CLAIMS

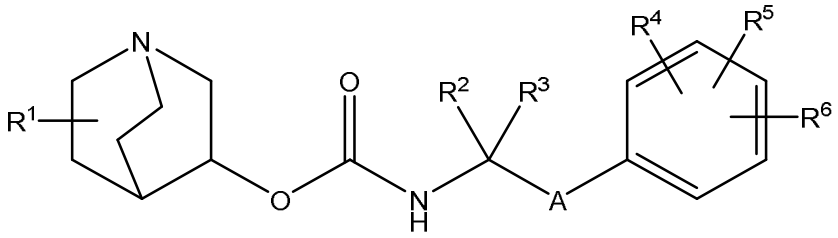
~~What is Claimed:~~

1. ~~A~~Use of a compound in the manufacture of a medicament for ~~method of~~ treating or preventing a neurodegenerative disease in a human subject by reducing glycosphingolipid concentration in brain tissue of the subject, whereby the concentration of glucosylceramide (GL-1) in the cerebrospinal fluid (CSF) of the subject is reduced by at least 30%, wherein the neurodegenerative disease is selected from Parkinson's disease (PD) and dementia with Lewy Bodies (DLB) and:

(a) wherein the subject does not have (*e.g.* has not been diagnosed as having, or being at risk of having) a lysosomal storage disease;

(b) wherein the subject is a heterozygous carrier of one or more glucocerebrosidase 1 gene (*GBA1*) mutations;

~~the method comprising administering to the subject an effective amount of~~ wherein the compound is a compound of formula (I),



(I)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is selected from hydrogen, halogen (*e.g.* fluorine), cyano, nitro, hydroxy, thio, amino, C_{1-6}-alkyl (*e.g.* methyl or ethyl), C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkyloxy, C_{2-6}-alkenyloxy, and C_{2-6}-alkynyloxy, wherein said alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, or alkynyloxy is optionally substituted with one or more (*e.g.* 1, 2, or 3) groups selected from halogen, cyano, nitro, hydroxy, thio, or amino;

R^2 and R^3 are independently selected from C_{1-3}-alkyl, optionally substituted by one or more (*e.g.* 1, 2, or 3) halogens, or R^2 and R^3 together form a cyclopropyl or cyclobutyl group, optionally substituted by one or more (*e.g.* 1 or 2) halogens;

R^4, R^5, and R^6 are each independently selected from hydrogen, halogen, nitro, hydroxy, thio, amino, C_{1-6}-alkyl, and C_{1-6}-alkyloxy, wherein said alkyl or alkyloxy is optionally substituted by one or more (*e.g.* 1, 2, or 3) groups selected from halogen, hydroxy, cyano, and C_{1-6}-alkyloxy; and

A is a 5- or 6-membered aryl or heteroaryl group (*e.g.* phenyl or thiazolyl), optionally substituted with 1, 2, or 3 groups independently selected from halogen, hydroxy, thio, amino, nitro, C_{1-6}-alkyloxy, and C_{1-6}-alkyl.

2. The ~~method~~ use of claim 1, wherein:

R^1 is selected from hydrogen, fluorine, methyl, and ethyl, wherein said methyl or ethyl is optionally substituted by 1 or 2 groups selected from halogen, hydroxy, thio, or amino;~~.~~

~~3. The method of claim 1 or 2, wherein~~ R^2 and R^3 are each independently selected from methyl and ethyl groups, optionally substituted with one or more fluorines;~~.~~

~~4. The method of any one of claims 1 to 3, wherein~~ R^4 is selected from a halogen (*e.g.* fluorine), C_{1-3}-alkyl (*e.g.* methyl), and C_{1-3}-alkyloxy (*e.g.* methoxy or ethoxy), wherein said alkyl or alkyloxy is optionally substituted by one or more (*e.g.* 1, 2, or 3) groups selected from a halogen and C_{1-3}-alkyloxy (*e.g.* methoxy or ethoxy);~~.~~

~~5. The method of any one of claims 1 to 4, wherein~~ R^5 and R^6 are each hydrogen;~~.~~

