.15, US, 62/162,193 2015.05.21, US, 62/165,034 2015.05.29, US, 62/167,986 2015.05.29, US, 62/168,246 2015.06.01, US, 62/169,414 2015.06.19, US, 62/182,225 2015.07.06, US, 62/189,089 2015.07.10, US, 62/191,189 2015.08.05, US, 62/201,494 2015.08.05, US, 62/201,513 2015.10.09, US, 62/239,530 2015.11.05, US, 62/251,534 2015.11.17, US, 62/256,349 2015.11.30, US, 62/261,115 2016.01.29, US, 62/289,162 2016.02.01, US, 62/289,643
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(54)	Title	Methods of treating a neurodegenerative disease			
(57)	Abstract				

The present application relates to new uses of 5-HT6 receptor antagonists, specifically high doses of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline, and to the combination of 5-HT6 receptor antagonists, specifically 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline, with, an acetylcholinesterase inhibitor for the treatment of a neurodegenerative disease.

Illustration of a 35 mg 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline/5 mg donepezil capsule formulation

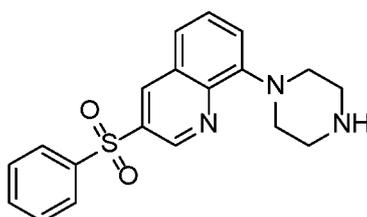


METHODS OF TREATING A NEURODEGENERATIVE DISEASE**CROSS REFERENCE TO RELATED APPLICATION**

[0001] This application claims the priority benefit under 35 U.S.C. 119(e) of U.S. Provisional Application No. 62/158,422, filed May 7, 2015; U.S. Provisional Application No. 62/162,060, filed May 15, 2015; U.S. Provisional Application No. 62/162,068, filed May 15, 2015; U.S. Provisional Application No. 62/162,138, filed May 15, 2015; U.S. Provisional Application No. 62/162,193, filed May 15, 2015; U.S. Provisional Application No. 62/165,034, filed May 21, 2015; U.S. Provisional Application No. 62/167,986, filed May 29, 2015; U.S. Provisional Application No. 62/168,246, filed May 29, 2015; U.S. Provisional Application No. 62/169,414, filed June 1, 2015; U.S. Provisional Application No. 62/182,225, filed June 19, 2015; U.S. Provisional Application No. 62/189,089, filed July 6, 2015; U.S. Provisional Application No. 62/191,189, filed July 10, 2015; U.S. Provisional Application No. 62/201,494, filed August 5, 2015; U.S. Provisional Application No. 62/201,513, filed August 5, 2015; U.S. Provisional Application No. 62/239,530, filed October 9, 2015; U.S. Provisional Application No. 62/251,534, filed November 5, 2015; U.S. Provisional Application No. 62/256,349, filed November 17, 2015; U.S. Provisional Application No. 62/261,115, filed November 30, 2015; U.S. Provisional Application No. 62/289,162, filed January, 29, 2016; and U.S. Provisional Application No. 62/289,643, filed February 1, 2016, the disclosures of which are incorporated by reference in their entirety. This application is also related to co-pending and co-owned U.S. Patent Application No. 15/____, filed on May 6, 2015, entitled "Compositions and Methods of Treating a Neurodegenerative Disease", (Attorney Docket No. 142956.01401), which is incorporated herein by reference in its entirety.

SUMMARY

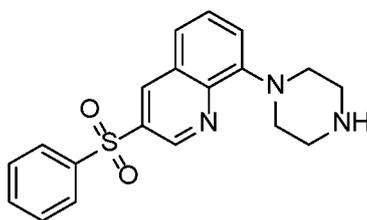
[0002] The present application relates to new uses of 5-HT₆ receptor antagonists, specifically 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline, **Formula I**,



Formula I

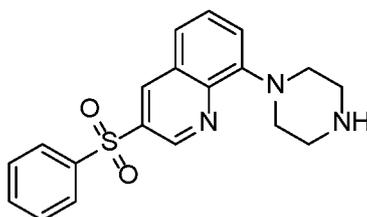
and to the combination of 5-HT₆ receptor antagonists, specifically high doses of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, with, at least one second therapeutic agent for the treatment of a neurodegenerative disease.

[0003] In one embodiment, the present application describes a method of treating a neurodegenerative disease in a subject in need thereof comprising administering to said patient a high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline **Formula I**

**Formula I**

or pharmaceutically acceptable salts, hydrates, polymorphs or solvates thereof.

[0004] In one embodiment, the present application describes a method of treating a neurodegenerative disease in a subject in need thereof comprising administering to said patient a combination of a high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline **Formula I**

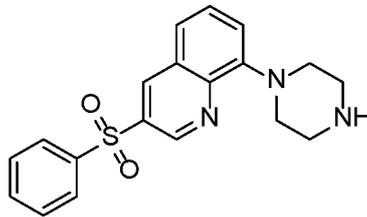
**Formula I**

or pharmaceutically acceptable salts, hydrates or solvates thereof, with a therapeutically effective amount of an acetylcholinesterase inhibitor.

[0005] In one embodiment, the present application describes a pharmaceutical composition for use in treating a neurodegenerative disease, comprising:

- a.) a high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline

Formula I



Formula I

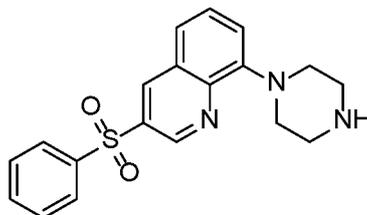
or pharmaceutically acceptable salts, hydrates or solvates thereof;

- b.) at least one acetylcholinesterase inhibitor; and
c.) at least one pharmaceutically acceptable excipient.

[0006] In one embodiment, the present application describes a pharmaceutical composition for use in treating a neurodegenerative disease, comprising:

- a.) a high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline

Formula I

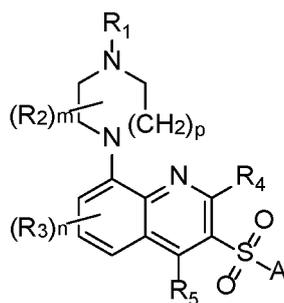


Formula I

or pharmaceutically acceptable salts, hydrates, polymorphs or solvates thereof; and

- b.) at least one pharmaceutically acceptable carrier or diluent.

[0007] In one embodiment, the present application describes 5-HT₆ receptor antagonists of **Formula II**:



Formula II

[0008] wherein: R_1 and R_2 independently represent hydrogen or C_{1-6} alkyl or R_1 is linked to R_2 to form a group $(CH_2)_2$, $(CH_2)_3$ or $(CH_2)_4$; R_3 , R_4 and R_5 independently represent hydrogen, halogen, cyano, $-CF_3$, $-CF_3O$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl or a group $-CONR_6R_7$; R_6 and R_7 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7-membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom; m represents an integer from 1 to 4, such that when m is an integer greater than 1, two R_2 groups may instead be linked to form a group CH_2 , $(CH_2)_2$ or $(CH_2)_3$; n represents an integer from 1 to 3; p represents 1 or 2; A represents a group $-Ar^1$ or $-Ar^2Ar^3$; Ar^1 , Ar^2 and Ar^3 independently represent an aryl group or a heteroaryl group, both of which may be optionally substituted by one or more (e.g. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6} alkoxy, aryl C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxy C_{1-6} alkyl, C_{3-7} cycloalkyl C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxy-carbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonyl C_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonyl C_{1-6} alkyl, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamido C_{1-6} alkyl, C_{1-6} alkylamido C_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamido C_{1-6} alkyl, arylcarboxamido C_{1-6} alkyl, aroyl, aroyl C_{1-6} alkyl, aryl C_{1-6} alkanoyl, or a group $CONR_8R_9$ or $SO_2NR_8R_9$, wherein R_8 and R_9 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7-membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom; or pharmaceutically acceptable salts, hydrates or solvates thereof.

BRIEF DESCRIPTION OF THE FIGURES

[0009] FIGURE 1 – Illustration of a 35 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline/5 mg donepezil capsule formulation. 35mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline immediate release tablet / 5mg donepezil immediate release tablet taken together in a suitable capsule with or without appropriate excipient backfill. 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline and donepezil tablet may be coated or uncoated, marked or unmarked. Donepezil tablets may be of a standard size produced by an approved generic manufacturer or may be shaped more specifically to fit the capsule. Shape may be round, cylindrical, oval, capsule, or otherwise configured to optimally fit within the volume of the capsule bottom. Tablets will be shaped such that automated capsule filling machinery may be employed for the manufacture. Capsule type may be chosen from commercially available and approved types.

[0010] FIGURE 2 – Illustration of a 35 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline/10 mg donepezil capsule formulation. 35mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline immediate release tablet / (2) 5mg donepezil immediate release tablet together in a suitable capsule with or without appropriate backfill excipient. 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline and donepezil tablet may be coated or uncoated, marked or unmarked. Donepezil tablets may be of a standard size produced by an approved generic manufacturer or may be shaped more specifically to fit the capsule. Shape may be round, cylindrical, oval, capsule, or otherwise configured to optimally fit within the volume of the capsule bottom. Tablets will be shaped such that automated capsule filling machinery may be employed for the manufacture. Capsule type may be chosen from commercially available and approved types.

[0011] FIGURE 3 – Illustration of a 35 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline/10 mg donepezil capsule formulation. 35mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline immediate release tablet / 10mg donepezil immediate release tablet together in a suitable capsule with or without appropriate backfill excipient. 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline and donepezil tablet may be coated or uncoated, marked or unmarked. Donepezil tablets may be of a standard size produced by an approved generic manufacturer or may be shaped more specifically to fit the capsule. Shape may be round, cylindrical, oval, capsule, or otherwise configured to optimally fit within the volume of the capsule bottom. Tablets will be shaped such that automated capsule filling machinery may be

employed for the manufacture. Capsule type may be chosen from commercially available and approved types.

[0012] FIGURE 4 – Illustration of a 35 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline/10 mg donepezil overcoated tablet formulation. 35mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline immediate release tablet / (2) 5mg donepezil immediate release tablets together in a suitable pharmaceutical or food grade coating. Coating encases three tablets. Coating is of sufficient mechanical strength to resist breakage. Coating is composed of pharmaceutically approved and/or food-grade appropriate constituents. Encasement may be transparent or opaque.

[0013] FIGURE 5 – Illustration of a 35 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline/10 mg donepezil overcoated tablet formulation. 35mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline immediate release tablet / 10mg donepezil immediate release tablet together in a suitable pharmaceutical or food grade coating. Coating encases three tablets. Coating is of sufficient mechanical strength to resist breakage. Coating is composed of pharmaceutically approved and/or food-grade appropriate constituents. Encasement may be transparent or opaque.

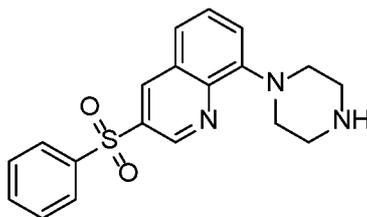
[0014] FIGURE 6 – Illustration of a 35 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline/5 mg donepezil overcoated tablet formulation. 35mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline immediate release tablet / 5mg donepezil immediate release tablet together in a suitable pharmaceutical or food grade coating. Coating encases three tablets. Coating is of sufficient mechanical strength to resist breakage. Coating is composed of pharmaceutically approved and/or food-grade appropriate constituents. Encasement may be transparent or opaque.

[0015] FIGURE 7 - Illustration of a 35 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline/5 mg donepezil or 35 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline/10 mg donepezil encased caplet formulation. 35mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline immediate release tablet / 5mg donepezil immediate release tablet or 35mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline immediate release tablet / 10 mg donepezil immediate release tablet together in a suitable pharmaceutical or food grade coating. Coating encases two tablets. Coating is of sufficient mechanical strength to resist breakage. Coating is composed

of pharmaceutically approved and/or food-grade appropriate constituents. Encasement may be transparent or opaque.

DESCRIPTION

[0016] The 5-HT₆ receptor antagonist 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline
Formula I



Formula I

has been demonstrated to have a dose dependent increase in efficacy vs. placebo in the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) score in clinical trial between 15 mg and 35 mg doses. However, these potential benefits were initially tempered with the potential for adverse events, in particular, the Central Nervous System (CNS) toxicity observed in dogs and rabbits described below. Applicants have surprisingly found that a high dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline is both efficacious and non-toxic contrary to the predictions of the animal models.

[0017] Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably C₁₋₄ alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

[0018] The term "aryl" includes phenyl and naphthyl. The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl,

benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like. Heteroaryl groups, as described above, may be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom except where otherwise indicated above. It will be appreciated that wherein the above mentioned aryl or heteroaryl groups have more than one substituent, said substituents may be linked to form a ring, for example a carboxyl and amine group may be linked to form an amide group.

[0019] The compounds described herein can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds described herein should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

[0020] The compounds described herein may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, e.g. as the hydrate. This invention includes within its scope stoichiometric solvates (e.g. hydrates) as well as compounds containing variable amounts of solvent (e.g. water). Certain compounds described herein are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

[0021] As used herein, the term "high dose" refers to a dose of a 5-HT₆ receptor antagonist, that may cause convulsions in a subject to which it is administered. As used herein, the term "high dose" refers to a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that may cause convulsions in a subject to which it is administered; would be expected to exceed the maximum tolerated dose for the subject to which it is administered; is associated with systemic exposures characterized by an AUC_{tau-ss} of about 8.2 µg.h/ml, a C_{max} of about 0.26 µg/ml; or a combination thereof; is associated with systemic exposures characterized by

an AUC, C_{\max} , or combinations thereof, that are about 2 to about 3 times higher than the mean clinical exposure achieved at the proposed clinical dose for monotherapy with 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline (i.e. mean $AUC_{\tau\text{-ss}}$ of about 3.2 $\mu\text{g}\cdot\text{h}/\text{ml}$ and C_{\max} of about 0.180 $\mu\text{g}/\text{ml}$); or is associated with a recorded systemic clinical exposure that is greater than the highest recorded systemic clinical exposure ($AUC_{0-\infty}$ of about 9.25 $\mu\text{g}\cdot\text{h}/\text{ml}$ and C_{\max} of about 0.293 $\mu\text{g}/\text{ml}$); or combinations thereof. In some embodiments, the term “high dose” refers to a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than about 10mg/kg/day. In some embodiments, the term “high dose” refers to a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than 15 mg/day. In some embodiments, the term “high dose” refers to a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than about 35 mg/day.

