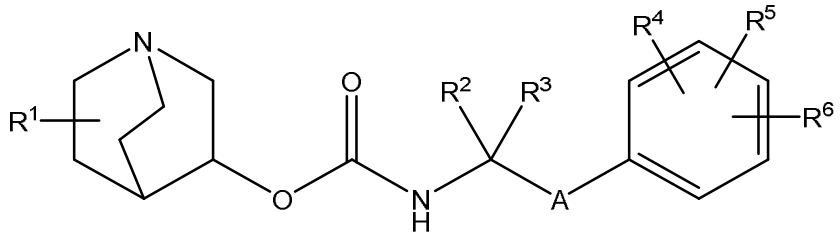
CLAIMS

1. Use of a compound in the manufacture of a medicament for 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;

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 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;

R^2 and R^3 are each independently selected from methyl and ethyl groups, optionally substituted with one or more fluorines;

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);

R^5 and R^6 are each hydrogen;

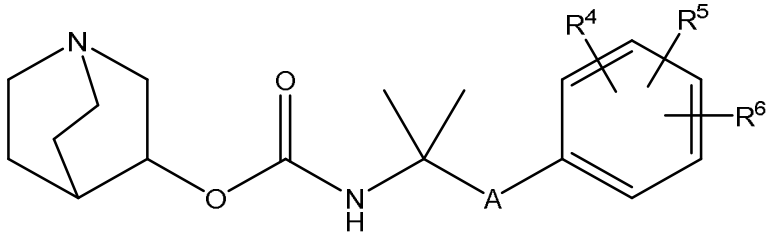
R^4 is fluorine or 2-methoxyethoxy, and R^5 and R^6 are hydrogen;

R^4 is positioned at the 4-position of the phenyl ring to which it is attached (*i.e.* *para* to the A substituent);

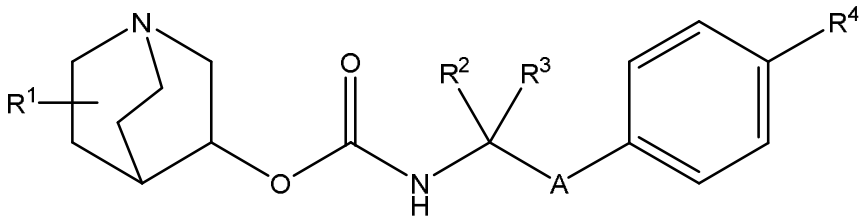
A is phenyl, optionally substituted with 1, 2, or 3 groups independently selected from halogen, hydroxy, thio, amino, nitro, C_{1-6}alkyloxy, and C_{1-6}alkyl (*e.g.* methyl), optionally wherein the two groups attached to the A substituent are positioned in a 1,3- or a 1,4- relationship to each other (*i.e.* meta or para); and/or

A is a 5-membered heteroaryl group which contains 1 or 2 heteroatoms selected from N and S, optionally wherein the two groups attached to the A substituent are positioned in a 1,3- relationship to each other (*i.e.* meta).

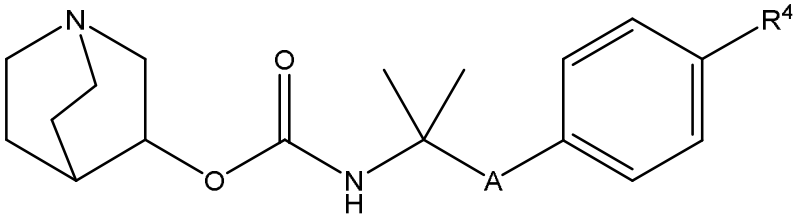
3. The use of claim 1 or claim 2, wherein said compound is a compound of formula (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), or (XI),



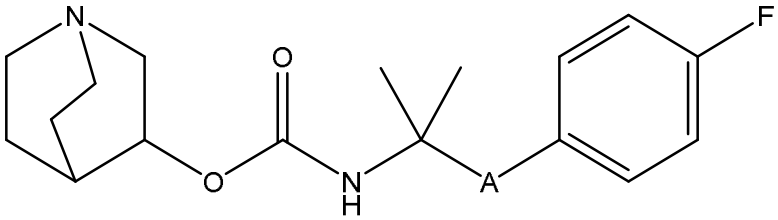
(II)