~~6. The method of any one of claims 1 to 5, wherein~~ R^4 is fluorine or 2-methoxyethoxy, and R^5 and R^6 are hydrogen;~~.~~

~~7. The method of any one of claims 1 to 6, wherein~~ R^4 is positioned at the 4-position of the phenyl ring to which it is attached (*i.e. para* to the A substituent);~~.~~

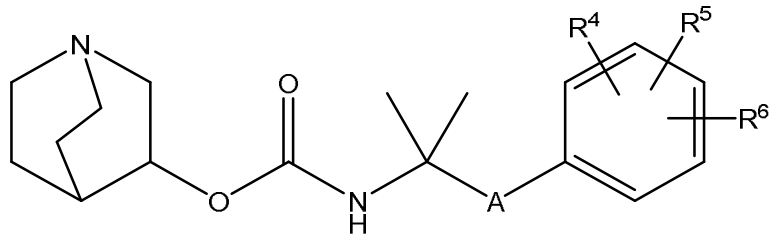
~~8. The method of any one of claims 1 to 7, wherein~~ A is phenyl, optionally substituted with 1, 2, or 3 groups independently selected from halogen, hydroxy, thio, amino, nitro, C_{1-6}alkyloxy, and C_{1-6}alkyl (*e.g.* methyl)~~.~~

~~9. The method of claim 8~~, optionally wherein the two groups attached to the A substituent are positioned in a 1,3- or a 1,4- relationship to each other (*i.e.* meta or para); and/or~~.~~

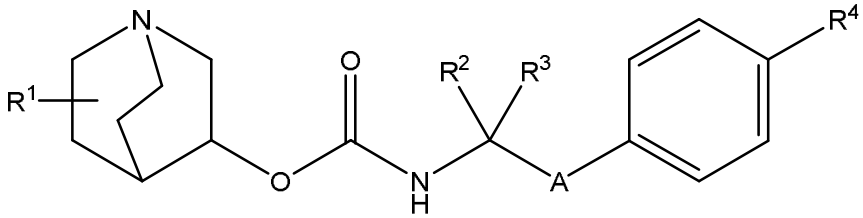
~~10. The method of any one of claims 1 to 7, wherein~~ A is a 5-membered heteroaryl group which contains 1 or 2 heteroatoms selected from N and S~~.~~

~~11. The method of claim 10~~, optionally wherein the two groups attached to the A substituent are positioned in a 1,3- relationship to each other (*i.e.* meta).

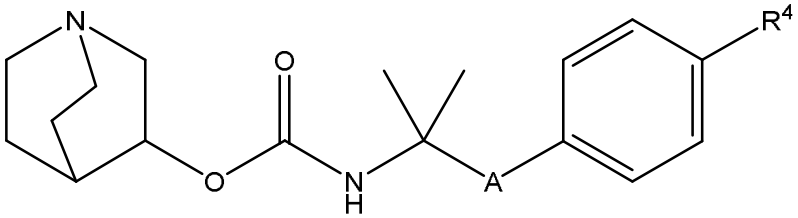
~~12~~3. The ~~method~~ use of ~~any one of claims 1 to 11~~claim 1 or claim 2, wherein said compound is a compound of formula (II), (III), ~~or~~ (IV), (V), (VI), (VII), (VIII), (IX), or (XI),



(II)



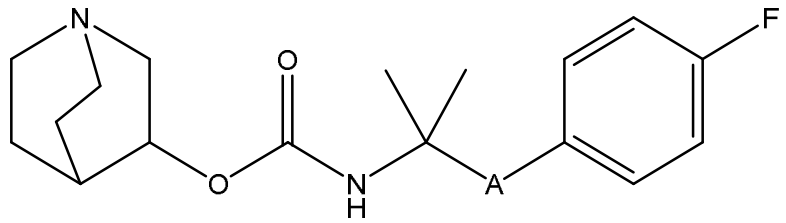
(III)



(IV)