[0022] As used herein, the term “high daily dose” refers to the amount of a 5-HT₆ receptor antagonist, per day that is administered or prescribed to a patient. This amount can be administered in multiple unit doses or in a single unit dose, in a single time during the day or at multiple times during the day. As used herein, the term “high daily dose” refers to the amount of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline per day that is administered or prescribed to a patient. This amount can be administered in multiple unit doses or in a single unit dose, in a single time during the day or at multiple times during the day. In some embodiments, a high daily dose is a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that may cause convulsions in a subject to which it is administered; would be expected to exceed the maximum tolerated dose for the subject to which it is administered; is associated with systemic exposures characterized by an $AUC_{\tau\text{-ss}}$ of about 8.2 $\mu\text{g}\cdot\text{h}/\text{ml}$, a C_{\max} of about 0.26 $\mu\text{g}/\text{ml}$; or a combination thereof; is associated with systemic exposures characterized by an AUC, C_{\max} , or combinations thereof, that are about 2 to about 3 times higher than the mean clinical exposure achieved at the proposed clinical dose for monotherapy with 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline (i.e. mean $AUC_{\tau\text{-ss}}$ of about 3.2 $\mu\text{g}\cdot\text{h}/\text{ml}$ and C_{\max} of about 0.180 $\mu\text{g}/\text{ml}$); or is associated with a recorded systemic clinical exposure that is greater than the highest recorded systemic clinical exposure ($AUC_{0-\infty}$ of about 9.25 $\mu\text{g}\cdot\text{h}/\text{ml}$ and C_{\max} of about 0.293 $\mu\text{g}/\text{ml}$); or combinations thereof. In some embodiments, the term “high dose” refers to a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than about 10mg/kg/day. In some embodiments, the term “high dose” refers to a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than 15 mg/day. In some

embodiments, the term "high dose" refers to a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than about 35 mg/day.

[0023] As used herein, the terms "high dose" and "high daily dose" refer to the numerical amount of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline as measured in milligrams (mg), or any equivalent measure of mass, such as, for example, nanograms, grains, scruples, drams, ounces, slugs, grams, pounds and kilograms, thereof, between and inclusive of 36 mg and 300 mg. Specifically, the "high dose" and "high daily dose" of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline as described in the present application may be any value from the group consisting of: 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299 and 300.

[0024] As used herein, the term "about" means plus or minus 10 % of a given value. For example, "about 50 %" means in the range of 45% to 55%.

[0025] As used herein, the terms "combination," "combined," and related terms refer to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a described compound may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a described compound, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle. Two or more agents are typically considered to be administered "in combination" when a patient or individual is simultaneously exposed to both

agents. In many embodiments, two or more agents are considered to be administered "in combination" when a patient or individual simultaneously shows therapeutically relevant levels of the agents in a particular target tissue or sample (e.g., in brain, in serum, etc.).

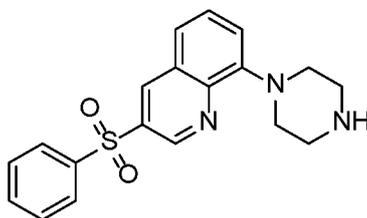
[0026] The term "pharmaceutically acceptable carrier" refers to a non-toxic carrier that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof. Pharmaceutically acceptable carriers that may be used in these compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Pharmaceutically acceptable carriers that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat and self-emulsifying drug delivery systems (SEDDS) such as α -tocopherol, polyethyleneglycol 1000 succinate, or other similar polymeric delivery matrices.

[0027] The term "therapeutically effective amount" as used herein refers to the amount of active compound or pharmaceutical agent that elicits the 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).

DETAILED DESCRIPTION:

[0028] In one embodiment, the present application describes a method of treating a neurodegenerative disease in a subject in need thereof comprising administering to said patient a high daily dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline **Formula I**



Formula I

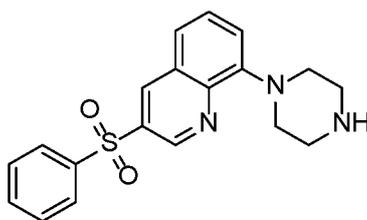
or pharmaceutically acceptable salts, hydrates, polymorphs or solvates thereof. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is provided at least once a day. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is provided to the subject by at least one route of administration selected from the group consisting of: orally; nasally; topically; buccally; sublingually; rectally; vaginally; and parenterally. Further embodiments are provided, wherein the at least one route of administration is orally. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is greater than 36 mg. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is administered once a day. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is 35 mg to 300 mg. Further embodiments are provided, wherein the high daily dose is 50 mg to 270 mg.

Further embodiments are provided, wherein the high daily dose is 60 mg to 230 mg. Further embodiments are provided, wherein the high daily dose is 70 mg to 200 mg. Further embodiments are provided, wherein the high daily dose is 70 mg. Further embodiments are provided, wherein the neurodegenerative disease is selected from Alzheimer's disease (including Alzheimer's disease with Lewy bodies, (AD)), Parkinson's disease (including Parkinson's disease chemically induced by exposure to environmental agents such as pesticides, insecticides, or herbicides and/or metals such as manganese, aluminum, cadmium, copper, or zinc, SNCA gene-linked Parkinson's disease, sporadic or idiopathic Parkinson's disease, or Parkin- or LRRK2-linked Parkinson's disease (PD)), autosomal-dominant Parkinson's disease, Diffuse Lewy Body Disease (DLBD) also known as Dementia with Lewy Bodies (DLB), Pure Autonomic Failure, Lewy body dysphagia, Incidental LBD, Inherited LBD (e.g., mutations of the alpha-synuclein gene, PARK3 and PARK4), multiple system atrophy (including Olivopontocerebellar Atrophy, Striatonigral Degeneration, Shy-Drager Syndrome (MSA)), combined Alzheimer's and Parkinson disease and/or MSA, Huntington's disease, synucleinopathies, disorders or conditions characterized by the presence of Lewy bodies, multiple sclerosis, Amyotrophic lateral sclerosis (ALS) dementia (including vascular dementia, Lewy body dementia, Parkinson's dementia, frontotemporal dementia), Down syndrome, Psychosis (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy such as, but not limited to, Parkinson's disease psychosis, Alzheimer's disease psychosis, Lewy body dementia psychosis), dyskinesia (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy), agitation (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy), conditions associated with dopaminergic therapy (including dystonia, myoclonus, or tremor), synucleinopathies, diseases, disorders or conditions associated with abnormal expression, stability, activities and/or cellular processing of α -synuclein, diseases, disorders or conditions characterized by the presence of Lewy bodies, and combinations thereof. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline is selected from a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that may cause convulsions in a subject to which it is administered; would be expected to exceed the maximum tolerated dose for the subject to which it is administered; is associated with systemic exposures characterized by an AUC_{1au-55} of about 8.2 $\mu\text{g}\cdot\text{h}/\text{ml}$, a C_{max} of about 0.26 $\mu\text{g}/\text{ml}$; or a combination thereof; is associated with systemic exposures characterized by an AUC, C_{max} , or combinations thereof, that are about 2 to about 3 times higher than the mean clinical exposure achieved at the proposed clinical dose

for monotherapy with 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline (i.e. mean $AUC_{\tau-ss}$ of about 3.2 $\mu\text{g}\cdot\text{h}/\text{ml}$ and C_{max} of about 0.180 $\mu\text{g}/\text{ml}$); or is associated with a recorded systemic clinical exposure that is greater than the highest recorded systemic clinical exposure ($AUC_{0-\infty}$ of about 9.25 $\mu\text{g}\cdot\text{h}/\text{ml}$ and C_{max} of about 0.293 $\mu\text{g}/\text{ml}$); a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than about 10mg/kg/day; a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than 15 mg/day; a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than about 35 mg/day or any combination thereof per day.

[0029] In one embodiment, the present application describes a method of treating a neurodegenerative disease in a subject in need thereof comprising administering to said patient a combination of a high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline

Formula I



Formula I

or pharmaceutically acceptable salts, hydrates or solvates thereof, with a therapeutically effective amount of an acetylcholinesterase inhibitor. Further embodiments are provided, wherein the neurodegenerative disease is selected from Alzheimer's disease (including Alzheimer's disease with Lewy bodies, (AD)), Parkinson's disease (including Parkinson's disease chemically induced by exposure to environmental agents such as pesticides, insecticides, or herbicides and/or metals such as manganese, aluminum, cadmium, copper, or zinc, SNCA gene-linked Parkinson's disease, sporadic or idiopathic Parkinson's disease, or Parkin- or LRRK2-linked Parkinson's disease (PD)), autosomal-dominant Parkinson's disease, Diffuse Lewy Body Disease (DLBD) also known as Dementia with Lewy Bodies (DLB), Pure Autonomic Failure, Lewy body dysphagia, Incidental LBD, Inherited LBD (e.g., mutations of the alpha-synuclein gene, PARK3 and PARK4), multiple system atrophy (including Olivopontocerebellar Atrophy, Striatonigral Degeneration, Shy-Drager Syndrome (MSA)), combined Alzheimer's and Parkinson disease and/or MSA, Huntington's disease, synucleinopathies, disorders or conditions characterized by the presence of Lewy bodies,

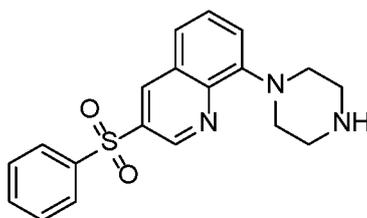
multiple sclerosis, Amyotrophic lateral sclerosis (ALS) dementia (including vascular dementia, Lewy body dementia, Parkinson's dementia, frontotemporal dementia), Down syndrome, Psychosis (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy such as, but not limited to, Parkinson's disease psychosis, Alzheimer's disease psychosis, Lewy body dementia psychosis), dyskinesia (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy), agitation (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy), conditions associated with dopaminergic therapy (including dystonia, myoclonus, or tremor), synucleinopathies, diseases, disorders or conditions associated with abnormal expression, stability, activities and/or cellular processing of α -synuclein, diseases, disorders or conditions characterized by the presence of Lewy bodies, and combinations thereof. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline is selected from a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that may cause convulsions in a subject to which it is administered; would be expected to exceed the maximum tolerated dose for the subject to which it is administered; is associated with systemic exposures characterized by an $AUC_{\tau-ss}$ of about 8.2 $\mu\text{g}\cdot\text{h}/\text{ml}$, a C_{max} of about 0.26 $\mu\text{g}/\text{ml}$; or a combination thereof; is associated with systemic exposures characterized by an AUC , C_{max} , or combinations thereof, that are about 2 to about 3 times higher than the mean clinical exposure achieved at the proposed clinical dose for monotherapy with 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline (i.e. mean $AUC_{\tau-ss}$ of about 3.2 $\mu\text{g}\cdot\text{h}/\text{ml}$ and C_{max} of about 0.180 $\mu\text{g}/\text{ml}$); or is associated with a recorded systemic clinical exposure that is greater than the highest recorded systemic clinical exposure ($AUC_{0-\infty}$ of about 9.25 $\mu\text{g}\cdot\text{h}/\text{ml}$ and C_{max} of about 0.293 $\mu\text{g}/\text{ml}$); a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than about 10mg/kg/day; a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than 15 mg/day; a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than about 35 mg/day or any combination thereof per day. Further embodiments are provided, wherein the acetylcholinesterase inhibitor is donepezil or pharmaceutically acceptable salts, hydrates, polymorphs or solvates thereof. Further embodiments are provided, wherein the therapeutically effective amount of donepezil is selected from about 5 mg, about 10 mg or about 23 mg per day. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is provided at least once a day. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is

provided to the subject by at least one route of administration selected from the group consisting of: orally; nasally; topically; buccally; sublingually; rectally; vaginally; and parenterally. Further embodiments are provided, wherein the at least one route of administration is orally. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is than 36 mg. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is administered once a day. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is 35 mg to 300 mg. Further embodiments are provided, wherein the high daily dose is 50 mg to 270 mg. Further embodiments are provided, wherein the high daily dose is 60 mg to 230 mg. Further embodiments are provided, wherein the high daily dose is 70 mg to 200 mg. Further, embodiments are provided, wherein the high daily dose is 70 mg.

[0030] In one embodiment, the present application describes a pharmaceutical composition for use in treating a neurodegenerative disease, comprising:

- a.) a high dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline **Formula**

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Formula I

or pharmaceutically acceptable salts, hydrates or solvates thereof;

- b.) at least one acetylcholinesterase inhibitor; and
c.) at least one pharmaceutically acceptable excipient.

Further embodiments are provided, wherein the neurodegenerative disease is selected from Alzheimer's disease (including mild or early-stage Alzheimer's disease, mild to moderate Alzheimer's disease, moderate or mid-stage Alzheimer's disease, moderate to severe

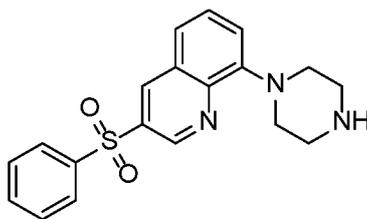
Alzheimer's disease, moderately severe Alzheimer's disease, severe Alzheimer's disease, Alzheimer's disease with Lewy bodies, (AD)), Parkinson's disease (including Parkinson's disease chemically induced by exposure to environmental agents such as pesticides, insecticides, or herbicides and/or metals such as manganese, aluminum, cadmium, copper, or zinc, SNCA gene-linked Parkinson's disease, sporadic or idiopathic Parkinson's disease, or Parkinson's- or LRRK2-linked Parkinson's disease (PD)), autosomal-dominant Parkinson's disease, Diffuse Lewy Body Disease (DLBD) also known as Dementia with Lewy Bodies (DLB), Pure Autonomic Failure, Lewy body dysphagia, Incidental LBD, Inherited LBD (e.g., mutations of the alpha-synuclein gene, PARK3 and PARK4), multiple system atrophy (including Olivopontocerebellar Atrophy, Striatonigral Degeneration, Shy-Drager Syndrome (MSA)), combined Alzheimer's and Parkinson disease and/or MSA, Huntington's disease, synucleinopathies, disorders or conditions characterized by the presence of Lewy bodies, multiple sclerosis, Amyotrophic lateral sclerosis (ALS) dementia (including vascular dementia, Lewy body dementia, Parkinson's dementia, frontotemporal dementia), Down syndrome, Psychosis (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy such as, but not limited to, Parkinson's disease psychosis, Alzheimer's disease psychosis, Lewy body dementia psychosis), dyskinesia (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy), agitation (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy), conditions associated with dopaminergic therapy (including dystonia, myoclonus, or tremor), synucleinopathies, diseases, disorders or conditions associated with abnormal expression, stability, activities and/or cellular processing of α -synuclein, diseases, disorders or conditions characterized by the presence of Lewy bodies, and combinations thereof. Further embodiments are provided, wherein the high dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline is selected from a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that may cause convulsions in a subject to which it is administered; would be expected to exceed the maximum tolerated dose for the subject to which it is administered; is associated with systemic exposures characterized by an $AUC_{\tau_{1/2-ss}}$ of about 8.2 $\mu\text{g}\cdot\text{h}/\text{ml}$, a C_{max} of about 0.26 $\mu\text{g}/\text{ml}$; or a combination thereof; is associated with systemic exposures characterized by an AUC , C_{max} , or combinations thereof, that are about 2 to about 3 times higher than the mean clinical exposure achieved at the proposed clinical dose for monotherapy with 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline (i.e. mean $AUC_{\tau_{1/2-ss}}$ of about 3.2 $\mu\text{g}\cdot\text{h}/\text{ml}$ and C_{max} of about 0.180 $\mu\text{g}/\text{ml}$); or is associated with a recorded systemic clinical exposure that is greater than the highest recorded systemic clinical exposure ($AUC_{0-\infty}$ of

about 9.25 $\mu\text{g}\cdot\text{h}/\text{ml}$ and C_{max} of about 0.293 $\mu\text{g}/\text{ml}$); a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than about 10mg/kg/day; a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than 15 mg/day; a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than about 35 mg/day or any combination thereof per day. Further embodiments are provided, wherein the acetylcholinesterase inhibitor is donepezil or pharmaceutically acceptable salts, hydrates, polymorphs or solvates thereof. Further embodiments are provided, wherein the therapeutically effective amount of donepezil is selected from about 5 mg, about 10 mg or about 23 mg per day. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is provided at least once a day. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is provided to the subject by at least one route of administration selected from the group consisting of: orally; nasally; topically; buccally; sublingually; rectally; vaginally; and parenterally. Further embodiments are provided, wherein the at least one route of administration is orally. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is greater than 36 mg. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is administered once a day. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is 35 mg to 300 mg. Further embodiments are provided, wherein the high daily dose is 50 mg to 270 mg. Further embodiments are provided, wherein the high daily dose is 60 mg to 230 mg. Further embodiments are provided, wherein the high daily dose is 70 mg to 200 mg. Further embodiments are provided, wherein the high daily dose is 70 mg.