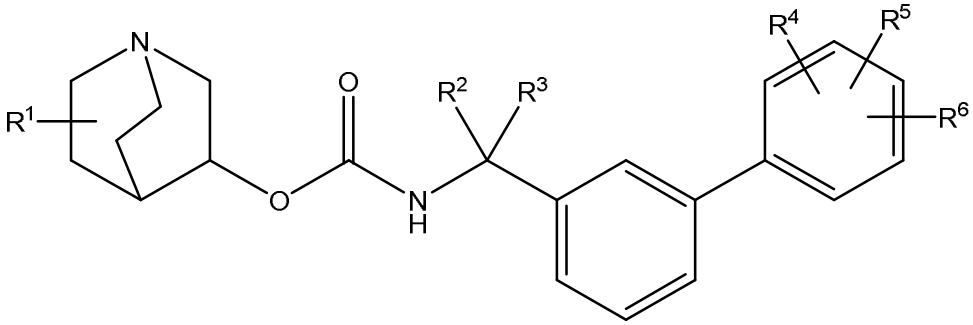
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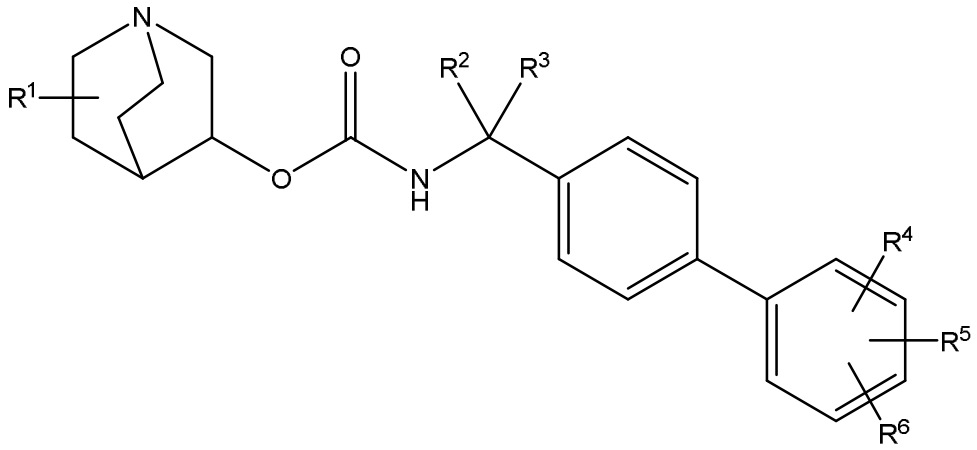
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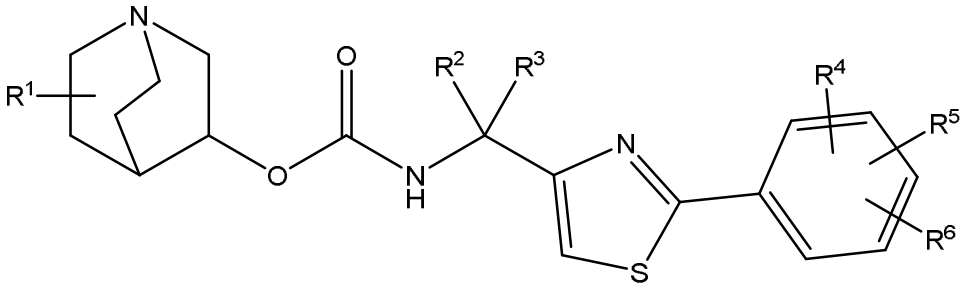
(V)



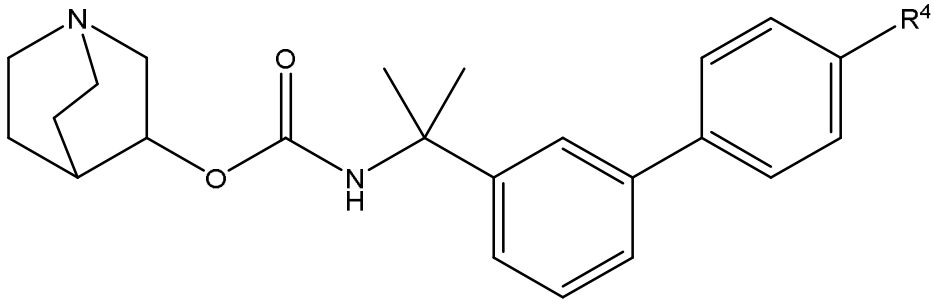
(VI)



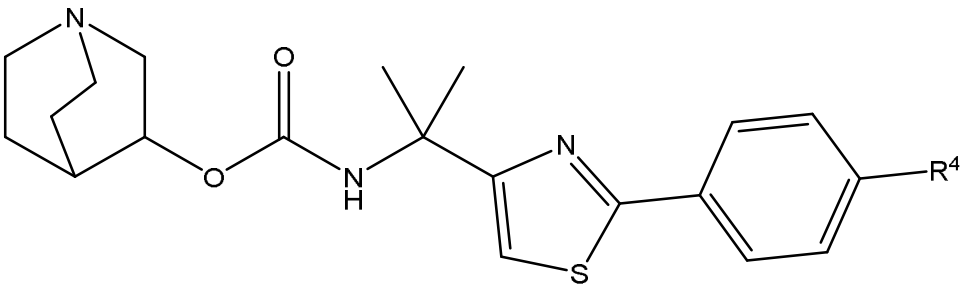
(VII)



(VIII)



(IX)



(XI)

or a pharmaceutically acceptable salt or prodrug thereof, optionally wherein the compound is a compound of formula (IX) or (XI) wherein R^4 is fluorine.

4. The 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, 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.

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

6. The 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.

7. The use of any one of claims 1 to 6, wherein the 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%).

8. The use of any one of claims 1 to 7, wherein the 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).

9. The use of any one of claims 1 to 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

(ii) said subject has been diagnosed as being at risk of developing Parkinson's disease, and wherein the treatment prevents or delays the onset and/or development of Parkinson's disease in the subject.

10. The use of claim 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, 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.

11. The use of 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).

12. The use of any one of claims 1 to 11, wherein the subject has a diagnosis of dementia with Lewy Bodies (DLB), optionally wherein said treatment prevents, reduces, or reverses the progression of dementia in the subject.

13. 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.

14. The use of claim 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%), 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).

15. The use of any one of claims 1 to 14, wherein said compound, or pharmaceutically acceptable salt or prodrug thereof, is for administration by systemic administration, *e.g.* via a non-parenteral route, optionally wherein said compound, or pharmaceutically acceptable salt or prodrug thereof, is administered orally; and/or 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).

16. The use of any one of claims 1 to 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.

17. The use of any one of claims 1 to 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%)..

18. The use of claim 1 or claim 13, 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).

19. The use of claim 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).

20. The use of claim 18 or claim 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).