~~or a pharmaceutically acceptable salt or prodrug thereof.~~

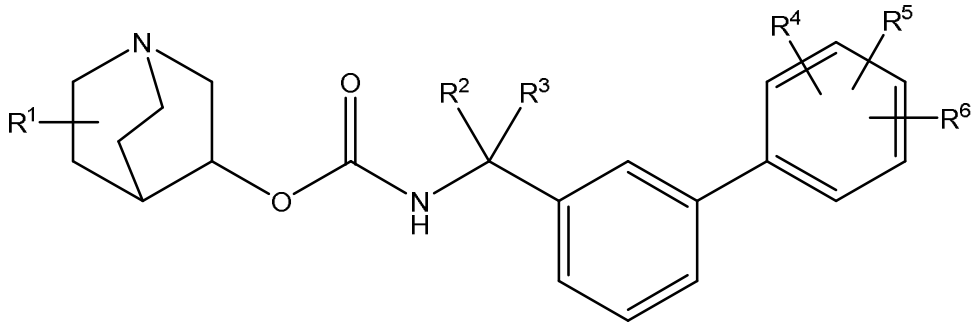
~~13. The method of any of claims 1 to 11, wherein said compound is a compound of formula (V),~~



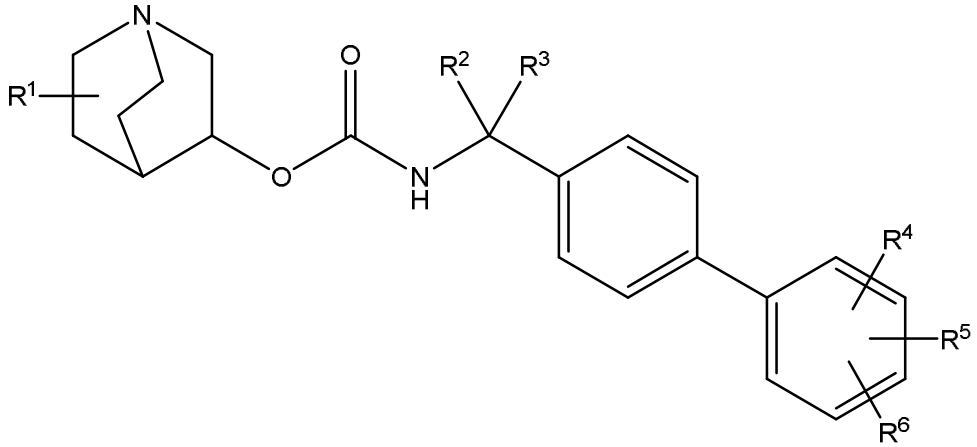
(V)

~~or a pharmaceutically acceptable salt or prodrug thereof.~~

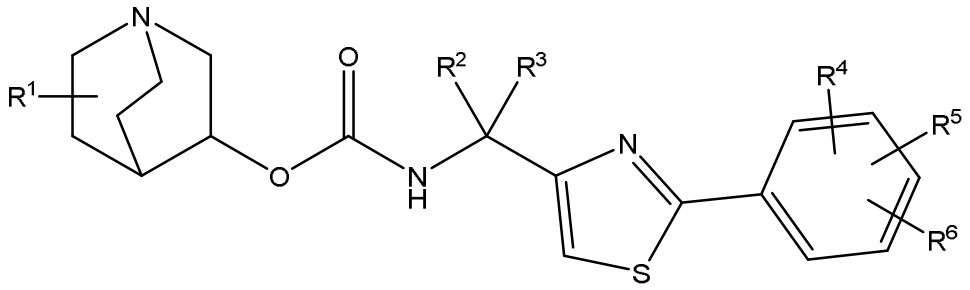
~~14. The method of any one of claims 1 to 11, wherein said compound is a compound of formula (VI), (VII), or (VIII),~~



(VI)