[0031] In one embodiment, the present application describes a pharmaceutical composition for use in treating a neurodegenerative disease, comprising:

- a.) a high dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline **Formula**

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**Formula I**

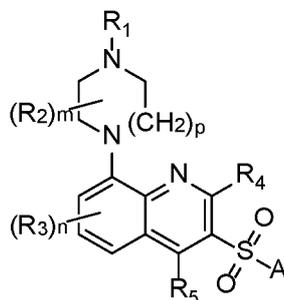
or pharmaceutically acceptable salts, hydrates, polymorphs or solvates thereof; and

- b.) at least one pharmaceutically acceptable carrier or diluent.

Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is provided at least once a day. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is provided to the subject by at least one route of administration selected from the group consisting of: orally; nasally; topically; buccally; sublingually; rectally; vaginally; and parenterally. Further embodiments are provided, wherein the at least one route of administration is orally. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is greater than 36 mg. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is once a day. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is 35 mg to 300 mg. Further embodiments are provided, wherein the high daily dose is 50 mg to 270 mg. Further embodiments are provided, wherein the high daily dose is 60 mg to 230 mg. Further embodiments are provided, wherein the high daily dose is 70 mg to 200 mg. Further embodiments are provided, wherein the high daily dose is 70 mg. Further embodiments are provided, wherein the neurodegenerative disease is selected from Alzheimer's disease (including Alzheimer's disease with Lewy bodies, (AD)), Parkinson's disease (including Parkinson's disease chemically induced by exposure to environmental agents such as pesticides, insecticides, or herbicides and/or metals such as manganese, aluminum, cadmium, copper, or zinc, SNCA gene-linked Parkinson's disease, sporadic or idiopathic Parkinson's disease, or Parkin- or LRRK2-linked Parkinson's disease (PD)), autosomal-dominant

Parkinson's disease, Diffuse Lewy Body Disease (DLBD) also known as Dementia with Lewy Bodies (DLB), Pure Autonomic Failure, Lewy body dysphagia, Incidental LBD, Inherited LBD (e.g., mutations of the alpha-synuclein gene, PARK3 and PARK4), multiple system atrophy (including Olivopontocerebellar Atrophy, Striatonigral Degeneration, Shy-Drager Syndrome (MSA)), combined Alzheimer's and Parkinson disease and/or MSA, Huntington's disease, synucleinopathies, disorders or conditions characterized by the presence of Lewy bodies, multiple sclerosis, Amyotrophic lateral sclerosis (ALS) dementia (including vascular dementia, Lewy body dementia, Parkinson's dementia, frontotemporal dementia), Down syndrome, Psychosis (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy such as, but not limited to, Parkinson's disease psychosis, Alzheimer's disease psychosis, Lewy body dementia psychosis), dyskinesia (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy), agitation (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy), conditions associated with dopaminergic therapy (including dystonia, myoclonus, or tremor), synucleinopathies, diseases, disorders or conditions associated with abnormal expression, stability, activities and/or cellular processing of α -synuclein, diseases, disorders or conditions characterized by the presence of Lewy bodies, and combinations thereof. Further embodiments are provided, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline is selected from a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that may cause convulsions in a subject to which it is administered; would be expected to exceed the maximum tolerated dose for the subject to which it is administered; is associated with systemic exposures characterized by an $AUC_{\tau-ss}$ of about 8.2 $\mu\text{g}\cdot\text{h}/\text{ml}$, a C_{max} of about 0.26 $\mu\text{g}/\text{ml}$; or a combination thereof; is associated with systemic exposures characterized by an AUC , C_{max} , or combinations thereof, that are about 2 to about 3 times higher than the mean clinical exposure achieved at the proposed clinical dose for monotherapy with 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline (i.e. mean $AUC_{\tau-ss}$ of about 3.2 $\mu\text{g}\cdot\text{h}/\text{ml}$ and C_{max} of about 0.180 $\mu\text{g}/\text{ml}$); or is associated with a recorded systemic clinical exposure that is greater than the highest recorded systemic clinical exposure ($AUC_{0-\infty}$ of about 9.25 $\mu\text{g}\cdot\text{h}/\text{ml}$ and C_{max} of about 0.293 $\mu\text{g}/\text{ml}$); a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than about 10mg/kg/day; a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than 15 mg/day; a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than about 35 mg/day or any combination thereof per day.

[0032] In one embodiment, the present application describes 5-HT₆ receptor antagonists of **Formula II**:



Formula II

wherein: R₁ and R₂ independently represent hydrogen or C₁₋₆ alkyl or R₁ is linked to R₂ to form a group (CH₂)₂, (CH₂)₃ or (CH₂)₄; R₃, R₄ and R₅ independently represent hydrogen, halogen, cyano, —CF₃, —CF₃O, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl or a group —CONR₆R₇; R₆ and R₇ independently represent hydrogen or C₁₋₆ alkyl or together may be fused to form a 5- to 7-membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom; *m* represents an integer from 1 to 4, such that when *m* is an integer greater than 1, two R₂ groups may instead be linked to form a group CH₂, (CH₂)₂ or (CH₂)₃; *n* represents an integer from 1 to 3; *p* represents 1 or 2; A represents a group —Ar¹ or —Ar²Ar³; Ar¹, Ar² and Ar³ independently represent an aryl group or a heteroaryl group, both of which may be optionally substituted by one or more (e.g. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C₁₋₆ alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C₁₋₆alkoxy, arylC₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkoxyC₁₋₆ alkyl, C₃₋₇cycloalkylC₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkoxy-carbonyl, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyloxy, C₁₋₆alkylsulfonyl C₁₋₆ alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonyl C₁₋₆ alkyl, C₁₋₆ alkylsulfonamido, C₁₋₆ alkylamido, C₁₋₆ alkylsulfonamido C₁₋₆ alkyl, C₁₋₆ alkylamidoC₁₋₆ alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamido C₁₋₆ alkyl, arylcarboxamido C₁₋₆ alkyl, aroyl, aroylC₁₋₆ alkyl, arylC₁₋₆ alkanoyl, or a group CONR₈R₉ or SO₂NR₈R₉, wherein R₈ and R₉ independently represent hydrogen or C₁₋₆ alkyl or together may be fused to form a 5- to 7-membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom; or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0033] In some embodiments, the neurodegenerative disease is selected from Alzheimer's disease (including mild or early-stage Alzheimer's disease, mild to moderate Alzheimer's disease, moderate or mid-stage Alzheimer's disease, moderate to severe Alzheimer's disease, moderately severe Alzheimer's disease, severe Alzheimer's disease, Alzheimer's disease with Lewy bodies, (AD)), Parkinson's disease (including Parkinson's disease chemically induced by exposure to environmental agents such as pesticides, insecticides, or herbicides and/or metals such as manganese, aluminum, cadmium, copper, or zinc, SNCA gene-linked Parkinson's disease, sporadic or idiopathic Parkinson's disease, or Parkin- or LRRK2-linked Parkinson's disease (PD)), autosomal-dominant Parkinson's disease, Diffuse Lewy Body Disease (DLBD) also known as Dementia with Lewy Bodies (DLB), Pure Autonomic Failure, Lewy body dysphagia, Incidental LBD, Inherited LBD (e.g., mutations of the alpha-synuclein gene, PARK3 and PARK4), multiple system atrophy (including Olivopontocerebellar Atrophy, Striatonigral Degeneration, Shy-Drager Syndrome (MSA)), combined Alzheimer's and Parkinson disease and/or MSA, Huntington's disease, synucleinopathies, disorders or conditions characterized by the presence of Lewy bodies, multiple sclerosis, Amyotrophic lateral sclerosis (ALS) dementia (including vascular dementia, Lewy body dementia, Parkinson's dementia, frontotemporal dementia), Down syndrome, Psychosis (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy such as, but not limited to, Parkinson's disease psychosis, Alzheimer's disease psychosis, Lewy body dementia psychosis), dyskinesia (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy), agitation (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy), conditions associated with dopaminergic therapy (including dystonia, myoclonus, or tremor), synucleinopathies, diseases, disorders or conditions associated with abnormal expression, stability, activities and/or cellular processing of α -synuclein, diseases, disorders or conditions characterized by the presence of Lewy bodies, and combinations thereof.

[0034] In some embodiments, the second therapeutic agent is a cholinesterase inhibitor. In some embodiments, the acetylcholinesterase inhibitor is donepezil ((*RS*)-2-[(1-benzyl-4-piperidyl)methyl]- 5,6-dimethoxy-2,3-dihydroinden-1-one) or pharmaceutically acceptable salts, hydrates or solvates thereof. In some embodiments, acetylcholinesterase inhibitors for use herein may include, but are not limited to physostigmine, neostigmine, pyridostigmine, ambenonium, demecarium, rivastigmine, a phenanthrene derivative, galantamine caffeine, a

piperidine tacrine (also known as tetrahydroaminoacridine), edrophonium, huperzine A, ladostigil, ungeremine, lactucopicrin, memantine, 6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-N-methyl-3-pyridinecarboxamide hydrochloride or 1-{6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-3-pyridinyl}-2-pyrrolidinone or pharmaceutically acceptable salts, hydrates or solvates thereof. In some embodiments, the acetylcholinesterase inhibitor is administered to a subject in need thereof in a therapeutically effective amount. In some embodiments, the acetylcholinesterase inhibitor is administered to a subject in need thereof in a subtherapeutic amount. A “subtherapeutic amount” refers to a dosage that is below that typically used for the subject agent in typical therapeutic or prophylactic use.

[0035] In some embodiments, the second therapeutic agent is donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof. In some embodiments, donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof is administered to a subject in need thereof in a therapeutically effective amount. In some embodiments, donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof is administered to a subject in need thereof in a daily dose of about 5 mg to about 25 mg. In some embodiments, donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof is administered to a subject in need thereof in a daily dose of about 5 mg, 10 mg or 23 mg. In some embodiments, donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof is administered to a subject in need thereof in a daily dose that is considered to sub therapeutic. A “sub therapeutic amount” refers to a dosage that is below that typically used for the subject agent in typical therapeutic or prophylactic use.

[0036] In some embodiments, the second therapeutic agent is an anticonvulsant. In some embodiments, anticonvulsants for use herein may include, but are not limited, to levetiracetam (Keppra), AMPA receptor antagonists, barbiturate anticonvulsants, benzodiazepine anticonvulsants, carbamate anticonvulsants, carbonic anhydrase inhibitor anticonvulsants, dibenzazepine anticonvulsants, fatty acid derivative anticonvulsants, gamma-aminobutyric acid analogs, gamma-aminobutyric acid reuptake inhibitors, hydantoin anticonvulsants, miscellaneous anticonvulsants, neuronal potassium channel openers, oxazolidinedione anticonvulsants, pyrrolidine anticonvulsants, succinimide anticonvulsants, triazine anticonvulsants or combinations thereof. In some embodiments, the anticonvulsant is administered to a subject in need thereof in a therapeutically effective amount. In some

embodiments, the anticonvulsant or pharmaceutically acceptable salts, hydrates or solvates thereof is administered to a subject in need thereof in a daily dose that is considered to sub therapeutic. A "sub therapeutic amount" refers to a dosage that is below that typically used for the subject agent in typical therapeutic or prophylactic use.

[0037] In some embodiments, the compounds for use in the methods described herein may be formulated as pharmaceutical compositions. Pharmaceutical compositions of this invention may comprise the compounds described herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. Such compositions may optionally comprise an additional therapeutic agent.

[0038] Embodiments described herein are directed to a combination of a high dose or a high daily dose of a 5-HT₆ receptor antagonist or pharmaceutically acceptable salts, hydrates or solvates thereof, with a second therapeutic agent for the treatment of a neurodegenerative disease. In some embodiments, the secondary therapeutic agent is an acetylcholinesterase inhibitor. In some embodiments, the acetylcholinesterase inhibitor is donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0039] Embodiments described herein are directed to a combination of a high dose or a high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, with a second therapeutic agent for the treatment of a neurodegenerative disease. In some embodiments, the secondary therapeutic agent is an acetylcholinesterase inhibitor. In some embodiments, the acetylcholinesterase inhibitor is donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0040] Embodiments herein are also directed to pharmaceutical compositions comprising a high dose or high daily dose of 3 a 5-HT₆ receptor antagonist or pharmaceutically acceptable salts, hydrates or solvates thereof, with a second therapeutic agent for the treatment of a neurodegenerative disease. In some embodiments, the secondary therapeutic agent is an acetylcholinesterase inhibitor. In some embodiments, the acetylcholinesterase inhibitor is donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0041] Embodiments herein are also directed to pharmaceutical compositions comprising a high dose or high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, with a second therapeutic

agent for the treatment of a neurodegenerative disease. In some embodiments, the secondary therapeutic agent is an acetylcholinesterase inhibitor. In some embodiments, the acetylcholinesterase inhibitor is donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0042] Alternatively or additionally, in some embodiments, described compositions and formulations may be administered in combination with one or more treatments for Alzheimer's disease such as NamzaricTM, Exelon®, Aricept® (donepezil hydrochloride), Namenda® (memantine hydrochloride), or galantamine. In some embodiments, described compositions and formulations may be administered in combination with one or more treatments for Parkinson's Disease such as ABT-126 (Abbott Laboratories), pozanicline (Abbott Laboratories), MABT-5102A (AC Immune), Affitope AD-01 (AFFiRiS GmbH), Affitope AD-02 (AFFiRiS GmbH), davunetide (Allon Therapeutics Inc), nilvadipine derivative (Archer Pharmaceuticals), Anapsos (ASAC Pharmaceutical International AIE), ASP-2535 (Astellas Pharma Inc), ASP-2905 (Astellas Pharma Inc), 1 IC-AZD-2184 (AstraZeneca pic), 1 IC-AZD-2995 (AstraZeneca pic), 18F-AZD-4694 (AstraZeneca pic), AV-965 (Avera Pharmaceuticals Inc), AVN-101 (Avineuro Pharmaceuticals Inc), immune globulin intravenous (Baxter International Inc), EVP-6124 (Bayer AG), nimodipine (Bayer AG), BMS-708163 (Bristol-Myers Squibb Co), CERE-110 (Ceregene Inc), CLL-502 (CLL Pharma), CAD-106 (Cytos Biotechnology AG), mimopezil ((Debiopharm SA), DCB-AD1 (Development Centre for Biotechnology), EGb-761 ((Dr Willmar Schwabe GmbH & Co), E-2012 (Eisai Co Ltd), ACC-001 (Elan Corp pic), bapineuzumab (Elan Corp pic), ELND-006 (Elan Pharmaceuticals Inc), atomoxetine (Eli Lilly & Co), LY-2811376 (Eli Lilly & Co), LY-451395 (Eli Lilly & Co), m266 (Eli Lilly & Co), semagacestat (Eli Lilly & Co), solanezumab (Eli Lilly & Co), AZD-103 (Ellipsis Neurotherapeutics Inc), FGLL (ENKAM Pharmaceuticals A/S), EHT-0202 (ExonHit Therapeutics SA), celecoxib (GD Searle & Co), GSK-933776A (GlaxoSmithKline pic), rosiglitazone XR (GlaxoSmithKline pic), SB-742457 (GlaxoSmithKline pic), R-1578 (Hoffmann-La Roche AG), HF-0220 (Hunter-Fleming Ltd), oxiracetam (ISF Societa Per Azioni), KD-501 (Kwang Dong Pharmaceutical Co Ltd), NGX-267 (Life Science Research Israel), huperzine A (Mayo Foundation), Dimebon (Medivation Inc), MEM-1414 (Memory Pharmaceuticals Corp), MEM-3454 (Memory Pharmaceuticals Corp), MEM-63908 (Memory Pharmaceuticals Corp), MK-0249 (Merck & Co Inc), MK-0752 (Merck & Co Inc), simvastatin (Merck & Co Inc), V-950 (Merck & Co Inc), memantine (Merz & Co GmbH), neramexane (Merz & Co GmbH), Epadel (Mochida Pharmaceutical Co

Ltd), 123I-MNI-330 (Molecular Neuroimaging Lie), gantenerumab (MorphoSys AG), NIC5-15 (Mount Sinai School of Medicine), huperzine A (Neuro-Hitech Inc), OXIGON (New York University), NP-12 (Noscira SA), NP-61 (Noscira SA), rivastigmine (Novartis AG), ECT-AD (NsGene A/S), arundic acid (Ono Pharmaceutical Co Ltd), PF-3084014 (Pfizer Inc), PF-3654746 (Pfizer Inc), RQ-00000009 (Pfizer Inc), PYM-50028 (Phytopharm pic), Gero-46 (PN Gerolymatos SA), PBT-2 (Prana Biotechnology Ltd), PRX-03140 (Predix Pharmaceuticals Inc), Exebryl-1 (ProteoTech Inc), PF-4360365 (Rinat Neuroscience Corp), HuCAL anti- beta amyloid monoclonal antibodies (Roche AG), EVT-302 (Roche Holding AG), nilvadipine (Roskamp Institute), galantamine (Sanochemia Pharmazeutika AG), SAR-110894 (sanofi-aventis), INM-176 (Scigenic & Scigen Harvest), mimopezil (Shanghai Institute of Materia Medica of the Chinese Academy of Sciences), NEBO-178 (Stegram Pharmaceuticals), SUVN-502 (Suven Life Sciences), TAK-065 (Takeda Pharmaceutical), ispronicline (Targacept Inc), rasagiline (Teva Pharmaceutical Industries), T-817MA (Toyama Chemical), PF-4494700 (TransTech Pharma Inc), CX-717 (University of California), 18F-FDDNP (University of California Los Angeles), GTS-21 (University of Florida), 18F-AV-133 (University of Michigan), 18F- AV-45 (University of Michigan), tetrathiomolybdate (University of Michigan), 123I- IMPY (University of Pennsylvania), 18F-AV-1/ZK (University of Pennsylvania), 11C-6- Me-BTA-1 (University of Pittsburgh), 18F-6-OH-BTA-1 (University of Pittsburgh), MCD-386 (University of Toledo), leuprolide acetate implant (Voyager Pharmaceutical Corp), aleplasinin (Wyeth), begacestat (Wyeth), GSI-136 (Wyeth), NSA- 789 (Wyeth), SAM-531 (Wyeth), CTS-21166 (Zapaq), and ZSET-1446 (Zenyaku Kogyo).

[0043] Alternatively or additionally, in some embodiments, described compositions and formulations may be administered in combination with one or more treatments for motor neuronal disorders, such as AEOL-10150 (Aeolus Pharmaceuticals Inc), riluzole (Aventis Pharma AG), ALS-08 (Avicena Group Inc), creatine (Avicena Group Inc), arimoclomol (Biorex Research and Development Co), mecobalamin (Eisai Co Ltd), talampanel (Eli Lilly & Co), R-7010 (F Hoffmann-La Roche Ltd), edaravone (Mitsubishi-Tokyo Pharmaceuticals Inc), arundic acid (Ono Pharmaceutical Co Ltd), PYM-50018 (Phytopharm pic), RPI-MN (ReceptoPharm Inc), SB-509 (Sangamo Biosciences Inc), olesoxime (Trophos SA), sodium phenylbutyrate (Ucyclyd Pharma Inc), and R-pramipexole (University of Virginia).

[0044] Alternatively or additionally, in some embodiments, described compositions and formulations may be administered in combination with one or more additional therapeutic agent that may include agents known to modify cholinergic transmission such as M1 muscarinic receptor agonists or allosteric modulators, M2 muscarinic antagonists, acetylcholinesterase inhibitors, nicotinic receptor agonists or allosteric modulators, 5-HT₄ receptor partial agonists or 5HT_{1A} receptor antagonists and NMDA receptor antagonists or modulators, glutamate antagonists, GABA-ergic antagonists, H3 antagonists, putative metabolic/mitochondrial modulators, or disease modifying agents such as β or γ -secretase inhibitors, Tau-targeted therapeutics, β -amyloid aggregation inhibitors and β -amyloid immunotherapies, an antidepressant, for example a tricyclic, a MAOI (Monoamine oxidase inhibitor), a SSRI (Selective Serotonin Reuptake Inhibitor), a SNRI (Serotonin and Noradrenaline Reuptake Inhibitor) or a NaSSA (noradrenergic and specific serotonergic antidepressant). Examples of specific antidepressant compounds include amitriptyline, clomipramine, citalopram, dosulepin, doxepin, fluoxetine, imipramine, lofepramine, mirtazapine, moclobemide, nortriptyline, paroxetine, phenelzine, reboxetine, sertraline, tranylcypromine, trazodone, or venlafaxine. In some embodiments, additional therapeutic agents may include antipsychotic drugs, such as olanzapine, clozapine, prisperidone, quetiapine, aripiprazole or paliperiden.

[0045] Alternatively or additionally, in some embodiments, described compositions and formulations may be administered in combination with one or more 5-HT_{2A} inverse agonists. Suitable 5-HT_{2A} inverse agonists include 1-[3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(2,4-difluorophenyl)urea (nelotanserin); 7-({4-[2-(4-fluorophenyl)ethyl]piperazin-1-yl}carbonyl)-1*H*-indole-3-carbonitrile (pruvanserin); (Z,E)-1-(2-fluorophenyl)-3-(4-hydroxyphenyl)-2-propen-1-one O-[2-(dimethylamino)ethyl]oxime (eplivanserin); (R)-(2,3-dimethoxyphenyl)-[1-[2-(4-fluorophenyl)ethyl]-4-piperidyl]methanol (volinanserin), α -phenyl-1-(2-phenylethyl)-4-piperidine methanol (glemanserin), 3-{2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl}quinazoline-2,4(1*H*,3*H*)-dione (ketanserin), 6-[2-[4-[bis(4-fluorophenyl)methylidene] piperidin-1-yl]ethyl]-7-methyl-[1,3]thiazolo[2,3-*b*]pyrimidin-5-one (ritanserin), N-(4-fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy) phenylmethyl) carbamide (pimavanserin), and pharmaceutically acceptable salts, hydrates or solvates thereof.

[0046] Accordingly the present invention provides a method for the treatment of a neurodegenerative disease in a patient in need thereof which comprises providing to said patient a high dose of 3 a 5-HT₆ receptor antagonist or pharmaceutically acceptable salts, hydrates or solvates thereof, and a therapeutically effective amount of an acetylcholinesterase inhibitor, such as, but not limited to donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0047] Accordingly the present invention provides a method for the treatment of a neurodegenerative disease in a patient in need thereof which comprises providing to said patient a high dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, and a therapeutically effective amount of an acetylcholinesterase inhibitor, such as, but not limited to donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0048] The present invention also provides a method for the treatment of a neurodegenerative disease in a patient in need thereof which comprises providing to said patient a high daily dose of a 5-HT₆ receptor antagonist or pharmaceutically acceptable salts, hydrates or solvates thereof, and a therapeutically effective amount of an acetylcholinesterase inhibitor, such as, but not limited to donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0049] The present invention also provides a method for the treatment of a neurodegenerative disease in a patient in need thereof which comprises providing to said patient a high daily dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, and a therapeutically effective amount of an acetylcholinesterase inhibitor, such as, but not limited to donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0050] Some embodiments are directed to the use of a combination of a high dose of a 5-HT₆ receptor antagonist or a pharmaceutically acceptable salt thereof and a second therapeutic agent in the manufacture of a medicament for use in the treatment of a neurodegenerative disease. In some embodiments, the second therapeutic agent is an acetylcholinesterase inhibitor, such as, but not limited to donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0051] Some embodiments are directed to the use of a combination of a high dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or a pharmaceutically acceptable salt thereof and a second therapeutic agent in the manufacture of a medicament for use in the treatment of a neurodegenerative disease. In some embodiments, the second therapeutic agent is an acetylcholinesterase inhibitor, such as, but not limited to donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0052] Some embodiments are directed to the use of a combination of a high daily dose of a 5-HT₆ receptor antagonist or a pharmaceutically acceptable salt thereof and a second therapeutic agent in the manufacture of a medicament for use in the treatment of a neurodegenerative disease. In some embodiments, the second therapeutic agent is an acetylcholinesterase inhibitor, such as, but not limited to donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0053] Some embodiments are directed to the use of a combination of a high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or a pharmaceutically acceptable salt thereof and a second therapeutic agent in the manufacture of a medicament for use in the treatment of a neurodegenerative disease. In some embodiments, the second therapeutic agent is an acetylcholinesterase inhibitor, such as, but not limited to donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0054] Some embodiments are directed to the treatment or prophylaxis of a neurodegenerative disease in mammals including humans, which comprises administering to the subject a high dose of a 5-HT₆ receptor antagonist or pharmaceutically acceptable salts, hydrates or solvates thereof, and a therapeutically effective amount of donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0055] Some embodiments are directed to the treatment or prophylaxis of a neurodegenerative disease in mammals including humans, which comprises administering to the subject a high dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, and a therapeutically effective amount of donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0056] Some embodiments are directed to the treatment or prophylaxis of a neurodegenerative disease in mammals including humans, which comprises administering to the subject a high daily dose of a 5-HT₆ receptor antagonist or pharmaceutically acceptable

salts, hydrates or solvates thereof, and a therapeutically effective amount of donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0057] Some embodiments are directed to the treatment or prophylaxis of a neurodegenerative disease in mammals including humans, which comprises administering to the subject a high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, and a therapeutically effective amount of donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0058] The two therapeutic agents may be administered simultaneously or sequentially and, when administration is sequential, either may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition.

[0059] The two therapeutic agents may be used either as separate formulations or as a single combined formulation. When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation.

[0060] Some embodiments are directed to pharmaceutical compositions comprising a high dose of a 5-HT₆ receptor antagonist or pharmaceutically acceptable salts, hydrates or solvates thereof, and an acetylcholinesterase inhibitor. Some embodiments are directed to pharmaceutical compositions comprising a high daily dose of a 5-HT₆ receptor antagonist or pharmaceutically acceptable salts, hydrates or solvates thereof, and an acetylcholinesterase inhibitor.

[0061] Some embodiments are directed to pharmaceutical compositions comprising a high dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, and an acetylcholinesterase inhibitor. Some embodiments are directed to pharmaceutical compositions comprising a high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, and an acetylcholinesterase inhibitor.

[0062] Some embodiments are directed to pharmaceutical compositions comprising a high dose of a 5-HT₆ receptor antagonist or pharmaceutically acceptable salts, hydrates or solvates thereof, and a therapeutically effective amount of donepezil or pharmaceutically

acceptable salts, hydrates or solvates thereof. Some embodiments are directed to pharmaceutical compositions comprising a high daily dose of a 5-HT₆ receptor antagonist or pharmaceutically acceptable salts, hydrates or solvates thereof, and a therapeutically effective amount of donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0063] Some embodiments are directed to pharmaceutical compositions comprising a high dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, and a therapeutically effective amount of donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof. Some embodiments are directed to pharmaceutical compositions comprising a high daily dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, and a therapeutically effective amount of donepezil or pharmaceutically acceptable salts, hydrates or solvates thereof.

[0064] The compounds of this invention may be employed in a conventional manner for controlling the disease described herein, including, but not limited to, a neurodegenerative disease, and for treating diseases or reducing the advancement or severity of effects. Such methods of treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques. For example, the compounds of this invention may be combined with a pharmaceutically acceptable adjuvant for administration to a patient suffering from a neurodegenerative disease in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of that disease.

[0065] Alternatively, the compounds of this invention may be used in compositions and methods for treating or protecting individuals against the diseases described herein, including but not limited to a neurodegenerative disease, over extended periods of time. The compounds may be employed in such compositions either alone or together with other compounds of this invention in a manner consistent with the conventional utilization of such compounds in pharmaceutical compositions. For example, a compound of this invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in prophylactically effective amounts to protect individuals over an extended period of time against the diseases described herein, including, but not limited to, neurodegenerative diseases.