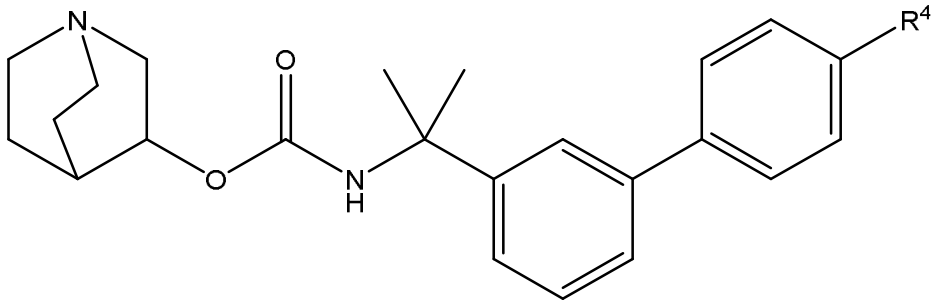
(VII)



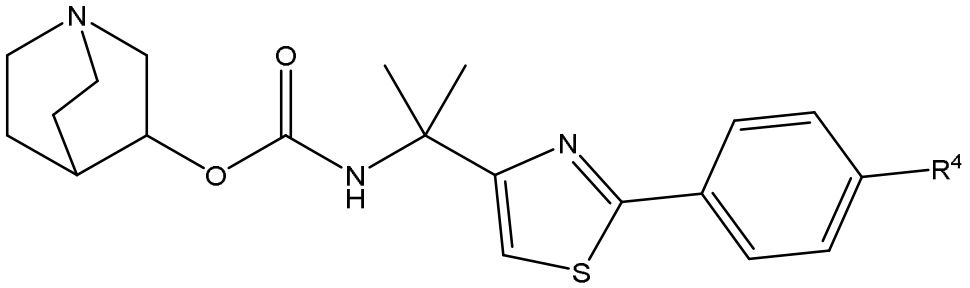
(VIII)

~~or a pharmaceutically acceptable salt or prodrug thereof.~~

~~15. The method of any of claims 1 to 11, wherein said compound is a compound of formula (IX) or (XI),~~



(IX)



(XI)

or a pharmaceutically acceptable salt or prodrug thereof~~.~~

~~16. The method of claim 15~~, optionally wherein the compound is a compound of formula (IX) or (XI) wherein R^4 is fluorine.

~~17~~4. The ~~method~~ use of claim 1, wherein said compound is selected from: quinuclidin-3-yl (2-(4'-fluoro-[1,1'-biphenyl]-3-yl)propan-2-yl)carbamate; (*S*)-quinuclidin-3-yl (2-(2-(4-

fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate; (*S*)-quinuclidin-3-yl (2-(4'-(2-methoxyethoxy)-[1,1'-biphenyl]-4-yl)propan-2-yl)carbamate; and the pharmaceutically acceptable salts and prodrugs thereof.

~~18. The method of claim 1, wherein said compound is quinuclidin-3-yl (2-(4'-fluoro-[1,1'-biphenyl]-3-yl)propan-2-yl)carbamate.~~

~~19. The method of claim 1, wherein said compound is (*S*)-quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate.~~

~~20. The method of claim 1~~, optionally wherein the compound is an acid addition salt form of (*S*)-quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate, selected from the hydrochloride, hydroxysuccinate, and malate.

~~21~~5. The ~~method~~ use of any one of claims 1 to ~~20~~4, wherein the subject is a heterozygous carrier of one or more glucocerebrosidase 1 gene (*GBA1*) mutations.

~~22. The method of claim 21~~, optionally wherein the one or more *GBA1* mutations are selected from L444P, 84GG, A456P, R120W, D409H, E235A, E340A, N370S, E326K, R496C, G193W, T369M, R496H, and S271G.

~~23~~6. The ~~method~~ use of any one of the preceding claims, wherein the brain tissue is (or comprises) neurons; and/or wherein said brain tissue is a neuron of the substantia nigra, cerebral cortex, hippocampus, frontal lobes, and/or temporal lobes of said subject.