[0066] When the compounds of this invention are administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according to this invention comprise a combination of a high dose or a high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, or any other compound described herein, and a second therapeutic agent. Additional therapeutic agents that are normally administered to treat a particular disease or condition may be referred to as "agents appropriate for the disease, or condition, being treated."

[0067] If pharmaceutically acceptable salts of the compounds of this invention are utilized in these compositions, those salts are preferably derived from inorganic or organic acids and bases. Included among such acid salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzene sulfonate, bisulfate, butyrate, citrate, camphorate, camphor sulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate. Base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth.

[0068] Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; aralkyl halides, such as benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

[0069] The compounds utilized in the compositions and methods of this invention may also be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those, which increase biological penetration into a given biological system (e.g., blood, lymphatic system, or

central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and/or alter rate of excretion.

[0070] According to a preferred embodiment, the compositions of this invention are formulated for pharmaceutical administration to a subject or patient, e.g., a mammal, preferably a human being. Such pharmaceutical compositions are used to ameliorate, treat or prevent any of the diseases described herein including but not limited to neurodegenerative diseases in a subject.

[0071] Agents of the invention are often administered as pharmaceutical compositions comprising an active therapeutic agent, i.e., and a variety of other pharmaceutically acceptable components. See Remington's Pharmaceutical Science (15th ed., Mack Publishing Company, Easton, Pa., 1980). The preferred form depends on the intended mode of administration and therapeutic application. The compositions can also include, depending on the formulation desired, pharmaceutically acceptable, non-toxic carriers or diluents, which are defined as vehicles commonly used to formulate pharmaceutical compositions for animal or human administration. The diluent is selected so as not to affect the biological activity of the combination. Examples of such diluents are distilled water, physiological phosphate-buffered saline, Ringer's solutions, dextrose solution, and Hank's solution. In addition, the pharmaceutical composition or formulation may also include other carriers, adjuvants, or nontoxic, nontherapeutic, nonimmunogenic stabilizers and the like.

[0072] In some embodiments, the present invention provides pharmaceutically acceptable compositions comprising a therapeutically effective amount of one or more of a described compound, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents for use in treating the diseases described herein, including, but not limited to a neurodegenerative disease. While it is possible for a described compound to be administered alone, it is preferable to administer a described compound as a pharmaceutical formulation (composition) as described herein. Described compounds may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other pharmaceuticals.

[0073] As described in detail, pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions

or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream or foam; sublingually; ocularly; transdermally; or nasally, pulmonary and to other mucosal surfaces.

[0074] Pharmaceutically acceptable salts of compounds described herein include conventional nontoxic salts or quaternary ammonium salts of a compound, e.g., from nontoxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids such as hydrochloride, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like. In other cases, described compounds may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. These salts can likewise be prepared in situ in the administration vehicle or the dosage form manufacturing process, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. See, for example, Berge et al, *supra*.

[0075] Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0076] Examples of pharmaceutically acceptable antioxidants include: water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium

metabisulfite, sodium sulfite and the like; oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[0077] Formulations for use in accordance with the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient, which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, and the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound, which produces a therapeutic effect. Generally, this amount will range from about 1% to about 99% of active ingredient, preferably from about 5% to about 70%, most preferably from about 10% to about 30%.

[0078] In certain embodiments, a formulation as described herein comprises an excipient selected from the group consisting of cyclodextrins, liposomes, micelle forming agents, e.g., bile acids, and polymeric carriers, e.g., polyesters and polyanhydrides; and a compound of the present invention. In certain embodiments, an aforementioned formulation renders orally bioavailable a described compound of the present invention.

[0079] Methods of preparing formulations or compositions comprising described compounds include a step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients (excipients). In general, formulations may be prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0080] The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-

toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as those described in Pharmacopeia Helvetica, or a similar alcohol. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0081] In some cases, in order to prolong the effect of a drug, it may be desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0082] Injectable depot forms are made by forming microencapsule matrices of the described compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions, which are compatible with body tissue.

[0083] The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers, which are commonly used include but are not limited to lactose and cellulose (carboxymethylcellulose). Lubricating agents, such as magnesium stearate, are also typically added. For oral

administration in a capsule form, useful diluents include but are not limited to lactose and cellulose (carboxymethylcellulose). When aqueous suspensions and solutions and propylene glycol are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[0084] Formulations described herein suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. Compounds described herein may also be administered as a bolus, electuary or paste.

[0085] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), an active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and non-ionic surfactants; absorbents, such as kaolin and bentonite clay; lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0086] Tablets may be made by compression or molding, optionally with one or more accessory ingredients (excipients). Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative,

disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made in a suitable machine in which a mixture of the powdered compound is moistened with an inert liquid diluent. If a solid carrier is used, the preparation can be in tablet form, placed in a hard gelatin capsule in powder or pellet form, or in the form of a troche or lozenge. The amount of solid carrier will vary, e.g., from about 2 to 800 mg, preferably about 1 mg to 400 mg. When a liquid carrier is used, the preparation can be, e.g., in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example, using the aforementioned carriers in a hard gelatin capsule shell.

[0087] Tablets **FIGURES 4-6** and other solid dosage forms, such as dragees, capsules **FIGURES 1-3**, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may alternatively or additionally be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be formulated for rapid release, e.g., freeze-dried. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0088] In some embodiments, the compositions described herein can be configured as overcoated tablet formulations such as, but not limited to, those shown in Figures 1-7. In some embodiments, the compositions described herein can be configured as an encased product coated edge-to-edge tablet formulations such as the example shown in Figure 7. In some embodiments, a flat-oval edge-to-edge formulation might also be obtained from a hard-gelatin or HPMC capsule manufactured using a flattened mold rather than a circular mold. In

some embodiments a “flattened” capsule would be a more desirable alternative to the standard circular capsule.

[0089] Oral dosage forms of the present application may be, for example, capsules or tablets containing between 35 mg and 300 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline (RVT-101). Optionally, the oral dosage forms of the present application may contain one or more additional therapeutic agents such as, for example, between 2 mg and 12 mg donepezil. The oral dosage forms of the present application optionally contain inactive carriers and diluents known to one of skill in the art such as, for example microcrystalline cellulose (10-150 mg), mannitol (10-100 mg), sodium starch glycolate (1-20 mg), hydroxypropyl methylcellulose (1-20 mg), magnesium stearate (1-10 mg) and purified water.

[0090] Liquid dosage forms for oral administration of compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[0091] Besides inert diluents, oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[0092] Suspensions, in addition to active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0093] The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient, which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to

release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

[0094] Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetaryl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-administered transdermal patches are also included in this invention.

[0095] The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

[0096] For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

[0097] Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Dissolving or dispersing the compound in the proper medium can make such dosage forms. Absorption enhancers can also be used to increase the flux of the compound across the skin. Either providing a rate controlling

membrane or dispersing the compound in a polymer matrix or gel can control the rate of such flux.

[0098] Examples of suitable aqueous and nonaqueous carriers, which may be employed in the pharmaceutical compositions of the invention, include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0099] Such compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Inclusion of one or more antibacterial and/or antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like, may be desirable in certain embodiments. It may alternatively or additionally be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents, which delay absorption such as aluminum monostearate and gelatin.

[0100] In certain embodiments, a described compound or pharmaceutical preparation is administered orally. In other embodiments, a described compound or pharmaceutical preparation is administered intravenously. Alternative routes of administration include sublingual, intramuscular, and transdermal administrations.

[0101] When compounds described herein are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1% to 99.5% (more preferably, 0.5% to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[0102] Preparations described herein may be given orally, parenterally, topically, or rectally. They are of course given in forms suitable for the relevant administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc.; administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administrations are preferred.

[0103] Such compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

[0104] Regardless of the route of administration selected, compounds described herein which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

[0105] Actual dosage levels of the active ingredients in the pharmaceutical compositions of the invention may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[0106] When formulated separately, the high dose or high daily dose of a 5-HT₆ receptor antagonist or pharmaceutically acceptable salts, hydrates or solvates thereof, and the second therapeutic agent may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

[0107] When formulated separately, the high dose or high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, and the second therapeutic agent may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

[0108] A pharmaceutical composition may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, and is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

[0109] Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

[0110] Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

[0111] For parenteral administration, fluid unit dosage forms are prepared utilizing a compound and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

[0112] The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

[0113] Compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredients. The pack may, for example, comprise metal or plastic foil, such as a blister pack. Where the compounds are intended for administration as two separate compositions these may be presented, for example, in the form of a twin pack.

[0114] Pharmaceutical compositions may also be prescribed to the patient in "patient packs" containing the whole course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional

prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions.

[0115] The 5HT₆ receptor antagonists of the present application may optionally be administered in combination with one or more additional therapeutic agents. The one or more additional therapeutic agents may be, for example, treatments for Alzheimer's disease, treatments for Parkinson's disease, treatments for motor neuronal disorders, agents known to modify cholinergic transmission and 5HT_{2A} inverse agonists.

[0116] The treatments for Alzheimer's disease may be, for example, NamzaricTM, Exelon®, Aricept® (donepezil hydrochloride), Namenda® (memantine hydrochloride), or galantamine.

[0117] The treatments for Parkinson's Disease may be, for example, ABT-126 (Abbott Laboratories), pozanicline (Abbott Laboratories), MABT-5102A (AC Immune), Affitope AD-01 (AFFiRiS GmbH), Affitope AD-02 (AFFiRiS GmbH), davunetide (Allon Therapeutics Inc), nilvadipine derivative (Archer Pharmaceuticals), Anapsos (ASAC Pharmaceutical International AIE), ASP-2535 (Astellas Pharma Inc), ASP-2905 (Astellas Pharma Inc), l 1C-AZD-2184 (AstraZeneca pic), l 1C-AZD-2995 (AstraZeneca pic), 18F-AZD- 4694 (AstraZeneca pic), AV-965 (Avera Pharmaceuticals Inc), AVN-101 (Avineuro Pharmaceuticals Inc), immune globulin intravenous (Baxter International Inc), EVP-6124 (Bayer AG), nimodipine (Bayer AG), BMS-708163 (Bristol-Myers Squibb Co), CERE-110 (Ceregene Inc), CLL-502 (CLL Pharma), CAD- 106 (Cytos Biotechnology AG), mimopezil ((Debiopharm SA), DCB-AD1 (Development Centre for Biotechnology), EGb-761 ((Dr Willmar Schwabe GmbH & Co), E-2012 (Eisai Co Ltd), ACC-001 (Elan Corp pic), bapineuzumab (Elan Corp pic), ELND-006(Elan Pharmaceuticals Inc), atomoxetine (Eli Lilly & Co), LY-2811376 (Eli Lilly & Co), LY- 451395 (Eli Lilly & Co), m266 (Eli Lilly & Co), semagacestat (Eli Lilly & Co), solanezumab (Eli Lilly & Co), AZD-103 (Ellipsis Neurotherapeutics Inc), FGLL (ENKAM Pharmaceuticals A/S), EHT-0202 (ExonHit Therapeutics SA), celecoxib (GD Searle & Co), GSK-933776A (GlaxoSmithKline pic), rosiglitazone XR (GlaxoSmithKline pic), SB-742457 (GlaxoSmithKline pic), R-1578 (Hoffmann-La Roche AG), HF-0220 (Hunter-Fleming Ltd), oxiracetam (ISF Societa Per Azioni),KD- 501 (Kwang Dong Pharmaceutical Co Ltd), NGX-267 (Life Science Research Israel), huperzine A (Mayo Foundation), Dimebon (Medivation Inc), MEM-1414 (Memory Pharmaceuticals Corp), MEM-3454 (Memory Pharmaceuticals Corp), MEM- 63908

(Memory Pharmaceuticals Corp), MK-0249 (Merck & Co Inc), MK-0752 (Merck & Co Inc), simvastatin (Merck & Co Inc), V-950 (Merck & Co Inc), memantine (Merz & Co GmbH), neramexane (Merz & Co GmbH), Epadel (Mochida Pharmaceutical Co Ltd), 123I-MNI-330 (Molecular Neuroimaging Lie), gantenerumab (MorphoSys AG), NIC5-15 (Mount Sinai School of Medicine), huperzine A (Neuro-Hitech Inc), OXIGON (New York University), NP- 12 (Noscira SA), NP-61 (Noscira SA), rivastigmine (Novartis AG), ECT-AD (NsGene A/S), arundic acid (Ono Pharmaceutical Co Ltd), PF-3084014 (Pfizer Inc), PF-3654746 (Pfizer Inc), RQ- 00000009 (Pfizer Inc), PYM-50028 (Phytopharm pic), Gero-46(PN Gerolymatos SA), PBT-2 (Prana Biotechnology Ltd), PRX-03140 (Predix Pharmaceuticals Inc), Exebryl-l (ProteoTech Inc), PF-4360365 (Rinat Neuroscience Corp), HuCAL anti- beta amyloid monoclonal antibodies (Roche AG), EVT-302 (Roche Holding AG), nilvadipine (Roskamp Institute), galantamine (Sanochemia Pharmazeutika AG), SAR-110894 (sanofi-aventis), INM-176 (Scigenic & Scigen Harvest), mimopezil (Shanghai Institute of Materia Medica of the Chinese Academy of Sciences), NEBO-178 (Stegram Pharmaceuticals), SUVN-502 (Suven Life Sciences), TAK-065 (Takeda Pharmaceutical), ispronicline (Targacept Inc), rasagiline (Teva Pharmaceutical Industries), T-817MA (Toyama Chemical), PF-4494700 (TransTech Pharma Inc), CX- 717 (University of California), 18F-FDDNP (University of California Los Angeles), GTS-21 (University of Florida), 18F-AV-133 (University of Michigan), 18F- AV-45 (University of Michigan), tetrathiomolybdate (University of Michigan), 123I- IMPY (University of Pennsylvania), 18F-AV-1/ZK (University of Pennsylvania), 11C-6- Me-BTA-1 (University of Pittsburgh), 18F-6-OH-BTA-1 (University of Pittsburgh), MCD-386 (University of Toledo), leuprolide acetate implant (Voyager Pharmaceutical Corp), aleplasinin (Wyeth), begacestat (Wyeth), GSI-136 (Wyeth), NSA- 789 (Wyeth), SAM-531 (Wyeth), CTS-21166 (Zapaq), and ZSET-1446 (Zenyaku Kogyo).

[0118] The treatments for motor neuronal disorders may be, for example, AEOL-10150 (Aeolus Pharmaceuticals Inc), riluzole (Aventis Pharma AG), ALS-08 (Avicena Group Inc), creatine (Avicena Group Inc), arimoclomol (Biorex Research and Development Co), mecobalamin (Eisai Co Ltd), talampanel (Eli Lilly & Co), R-7010 (F Hoffmann-La Roche Ltd), edaravone (Mitsubishi-Tokyo Pharmaceuticals Inc), arundic acid (Ono Pharmaceutical Co Ltd), PYM-50018 (Phytopharm pic), RPI-MN (ReceptoPharm Inc), SB-509 (Sangamo Biosciences Inc), olesoxime (Trophos SA), sodium phenylbutyrate (Ucyclyd Pharma Inc), and R-pramipexole (University of Virginia).