~~24. A method of treating or preventing a neurodegenerative disease in a human subject by reducing glycosphingolipid concentration in brain tissue of the subject, whereby the concentration of glucosylceramide (GL-1) in the cerebrospinal fluid (CSF) of the subject is reduced by at least 30%, wherein the neurodegenerative disease is selected from Parkinson's disease (PD) and dementia with Lewy Bodies (DLB), and wherein the subject is a heterozygous carrier of one or more glucocerebrosidase 1 gene (*GBA1*) mutations; the method comprising administering to the subject an effective amount of a compound of formula (I) as defined in any one of claims 1 to 20.~~

~~25. The method of claim 24, wherein the one or more *GBA1* mutations are selected from L444P, 84GG, A456P, R120W, D409H, E235A, E340A, N370S, E326K, R496C, G193W, T369M, R496H, and S271G.~~

~~26~~7. The ~~method~~ use of any one of claims 1 to ~~25~~6, wherein the ~~method~~ treatment results in a reduction in GL-1 concentration in CSF of at least 40% (*e.g.* at least 50%, at least 60%, or at least 70%).

~~27~~8. The ~~method~~ use of any one of claims 1 to ~~26~~7, wherein the ~~method~~ treatment results in the reduction in GL-1 concentration in the CSF within 3 months of commencing treatment (*e.g.* within 2 months, 4 weeks, 2 weeks, or 1 week of commencing treatment).

~~28~~9. The ~~method~~ use of any one of claims 1 to ~~27~~8, wherein:

(i) said subject has been diagnosed as having Parkinson's disease (*e.g.* early-stage Parkinson's disease)~~.~~, optionally wherein the treatment prevents, reduces, or reverses motor dysfunction (*e.g.* tremor), bradykinesia, rigidity, postural instability, and/or impaired balance; or

~~29. The method of any one of claims 1 to 27, wherein~~(ii) said subject has been diagnosed as being at risk of developing Parkinson's disease, and wherein the ~~method~~ treatment prevents or delays the onset and/or development of Parkinson's disease in the subject.

~~30. The method of any one of claims 1 to 28, wherein the subject has a diagnosis of Parkinson's disease, and wherein the method prevents, reduces, or reverses motor dysfunction (*e.g.* tremor), bradykinesia, rigidity, postural instability, and/or impaired balance.~~

~~31~~10. The ~~method~~ use of claim ~~28~~9, wherein the subject has a diagnosis of Parkinson's disease and wherein the subject has at least one of the following characteristics: i) a family history of Parkinson's disease; ii) a baseline Montreal Cognitive Assessment (MoCA) score of ≤ 26 (for example, from 20 to 25); and iii) a Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Part II + III) score of at least 35~~.~~

~~32. The method of claim 28~~, or wherein the subject has a diagnosis of early-stage Parkinson's disease characterized by: i) at least two of the following conditions: resting tremor, postural instability, akinesia/hypokinesia, and muscle rigidity; ii) a Hoehn and Yahr Scale stage of ≤2 at baseline; and/or iii) a Parkinson's diagnosis of ≥2 years.

~~33~~11. The ~~method~~ use of ~~any one of claims 28 to 31~~claim 9 or claim 10, wherein the subject has been treated historically with medications selected from dihydroxyphenylalanine (DOPA)

or derivatives thereof (*e.g.* levodopa/carbidopa), monamine oxidase B inhibitors (*e.g.* rasagiline or selegiline), dopamine agonists (*e.g.* ropinirole, bromocriptine, cabergoline, pergolide, pramipexole, or apomorphine), Catechol-O-methyltransferase inhibitors (*e.g.* entacapone, tolcapone), anticholinergics (*e.g.* artane, cogentin), adamantane derivatives, and/or acetylcholinesterase inhibitors (*e.g.* tacrine, rivastigmine, galantamine, donepezil, or memantine).

~~34~~12. The ~~method~~ use of any one of claims 1 to ~~27~~11, wherein the subject has a diagnosis of dementia with Lewy Bodies (DLB)~~.~~

~~35. The method of claim 34~~, optionally wherein said ~~method~~ treatment prevents, reduces, or reverses the progression of dementia in the subject.

~~36~~13. ~~A~~ Use of a compound of formula (I) as defined in any one of claims 1 to 4, or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for use in a therapeutic method of reducing glycosphingolipid concentration in brain tissue of a human subject in need thereof, whereby the concentration of glucosylceramide (GL-1) in the cerebrospinal fluid (CSF) of the subject is reduced as a result of the method, wherein the subject does not have (*e.g.* has not been diagnosed as having, or being at risk of having) a lysosomal storage disease~~; the method comprising administering to the subject an effective amount of a compound of formula (I) as defined in any one of claims 1 to 20~~.

~~37~~14. The ~~method~~ use of claim ~~36~~13, wherein the therapeutic method results in a reduction in GL-1 concentration in CSF of at least 30% (*e.g.* at least 40%, at least 50%, at least 60%, or at least 70%)~~.~~

~~38. The method of claim 37~~, optionally wherein the therapeutic method results in the reduction in GL-1 concentration in the CSF is within 3 months of commencing treatment (*e.g.* within 2 months, 1 month, 3 weeks, 2 weeks, or 1 week of commencing treatment).

~~39. The method of any one of claims 1 to 38, wherein said brain tissue is a neuron of the substantia nigra, cerebral cortex, hippocampus, frontal lobes, and/or temporal lobes of said subject.~~

~~40~~15. The ~~method~~ use of any one of claims 1 to ~~39~~14, wherein said compound, or pharmaceutically acceptable salt or prodrug thereof, is ~~administered~~ for administration by systemic administration, *e.g.* via a non-parenteral route.

~~41. The method of claim 40~~, optionally wherein said compound, or pharmaceutically acceptable salt or prodrug thereof, is administered orally; and/or.

~~42. The method of any one of claims 1 to 41,~~ wherein said subject is administered a daily dose of about 2 mg to about 30 mg of said compound, or pharmaceutically acceptable salt or prodrug thereof (*e.g.* from 2 mg to 20 mg, or from 2 mg to 10 mg, or from 4 mg to 8 mg, or from 10 to 20 mg, from 4 mg to 15 mg, or a dose selected from 4, 8, and 15 mg).

~~43~~16. The ~~method~~ use of any one of claims 1 to ~~42~~15, wherein the treatment or therapeutic method prevents, reduces, or reverses deterioration in cognitive domains in the subject, optionally wherein the treatment or therapeutic method prevents, reduces, or reverses deterioration in attention and concentration, executive functions, memory (*e.g.* working memory), language, visuo-constructional skills, conceptual thinking, calculations, orientation, decision making, and/or problem solving.

~~44~~17. The ~~method~~ use of any one of claims 1 to ~~42~~16, wherein the treatment or therapeutic method is effective to improve cognitive ability or reduce cognitive deficits in the subject as measured by a reduction in the time taken to complete the trail-making test (TMT), TMT-A and/or TMT-B, a reduction in the difference between TMT-A time and TMT-B time (TMT-B – TMT-A), for example, a reduction of at least 10%, or at least 20%, or at least 30%, or at least 40%, or at least 50% (*e.g.* wherein TMT-A decreases by 5-20%, and/or TMT-B decreases by 25-30%, and/or [TMT-B – TMT-A] decreases by 25-30%).

~~45. The method of claim 43, wherein the method prevents, reduces, or reverses deterioration in attention and concentration, executive functions, memory (*e.g.* working memory), language, visuo-constructional skills, conceptual thinking, calculations, orientation, decision making, and/or problem solving~~.

~~46~~18. The ~~method~~ use of claim 1 or claim 13~~, claim 24 or claim 36~~, wherein the subject is a heterozygous carrier of one or more glucocerebrosidase 1 gene (*GBA1*) mutations, and the compound is a malate acid addition salt of (*S*)-quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-

4-yl)propan-2-yl)carbamate and is orally administered at a daily dose of about 15 mg (measured as the equivalent amount of free base).