[0119] The agents known to modify cholinergic transmission may be, for example, M1 muscarinic receptor agonists or allosteric modulators, M2 muscarinic antagonists, acetylcholinesterase inhibitors, nicotinic receptor agonists or allosteric modulators, 5-HT₄ receptor partial agonists or 5HT_{1A} receptor antagonists and NMDA receptor antagonists or modulators, glutamate antagonists, GABA-ergic antagonists, H3 antagonists, putative metabolic/mitochondrial modulators, or disease modifying agents such as β or γ -secretase inhibitors, Tau-targeted therapeutics, β -amyloid aggregation inhibitors and β -amyloid immunotherapies, an antidepressant, for example a tricyclic, a MAOI (Monoamine oxidase inhibitor), a SSRI (Selective Serotonin Reuptake Inhibitor), a SNRI (Serotonin and Noradrenaline Reuptake Inhibitor) or a NaSSA (noradrenergic and specific serotonergic antidepressant). Examples of specific antidepressant compounds include amitriptyline, clomipramine, citalopram, dosulepin, doxepin, fluoxetine, imipramine, lofepramine, mirtazapine, moclobemide, nortriptyline, paroxetine, phenelzine, reboxetine, sertraline, tranylcypromine, trazodone, or venlafaxine. In some embodiments, additional therapeutic agents may include antipsychotic drugs, such as olanzapine, clozapine, prisperidone, quetiapine, aripiprazole or paliperiden.

[0120] Suitable 5-HT_{2A} inverse agonists include 1-[3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(2,4-difluorophenyl)urea (nelotanserin); 7-({4-[2-(4-fluorophenyl)ethyl] piperazin-1-yl}carbonyl)-1*H*-indole-3-carbonitrile (pruvanserin); (Z,E)-1-(2-fluorophenyl)-3-(4-hydroxyphenyl)-2-propen-1-one O-[2-(dimethylamino)ethyl]oxime (eplivanserin); (R)-(2,3-dimethoxyphenyl)-[1-[2-(4-fluorophenyl)ethyl]-4-piperidyl]methanol (volinanserin), α -phenyl-1-(2-phenylethyl)-4-piperidine methanol (glemanserin), 3-{2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl}quinazoline-2,4(1*H*,3*H*)-dione (ketanserin), 6-[2-[4-[bis(4-fluorophenyl)methylidene] piperidin-1-yl]ethyl]-7-methyl-[1,3]thiazolo[2,3-*b*]pyrimidin-5-one (ritanserin), N-(4-fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy) phenylmethyl) carbamide (pimavanserin), and pharmaceutically acceptable salts, hydrates or solvates thereof.

[0121] It will be understood that the administration of the combination by means of a single patient pack, or patient packs of each composition, including a package insert directing the patient to the correct use of the combination is a desirable additional embodiment. Some embodiments are directed to a patient pack comprising at least one active ingredient, of the combination and an information insert containing directions on the use of the combination.

Some embodiments are directed to a double pack comprising in association for separate administration of a 5-HT₆ receptor antagonist and the second therapeutic agent. Some embodiments are directed to a patient pack comprising at least one active ingredient, of the combination and an information insert containing directions on the use of the combination. Some embodiments are directed to a double pack comprising in association for separate administration of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline and the second therapeutic agent.

DOSING:

[0122] The high dose or high daily dose of a 5-HT₆ receptor antagonist or pharmaceutically acceptable salts, hydrates or solvates thereof, used in the treatment of a neurodegenerative disease will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide, suitable unit doses may be high doses as defined herein, and such unit doses will preferably be administered once a day, although administration more than once a day may be required; and such therapy may extend for a number of weeks or months.

[0123] The high dose or high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, used in the treatment of a neurodegenerative disease will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide, suitable unit doses may be high doses as defined herein, doses greater than about 35 mg, for example about 36 to about 1,000 mg; and such unit doses will preferably be administered once a day, although administration more than once a day may be required; and such therapy may extend for a number of weeks or months.

[0124] The 5-HT₆ receptor antagonist 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline has been demonstrated to have a dose dependent increase in efficacy vs. placebo in the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) score in clinical trial between 15 mg and 35 mg doses. However, these potential benefits were initially tempered with the potential for adverse events, in particular, the Central Nervous System (CNS) toxicity observed in dogs and rabbits described below. Applicants have surprisingly found that a high dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline is both efficacious and non-toxic contrary to the predictions of the animal models.

[0125] The 35 mg dose 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline was evaluated in four Phase 2 trials and is the dose being evaluated in a Phase 3 pivotal study. In the AZ310866 Phase 2b study, there was a dose dependent increase in efficacy vs placebo in the ADAS-Cog score between 15 mg (-0.7 units) and 35 mg (-1.7 units). These data suggested that further benefit may be achieved with doses higher than 35 mg as higher plasma concentrations could produce an incremental increase in efficacy. These benefits need to be balanced with the potential for adverse events, in particular, the CNS toxicity observed in dogs and rabbits described below. In nonclinical studies, 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline caused seizures in rabbits and dogs but not in rodents (mice or rats). In the rat maximal electroshock seizure threshold test, 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline did not decrease the seizure threshold at an extrapolated C_{max} of ~1887 ng/mL. In rabbits, seizures were produced after a single dose at 300 mg/kg, which exceeded the maximum tolerated repeat-dose level (MTD). In dogs, seizures occurred in 2 dogs only after daily dosing for 8 weeks at the MTD (3 weeks at 10 mg/kg/day followed by 5 weeks at 15 mg/kg/day), but did not occur when the dose level was reduced for the rest of the 26-week study or in dogs given 7.5 mg/kg/day for the entire 26 weeks. In the 26-week dog study, one high-dose dog had seizures on Day 55 and was euthanized. A second dog had seizures on Day 59 and survived. For the second dog, plasma samples taken approximately 5 minutes and two hours after the seizure (4 and 6 hours post dose on Day 59) had concentrations of 1570 and 1440 ng/mL, respectively. For the first dog that experienced a seizure on Day 55, there are no plasma concentration data at the time of seizure; however, this dog had a C_{max} of 1700 ng/mL on Day 53/54. In summary, a plasma concentration >1570 ng/mL may be associated with an increased seizure risk in dogs (of note, other mid- and high-dose dogs that did not experience any seizure activity achieved plasma concentrations of up to 1937 ng/mL). In a human study of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline, elderly subjects received 35 mg once daily of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline for 28 days. The mean C_{max} in this study was 181 ng/ml in males and 177 ng/ml in females. The highest recorded C_{max} in this study was 307 ng/ml. Given the linear human pharmacokinetics established in the phase I and II clinical trials, multiple dosing with a 70 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline dose would be expected to produce a mean C_{max} value of approximately 360 ng/mL and a maximum value of 714 ng/ml in patients. This mean value is approximately 1/4th the C_{max} value observed in dogs with seizures. The maximum concentration that may be achieved is approximately 1/2 the C_{max} value observed in the 2 dogs with seizures. To further understand the risk to humans, SimCYP population PBPK

modelling was used to predict brain concentrations of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline in dogs exposed to the concentrations linked with seizures, and to compare these with predicted human brain concentrations at the clinical dose of 35mg. The simulations predicted that the human steady-state brain concentrations following repeat administration with 35 mg would be approximately 40-fold lower than the brain concentrations associated with seizures in dogs. Assuming linear pharmacokinetics, the human steady-state brain concentrations with 70 mg would be approximately 20-fold lower than the brain concentrations associated with convulsions in dogs. Upon review of clinical data, no seizures were observed in studies with healthy subjects (n=225) who received single doses of up to 175 mg and repeat doses of up to 50 mg for 13 days. Furthermore, in Phase 2 studies encompassing 1024 patients with Alzheimer's disease at doses of 5mg to 35 mg per day, two subjects reported seizures, both in the Phase 2b study with 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline administered as adjunctive therapy to donepezil. One subject was in the placebo group and one in the 15 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline group. The subject receiving 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline was hospitalized with a suspicion of a TIA and experienced a seizure, which was reported by the PI as not attributable to study drug. Overall, these data suggest efficacy without seizure at doses higher than 30 mg, contrary to that predicted by the animal models.

[0126] The high doses or high daily dose of a 5-HT₆ receptor antagonist or pharmaceutically acceptable salts, hydrates or solvates thereof, used in combination with a second therapeutic agent may be the same as when it is used on its own or may be different. In a particular embodiment, it may be possible that the dose of either drug used may be higher when used in combination than when used separately. In a particular embodiment, the high dose or high daily dose of a 5-HT₆ receptor antagonist or pharmaceutically acceptable salts, hydrates or solvates thereof, will be increased when combined with an acetylcholinesterase inhibitor, such as, but not limited to donepezil. In some embodiments, the high dose or high daily dose of a 5-HT₆ receptor antagonist or pharmaceutically acceptable salts, hydrates or solvates thereof, used in combination with a second therapeutic agent will be a high dose as defined herein. The high doses or high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, used in combination with a second therapeutic agent may be the same as when it is used on its own or may be different. In a particular embodiment, it may be possible that the dose of either drug used may be higher when used in combination than when used

separately. In a particular embodiment, the high dose or high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, will be increased when combined with an acetylcholinesterase inhibitor, such as, but not limited to donepezil. In some embodiments, the high dose or high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof, used in combination with a second therapeutic agent will be a high dose as defined herein.

[0127] The dose when using the compounds of the present invention can vary within wide limits, and as is customary and is known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the illness to be treated, on the condition of the patient, on the compound employed or on whether an acute or chronic disease state is treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention. Representative doses of the present invention include, but not limited to, about 35 mg to about 5000 mg, about 35 mg to about 2500 mg, about 35 mg to about 1000 mg, 35 mg to about 500 mg, 35 mg to about 250 mg, and about 35 mg to 100 mg and inclusive of any individual dose therein. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or 4, doses. Depending on the individual and as deemed appropriate from the patient's physician or care-giver it may be necessary to deviate upward or downward from the doses described herein.

[0128] One possible dosing range of the present application is a once-daily of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline from 35 mg to 300 mg, as described in the present application. Specifically such a dose range may be any value from the group consisting of: 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194,

195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299 and 300.

[0129] The amount of active ingredient, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate in vivo data obtained in a model system, typically an animal model, to another, such as a human. In some circumstances, these extrapolations may merely be based on the weight of the animal model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weights, but rather incorporate a variety of factors. Representative factors include the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, on whether an acute or chronic disease state is being treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention and as part of a drug combination. The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety factors as cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

[0130] The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example 2, 3 or 4,

part administrations. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

EXAMPLES

[0131] Example 1 - Pharmacokinetics and Safety of 3-PHENYLSULFONYL-8-PIPERAZINYL-1YL-QUINOLINE in Healthy Elderly Adults and Effect of Food in Healthy Adults

[0132] To investigate the safety and tolerability of 3-PHENYLSULFONYL-8-PIPERAZINYL-1YL-QUINOLINE at doses of 35 mg and 70 mg following repeat oral administration in 30 healthy, elderly subjects aged 60-85; to characterize the pharmacokinetics (PK) of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline at doses of 35 mg and 70 mg following repeat oral administration in healthy, elderly subjects.

[0133] Statistical Methods: Safety and PK data will be presented in tabular and/or graphical format and summarized descriptively. To evaluate the effect of food, log-transformed PK parameters will be analyzed by a mixed effect model. The 90 percent confidence interval (CI) for the ratio of population geometric means between the fasted and fed states will be reported for C_{max}, AUC(0-∞), AUC(0-t).

[0134] Prior to the initiation of a pivotal Phase 3 program with 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline, new tablets for clinical trials must be manufactured using a new manufacturing site. As such, the tablets produced for use in Phase 3 are being evaluated in healthy subjects to demonstrate that the exposure from the new drug product is comparable to that previously described in studies using drug product manufactured by GSK. In addition, the highest dose evaluated in multiple dose studies to date is 50 mg per day. As 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline is being considered for development in other Central Nervous System (CNS) disorders in older adults, an evaluation of the PK and safety at a higher dose is warranted to enable higher doses in future studies for other indications. The effect of food on 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline pharmacokinetics was established early in the development program at a 50 mg dose and with a capsule formulation.

[0135] The 35 mg dose was evaluated in four Phase 2 trials and is the dose being evaluated in a Phase 3 pivotal study. In the AZ310866 Phase 2b study, there was a dose dependent increase in efficacy vs placebo in the ADAS-Cog score between 15 mg (-0.7 units) and 35 mg (-1.7 units). These data suggest that further benefit may be achieved with doses higher than 35 mg as higher plasma concentrations could produce an incremental increase in efficacy. These benefits need to be balanced with the potential for adverse events, in particular, the CNS toxicity observed in dogs and rabbits described below. In nonclinical studies, 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline caused seizures in rabbits and dogs but not in rodents (mice or rats). In the rat maximal electroshock seizure threshold test, 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline did not decrease the seizure threshold at an extrapolated C_{max} of ~1887 ng/mL. In rabbits, seizures were produced after a single dose at 300 mg/kg, which exceeded the maximum tolerated repeat-dose level (MTD). In dogs, seizures occurred in 2 dogs only after daily dosing for 8 weeks at the MTD (3 weeks at 10 mg/kg/day followed by 5 weeks at 15 mg/kg/day), but did not occur when the dose level was reduced for the rest of the 26-week study or in dogs given 7.5 mg/kg/day for the entire 26 weeks. In the 26-week dog study, one high-dose dog had seizures on Day 55 and was euthanized. A second dog had seizures on Day 59 and survived. For the second dog, plasma samples taken approximately 5 minutes and two hours after the seizure (4 and 6 hours post dose on Day 59) had SB742457 concentrations of 1570 and 1440 ng/mL, respectively. For the first dog that experienced a seizure on Day 55, there are no plasma concentration data at the time of seizure; however, this dog had a C_{max} of 1700 ng/mL on Day 53/54. In summary, a plasma concentration >1570 ng/mL may be associated with an increased seizure risk in dogs (of note, other mid- and high-dose dogs that did not experience any seizure activity achieved plasma concentrations of up to 1937 ng/mL). In study SB742457/005, elderly subjects received 35 mg once daily of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline for 28 days. The mean C_{max} in this study was 181 ng/ml in males and 177 ng/ml in females. The highest recorded C_{max} in this study was 307 ng/ml. Given the linear human pharmacokinetics established in the phase I and II clinical trials, multiple dosing with a 70 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline dose would be expected to produce a mean C_{max} value of approximately 360 ng/mL and a maximum value of 714 ng/ml in patients. This mean value is approximately 1/4th the C_{max} value observed in dogs with seizures. The maximum concentration that may be achieved is approximately 1/2 the C_{max} value observed in the 2 dogs with seizures. To further understand the risk to humans, SimCYP population PBPK modelling was used to predict brain concentrations of 3-phenylsulfonyl-8-piperazinyl-

1-yl-quinoline in dogs exposed to the concentrations linked with seizures, and to compare these with predicted human brain concentrations at the clinical dose of 35mg. The simulations predicted that the human steady-state brain concentrations following repeat administration with 35 mg would be approximately 40-fold lower than the brain concentrations associated with seizures in dogs. Assuming linear pharmacokinetics, the human steady-state brain concentrations with 70 mg would be approximately 20-fold lower than the brain concentrations associated with convulsions in dogs. Upon review of clinical data, no seizures were observed in studies with healthy subjects (n=225) who received single doses of up to 175 mg and repeat doses of up to 50 mg for 13 days. Furthermore, in Phase 2 studies encompassing 1024 patients with Alzheimer's disease at doses of 5mg to 35 mg per day, two subjects reported seizures, both in the Phase 2b study with 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline administered as adjunctive therapy to donepezil. One subject was in the placebo group and one in the 15 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline group. The subject receiving RTV-101 was hospitalized with a suspicion of a TIA and experienced a seizure, which was reported by the PI as not attributable to study drug. Overall, these data suggest efficacy without seizure at doses higher than 30 mg, contrary to that predicted by the animal models.

[0136] Part 1 is a placebo-controlled, randomized, repeat dose study of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline in two cohorts of healthy, elderly subjects. Subjects will be admitted to the clinical unit on Day -1 and remain in the unit until Day 8. Each subject will receive single 35 mg or 70 mg doses of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline /placebo for 7 days. The 70 mg cohort will be dosed in groups of three and separated by at least 3 days. Safety assessments will be collected throughout the treatment period. Serial PK samples will be collected throughout the treatment period and for up to 168 hours following the last dose of study drug (via outpatient visits). Each subject will participate in the study for approximately 7 weeks i.e., 30 day screening period, 1-week treatment period, and a 10 - 14 day follow-up period.

[0137] All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

[0138] Blood samples for PK analysis of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline and metabolites will be collected at the time points indicated in Time and Events Tables. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

[0139] Final analysis will be performed after the completion of the study and final datasets authorization. Data listings will be sorted by subject, period, day/time, and treatment; summaries will be presented by treatment, day/time. Subjects received placebo in Cohorts 1 and 2 will be combined. Unless stated otherwise, descriptive summaries will include n, mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum for continuous variables, n and percent for categorical variables, and geometric mean, 95% confidence interval (CI), and the between-subject CV (%CVb) based on the geometric mean for the log_e-transformed PK parameters. Version 9.2 or higher of the SAS system will be used to analyze the data as well as to generate tables, figures, and listings. Complete details will be documented in the Statistical Analysis Plan (SAP).

[0140] Plasma 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline concentration-time data will be analyzed by non-compartmental methods with Phoenix WinNonlin or other pharmacokinetic software programs. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the primary pharmacokinetic parameters will be determined for: Part 1: AUC(0- τ), C τ , C_{min}, C_{max}, CL/F, t_{max}, and t_{1/2}.

[0141] Additional PK parameters may be calculated. Pharmacokinetic data will be presented in graphical and tabular form and will be summarized descriptively. The planned statistical comparisons for PK parameters are listed below.

[0142] The dose proportionality between the 2 doses will be assessed using an ANOVA model based on the dose-normalized PK parameter. The parameters will be log_e transformed prior to analysis. The ratio of geometric least squares (GLS) means and the corresponding 90% confidence interval will be estimated for AUC(0- τ), C τ and C_{min}, C_{max}.

[0143] Additional comparisons may be performed and details on PK analyses will be provided in the SAP.

[0144] Example 2 – 70 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline:

[0145] A tablet containing 70 mg of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline as the active ingredient was prepared according to the following:

Component	Theoretical Unit Quantity (mg/tablet)	Function	Reference to Standard
Tablet Strength	70	NA	NA
Intra-granular			
3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline	70.0	Active	In-House
Microcrystalline cellulose	25-30	Filler	Ph Eur. and USP/NF
Mannitol	33.8-27.8	Filler	Ph Eur. and USP/NF
Sodium starch glycolate	4.2	Disintegrant	Ph. Eur. and USP/NF
Hypromellose 2910	7.0	Binder	Ph. Eur. and USP/NF
Purified water	qs	Binding Fluid	Ph. Eur. and USP/NF
Extra-granular			
Mannitol	89.5-83.5	Filler	Ph Eur. and USP/NF
Microcrystalline cellulose	57-63	Filler	Ph Eur. and USP/NF
Sodium starch glycolate	10.5	Disintegrant	Ph Eur. and USP/NF
Magnesium stearate	3	Lubricant	Ph Eur. and USP/NF
Tablet Core Weight	300.0	-	-

[0146] Example 3 – 35 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline/5 mg donepezil:

[0147] A tablet containing 35 mg of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline/5 mg donepezil as the active ingredients was prepared according to the following:

Component Name	Unit weight	Unit weight	Unit weight
	mg/tab	mg/tab	mg/tab
3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline	35	35	35
donepezil HCl	5	5	5
Microcrystalline Cellulose NF (Avicel PH101)	60-50		
Mannitol USP (Pearlitol 160C, USP)	25-35		
Sodium Starch Glycolate, NF (Intragranular)	4.5		
Hydroxypropyl Methylcellulose 2910 USP 6 CPS	9		
Microcrystalline Cellulose NF, Ph. Eur, JP (Avicel PH102)	64-52	145-140	155-150
Mannitol Pearlitol 200SD Roquette	36-44	50-55	40-45
Sodium Starch Glycolate, NF	8.5-12.5	12.5	
Magnesium Stearate NF/EP Non-Bovine #5712	3	2.5	2.5
Croscarmellose sodium			12.5

Tablet Weight	250	250	250
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[0148] Example 4 – 35 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline/10 mg donepezil:

[0149] A tablet containing 35 mg of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline/10 mg donepezil as the active ingredients was prepared according to the following:

Component Name	Unit weight	Unit weight	Unit weight
	mg/tab	mg/tab	mg/tab
3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline	35	35	35
donepezil HCl	10	10	10
Microcrystalline Cellulose NF (Avicel PH101)	45-55		
Mannitol USP (Pearlitol 160C,USP)	35-25		
Sodium Starch Glycolate, NF (Intragranular)	4.5		
Hydroxypropyl Methylcellulose 2910 USP 6 CPS	9		
Microcrystalline Cellulose NF, Ph. Eur, JP (Avicel PH102)	55-50	135-145	145-155
Mannitol Pearlitol 200SD Roquette	42-47	45-44	35-45
Sodium Starch Glycolate, NF	9.5-12.5	12.5	
Magnesium Stearate NF/EP Non-Bovine #5712	3	2.5	2.5
Croscarmellose sodium			12.5
Tablet Weight	250	250	250

[0150] Example 5 – Bilayer tablet 35 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline/5 mg donepezil:

[0151] A bilayer tablet containing 35 mg of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline/5 mg donepezil as the active ingredients was prepared according to the following:

Component Name	Unit weight
	mg/tab
3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline	35
Microcrystalline Cellulose NF (Avicel PH101)	12.5-15.5
Mannitol USP (Pearlitol 160C,USP)	16-14
Sodium Starch Glycolate, NF	7.5-6.5
Hydroxypropyl Methylcellulose 2910 USP 6 CPS	3-4
Microcrystalline Cellulose NF, Ph. Eur, JP (Avicel PH102)	30-36
Mannitol Pearlitol 200SD Roquette	43-37
Magnesium Stearate NF/EP Non-Bovine #5712	1.5-2.5

Total layer weight	150
Component Name	Unit weight
	mg/tab
Donepezil HCl	5
Sodium Starch Glycolate, NF	7-8
Hydroxypropyl Methylcellulose 2910 USP 6 CPS	9-5
Microcrystalline Cellulose NF, Ph. Eur, JP (Avicel PH102)	62-59
Mannitol Pearlitol 200SD Roquette	16-21
Magnesium Stearate NF/EP Non-Bovine #5712	1-2
Total layer weight	100
Total tablet weight	250

[0152] Example 6 – Bilayer tablet 35 mg 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline/10 mg donepezil:

[0153] A bilayer tablet containing 35 mg of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline/10 mg donepezil as the active ingredients was prepared according to the following:

Component Name	Unit weight
	mg/tab
3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline	35
Microcrystalline Cellulose NF (Avicel PH101)	16-12
Mannitol USP (Pearlitol 160C, USP)	14-16.5
Sodium Starch Glycolate, NF	8-6
Hydroxypropyl Methylcellulose 2910 USP 6 CPS	3-4
Microcrystalline Cellulose NF, Ph. Eur, JP (Avicel PH102)	32-28
Mannitol Pearlitol 200SD Roquette	40-47
Magnesium Stearate NF/EP Non-Bovine #5712	1.5-2
Total layer weight	150
Component Name	Unit weight
	mg/tab
Donepezil HCl	10
Sodium Starch Glycolate, NF	7-8
Hydroxypropyl Methylcellulose 2910 USP 6 CPS	6-4
Microcrystalline Cellulose NF, Ph. Eur, JP (Avicel PH102)	61-55
Mannitol Pearlitol 200SD Roquette	15-21

Magnesium Stearate NF/EP Non-Bovine #5712	1-2
Total layer weight	100
Total tablet weight	250

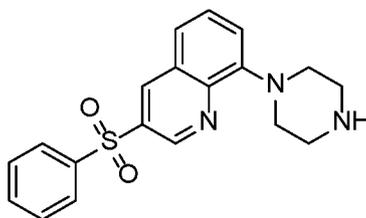
[0154] Although the present disclosure has been described in considerable detail with reference to certain preferred versions thereof, other versions are possible. Therefore, the spirit and scope of the application should not be limited to the description of the preferred versions described herein.

[0155] Although compositions, materials, and methods similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable preparations, methods and materials are described herein. All publications mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present specification, including definitions will control. In addition, the particular embodiments discussed below are illustrative only and not intended to be limiting.

[0156] 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 application, 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.

WHAT IS CLAIMED IS:

1. A method of treating a neurodegenerative disease in a subject in need thereof comprising: administering to said patient a high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-quinoline **Formula I**

**Formula I**

or pharmaceutically acceptable salts, hydrates, polymorphs or solvates thereof.

2. The method of claim 1, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is provided at least once a day.

3. The method of claim 1, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is provided to the subject by at least one route of administration selected from the group consisting of: orally; nasally; topically; buccally; sublingually; rectally; vaginally; and parenterally.

4. The method of claim 3, wherein the at least one route of administration is orally.

5. The method of claim 1, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is greater than about 36 mg.

6. The method of claim 5, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is administered once a day.

7. The method of claim 6, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is about 35 mg to about 300 mg.
8. The method of claim 7, wherein the high daily dose is about 50 mg to about 270 mg.
9. The method of claim 7, wherein the high daily dose is about 60 mg to about 230 mg.
10. The method of claim 7, wherein the high daily dose is about 70 mg to about 200 mg.
11. The method of claim 1, wherein the neurodegenerative disease is selected from Alzheimer's disease (including mild or early-stage Alzheimer's disease, mild to moderate Alzheimer's disease, moderate or mid-stage Alzheimer's disease, moderate to severe Alzheimer's disease, moderately severe Alzheimer's disease, severe Alzheimer's disease, Alzheimer's disease with Lewy bodies, (AD)), Parkinson's disease (including Parkinson's disease chemically induced by exposure to environmental agents such as pesticides, insecticides, or herbicides and/or metals such as manganese, aluminum, cadmium, copper, or zinc, SNCA gene-linked Parkinson's disease, sporadic or idiopathic Parkinson's disease, or Parkin- or LRRK2-linked Parkinson's disease (PD)), autosomal-dominant Parkinson's disease, Diffuse Lewy Body Disease (DLBD) also known as Dementia with Lewy Bodies (DLB), Pure Autonomic Failure, Lewy body dysphagia, Incidental LBD, Inherited LBD (e.g., mutations of the alpha-synuclein gene, PARK3 and PARK4), multiple system atrophy (including Olivopontocerebellar Atrophy, Striatonigral Degeneration, Shy-Drager Syndrome (MSA)), combined Alzheimer's and Parkinson disease and/or MSA, Huntington's disease, synucleinopathies, disorders or conditions characterized by the presence of Lewy bodies, multiple sclerosis, Amyotrophic lateral sclerosis (ALS) dementia (including vascular dementia, Lewy body dementia, Parkinson's dementia, frontotemporal dementia), Down syndrome, Psychosis (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy such as, but not limited to, Parkinson's disease psychosis, Alzheimer's disease psychosis, Lewy body dementia psychosis), dyskinesia (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy), agitation (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy), conditions associated with dopaminergic therapy (including dystonia, myoclonus, or tremor), synucleinopathies, diseases, disorders or conditions associated with abnormal expression, stability, activities and/or cellular processing of α -

synuclein, diseases, disorders or conditions characterized by the presence of Lewy bodies, and combinations thereof

12. The method of claim 1, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline is selected from a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that may cause convulsions in a subject to which it is administered; would be expected to exceed the maximum tolerated dose for the subject to which it is administered; is associated with systemic exposures characterized by an $AUC_{\tau-ss}$ of about 8.2 $\mu\text{g}\cdot\text{h}/\text{ml}$, a C_{\max} of about 0.26 $\mu\text{g}/\text{ml}$; or a combination thereof; is associated with systemic exposures characterized by an AUC , C_{\max} , or combinations thereof, that are about 2 to about 3 times higher than the mean clinical exposure achieved at the proposed clinical dose for monotherapy with 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline (i.e. mean $AUC_{\tau-ss}$ of about 3.2 $\mu\text{g}\cdot\text{h}/\text{ml}$ and C_{\max} of about 0.180 $\mu\text{g}/\text{ml}$); or is associated with a recorded systemic clinical exposure that is greater than the highest recorded systemic clinical exposure ($AUC_{0-\infty}$ of about 9.25 $\mu\text{g}\cdot\text{h}/\text{ml}$ and C_{\max} of about 0.293 $\mu\text{g}/\text{ml}$); a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than about 10mg/kg/day; a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than 15 mg/day; a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than about 35 mg/day or any combination thereof per day.

13. The method of claim 1, further comprising a therapeutically effective amount of an acetylcholinesterase inhibitor.

14. The method of claim 13, wherein the acetylcholinesterase inhibitor is donepezil or pharmaceutically acceptable salts, hydrates, polymorphs or solvates thereof.

15. The method of claim 14, wherein the therapeutically effective amount of donepezil is selected from about 5 mg, about 10 mg or about 23 mg per day.