~~47~~19. The ~~method~~ use of claim ~~46~~18, wherein the concentration of the compound (measured as the equivalent amount of free base) in the CSF of the subject is at least 4 ng/ml (*e.g.* at least 8 ng/ml, or at least 10 ng/ml), within 3 months of commencing treatment (*e.g.* within 2 months, 1 month, 3 weeks, 2 weeks, or 1 week of commencing treatment).

~~48~~20. The ~~method~~ use of claim ~~46~~ 18 or claim ~~47~~19, wherein the treatment or therapeutic method results in increased blood flow in the brain (*e.g.* in one or more of the frontal, occipital, parietal, or temporal lobes), for example, as shown by fMRI imaging and/or increased nodal connectivity in the brain (*e.g.* between posterior and anterior aspects of the brain, and/or between occipital-parietal structures and frontal, temporal, and/or limbic structures, for example, as shown by fMRI imaging).

~~49. A compound, or a pharmaceutically acceptable salt or prodrug thereof, as defined in any one of claims 1 to 20 for use in a method of treating or preventing a neurodegenerative disease in a human subject by reducing glycosphingolipid concentration in brain tissue of the subject, whereby the concentration of glucosylceramide (GL-1) in the cerebrospinal fluid (CSF) of the subject is reduced by at least 30%, wherein the neurodegenerative disease is selected from Parkinson's disease (PD) and dementia with Lewy Bodies (DLB), and wherein the subject does not have (*e.g.* has not been diagnosed as having, or being at risk of having) a lysosomal storage disease.~~

~~50. The compound for use according to claim 49, wherein said method of treating or preventing is as defined in any one of claims 21 to 23, 26 to 35, or 39 to 48.~~

~~51. Use of a compound, or a pharmaceutically acceptable salt or prodrug thereof, as defined in any one of claims 1 to 20 in the manufacture of a medicament for use in a method of treating or preventing a neurodegenerative disease in a human subject by reducing glycosphingolipid concentration in brain tissue of the subject, whereby the concentration of glucosylceramide (GL-1) in the cerebrospinal fluid (CSF) of the subject is reduced by at least 30%, wherein the neurodegenerative disease is selected from Parkinson's disease (PD) and dementia with Lewy Bodies (DLB), and wherein the subject does not have (*e.g.* has not been diagnosed as having, or being at risk of having) a lysosomal storage disease.~~

~~52. The use of claim 51, wherein said method of treating or preventing is as defined in any one of claims 21 to 23, 26 to 35, or 39 to 48.~~

~~53. A compound, or a pharmaceutically acceptable salt or prodrug thereof, as defined in any one of claims 1 to 20 for use in a method of treating or preventing a neurodegenerative disease in a human subject by reducing glycosphingolipid concentration in brain tissue of the subject, whereby the concentration of glucosylceramide (GL-1) in the cerebrospinal fluid (CSF) of the subject is reduced by at least 30%, wherein the neurodegenerative disease is selected from Parkinson's disease (PD) and dementia with Lewy Bodies (DLB), and wherein the subject is a heterozygous carrier of one or more glucocerebrosidase 1 gene (*GBA1*) mutations.~~

~~54. The compound for use according to claim 53, wherein said method of treating or preventing is as defined in any one of claims 25 to 35, or 39 to 48.~~

~~55. Use of a compound, or a pharmaceutically acceptable salt or prodrug thereof, as defined in any one of claims 1 to 20 in the manufacture of a medicament for use in a method of treating or preventing a neurodegenerative disease in a human subject by reducing glycosphingolipid concentration in brain tissue of the subject, whereby the concentration of glucosylceramide (GL-1) in the cerebrospinal fluid (CSF) of the subject is reduced by at least 30%, wherein the neurodegenerative disease is selected from Parkinson's disease (PD) and dementia with Lewy Bodies (DLB), and wherein the subject is a heterozygous carrier of one or more glucocerebrosidase 1 gene (*GBA1*) mutations.~~

~~56. The use of claim 55, wherein said method of treating or preventing is as defined in any one of claims 25 to 35, or 39 to 48.~~