16. The method of claim 13, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is provided to the subject by at least one route of administration selected from the group consisting of: orally; nasally; topically; buccally; sublingually; rectally; vaginally; and parenterally;

17. The method of claim 16, wherein the at least one route of administration is orally.

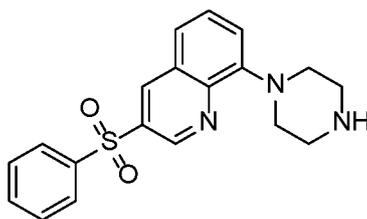
18. The method of claim 13, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is administered once a day.

19. The method claim 1, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is about 70 mg.

20. The method claim 13, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is about 70 mg.

21. A pharmaceutical composition for use in treating a neurodegenerative disease, comprising:

a.) a high daily dose of 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline **Formula I**



Formula I

or pharmaceutically acceptable salts, hydrates or solvates thereof; and

b.) at least one pharmaceutically acceptable excipient.

22. The pharmaceutical composition of claim 21, wherein the neurodegenerative disease is selected from Alzheimer's disease (including mild or early-stage Alzheimer's disease, mild to moderate Alzheimer's disease, moderate or mid-stage Alzheimer's disease, moderate to severe Alzheimer's disease, moderately severe Alzheimer's disease, severe Alzheimer's disease, Alzheimer's disease with Lewy bodies, (AD)), Parkinson's disease (including Parkinson's disease chemically induced by exposure to environmental agents such as pesticides, insecticides, or herbicides and/or metals such as manganese, aluminum, cadmium, copper, or zinc, SNCA gene-linked Parkinson's disease, sporadic or idiopathic Parkinson's disease, or Parkinson's- or LRRK2-linked Parkinson's disease (PD)), autosomal-dominant

Parkinson's disease, Diffuse Lewy Body Disease (DLBD) also known as Dementia with Lewy Bodies (DLB), Pure Autonomic Failure, Lewy body dysphagia, Incidental LBD, Inherited LBD (e.g., mutations of the alpha-synuclein gene, PARK3 and PARK4), multiple system atrophy (including Olivopontocerebellar Atrophy, Striatonigral Degeneration, Shy-Drager Syndrome (MSA)), combined Alzheimer's and Parkinson disease and/or MSA, Huntington's disease, synucleinopathies, disorders or conditions characterized by the presence of Lewy bodies, multiple sclerosis, Amyotrophic lateral sclerosis (ALS) dementia (including vascular dementia, Lewy body dementia, Parkinson's dementia, frontotemporal dementia), Down syndrome, Psychosis (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy such as, but not limited to, Parkinson's disease psychosis, Alzheimer's disease psychosis, Lewy body dementia psychosis), dyskinesia (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy), agitation (including agitation caused by a neurodegenerative disease or associated with dopaminergic therapy), conditions associated with dopaminergic therapy (including dystonia, myoclonus, or tremor), synucleinopathies, diseases, disorders or conditions associated with abnormal expression, stability, activities and/or cellular processing of α -synuclein, diseases, disorders or conditions characterized by the presence of Lewy bodies, and combinations thereof

23. The pharmaceutical composition of claim 21, wherein the high dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline is selected from a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that may cause convulsions in a subject to which it is administered; would be expected to exceed the maximum tolerated dose for the subject to which it is administered; is associated with systemic exposures characterized by an $AUC_{\text{tau-ss}}$ of about 8.2 $\mu\text{g}\cdot\text{h}/\text{ml}$, a C_{max} of about 0.26 $\mu\text{g}/\text{ml}$; or a combination thereof; is associated with systemic exposures characterized by an AUC , C_{max} , or combinations thereof, that are about 2 to about 3 times higher than the mean clinical exposure achieved at the proposed clinical dose for monotherapy with 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline (i.e. mean $AUC_{\text{tau-ss}}$ of about 3.2 $\mu\text{g}\cdot\text{h}/\text{ml}$ and C_{max} of about 0.180 $\mu\text{g}/\text{ml}$); or is associated with a recorded systemic clinical exposure that is greater than the highest recorded systemic clinical exposure ($AUC_{0-\infty}$ of about 9.25 $\mu\text{g}\cdot\text{h}/\text{ml}$ and C_{max} of about 0.293 $\mu\text{g}/\text{ml}$); a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than about 10mg/kg/day; a dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline that is greater than 15 mg/day; a dose of 3-phenylsulfonyl-8-

piperazinyl-1-yl-quinoline that is greater than about 35 mg/day or any combination thereof per day.

24. The pharmaceutical composition of claim 21, further comprising:

c.) at least one acetylcholinesterase inhibitor.

25. The pharmaceutical composition of claim 24, wherein the acetylcholinesterase inhibitor is donepezil or pharmaceutically acceptable salts, hydrates, polymorphs or solvates thereof.

26. The pharmaceutical composition of claim 25, wherein the therapeutically effective amount of donepezil is selected from about 5 mg, about 10 mg or about 23 mg per day.

27. The pharmaceutical composition of claims 26, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is administered once a day.

28. The pharmaceutical composition of claim 21, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is provided to the subject by at least one route of administration selected from the group consisting of: orally; nasally; topically; buccally; sublingually; rectally; vaginally; and parenterally.

29. The pharmaceutical composition of claim 28, wherein the at least one route of administration of orally.

30. The pharmaceutical composition of claim 21, wherein the high daily dose of 3-phenylsulfonyl-8-piperazinyl-1-yl-quinoline or pharmaceutically acceptable salts, hydrates or solvates thereof is provided in a dose greater than about 36 mg.

31. The pharmaceutical composition of claim 30, wherein the high daily dose is about 35 mg to about 300 mg.

32. The pharmaceutical composition of claim 31, wherein the high daily dose is about 50 mg to about 270 mg.

33. The pharmaceutical composition of claim 31, wherein the high daily dose is about 60 mg to about 230 mg.
34. The pharmaceutical composition of claim 31, wherein the high daily dose is about 70 mg to about 200 mg.
35. The pharmaceutical composition of claim 31, wherein the high daily dose is about 70 mg.

FIGURE 1

Illustration of a 35 mg 3-phenylsulfonyl-8-piperazinyl-1yl-quinoline/5 mg donepezil capsule formulation.

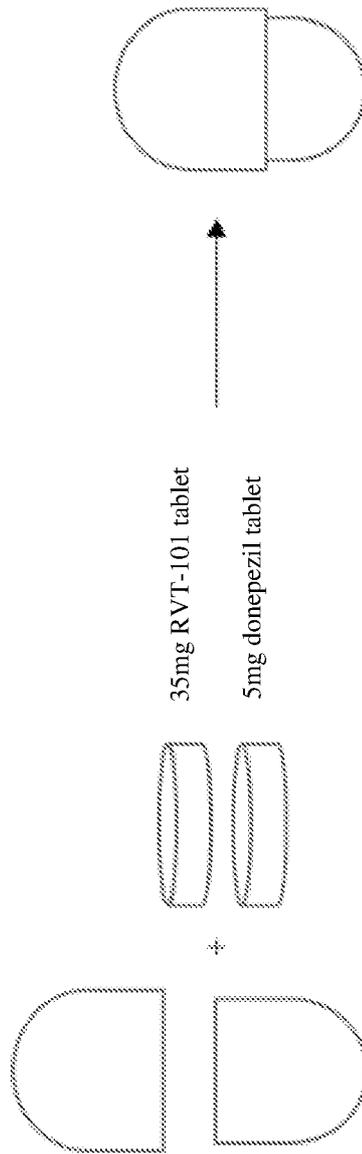


FIGURE 2

Illustration of a 35 mg 3-phenylsulfonyl-8-piperazinyll-1-yl-quinoline/10 mg donepezil capsule formulation.

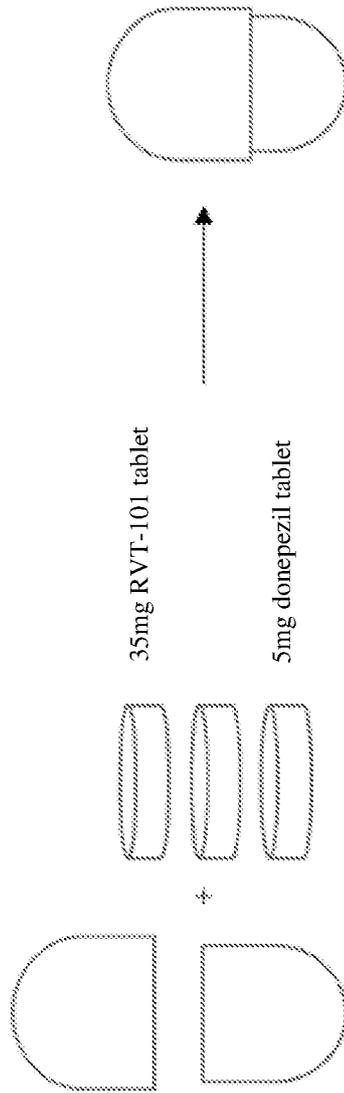


FIGURE 3

Illustration of a 35 mg 3-phenylsulfonyl-8-piperazinyll-1-yl-quinoline/10 mg donepezil capsule formulation.

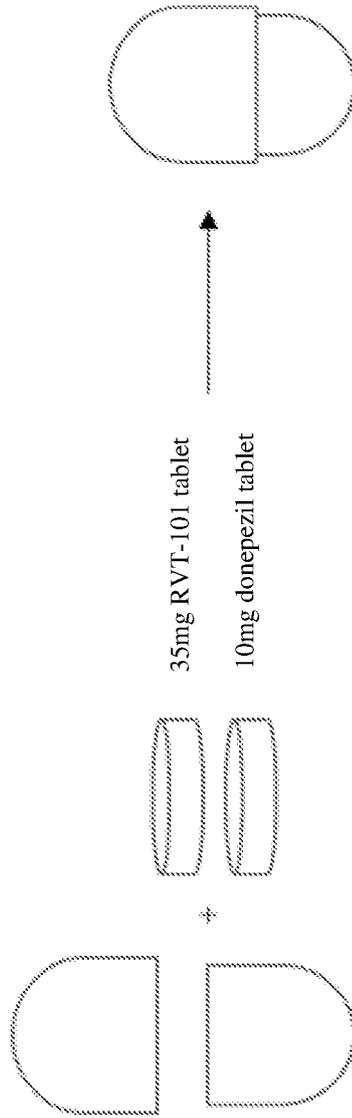


FIGURE 4

Illustration of a 35 mg 3-phenylsulfonyl-8-piperazinyll-1-yl-quinoline/10 mg donepezil overcoated tablet formulation.

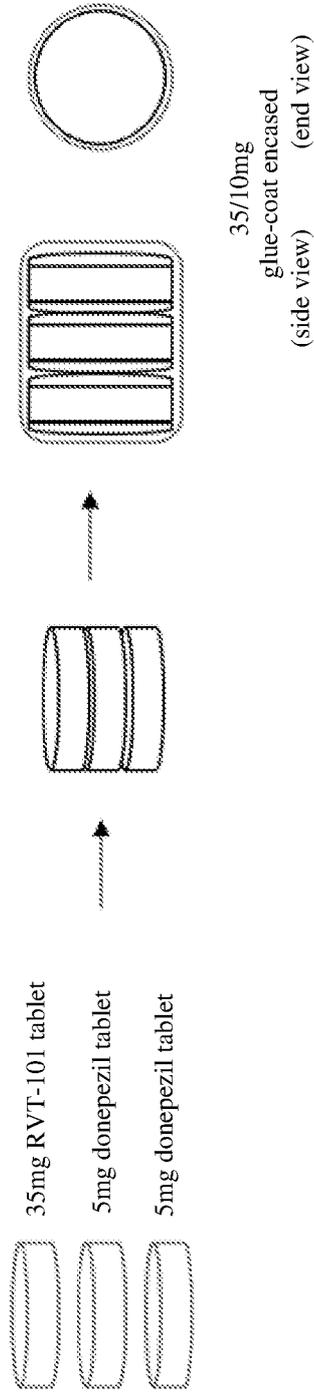


FIGURE 5

Illustration of a 35 mg 3-phenylsulfonyl-8-piperazinyll-1-yl-quinoline/10 mg donepezil overcoated tablet formulation.

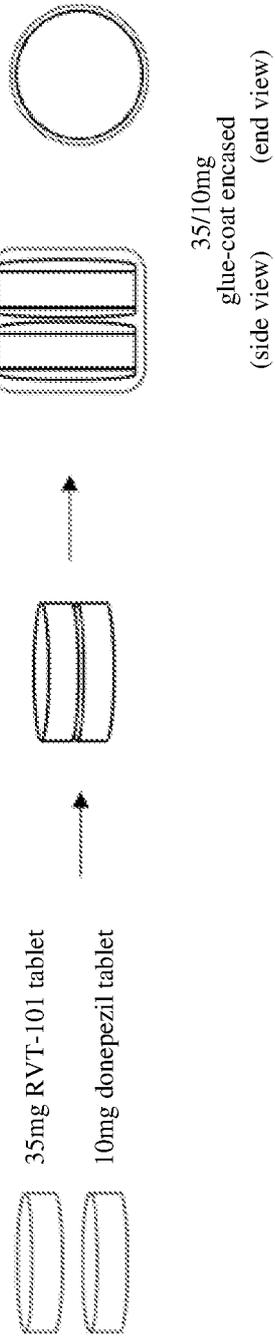


FIGURE 6

Illustration of a 35 mg 3-phenylsulfonyl-8-piperazinyloxy-quinoline/5 mg donepezil overcoated tablet formulation.

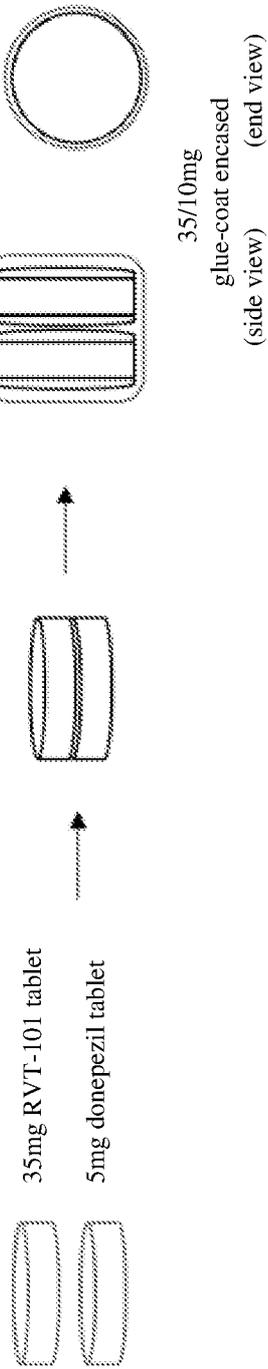


FIGURE 7

Illustration of a 35 mg 3-phenylsulfonyl-1-yl-piperazine/8-piperazine/1-yl-quinoline/10 mg donepezil encased caplet formulation.

