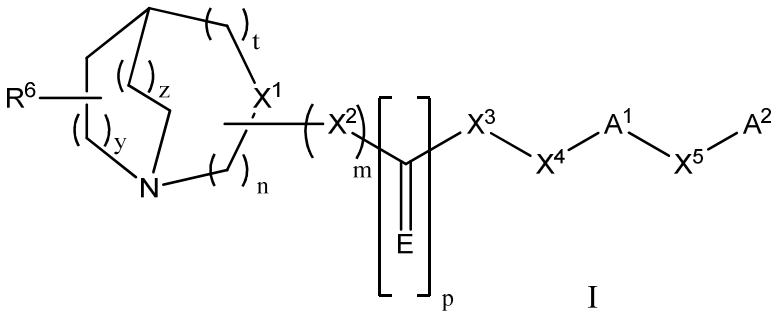
Claims

1. A compound represented by the following structural formula,



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or a pharmaceutically acceptable salt thereof, wherein:

n is 1, 2 or 3;

m is 1;

p is 1;

t is 0 or 1;

y is 1;

z is 0 or 1;

E is O;

X^1 is CR^1;

X^2 is O;

X^3 is -NH, or $–NR^3$;

X^4 is CR^4R^5;

X^5 is a direct bond or O;

R^1 is H, or $(C_1$-$C_6)$alkyl;

R^3 is -H or $(C_1$-$C_6)$alkyl;

R^4 and R^5 are independently selected from H, $(C_1$-$C_6)$alkyl, or taken together with the carbon to which they are attached to form a spiro $(C_3$-$C_{10})$cycloalkyl ring or spiro $(C_3$-$C_{10})$cycloalkoxy ring;

R^6 is -H or

$(C_1$-$C_6)$alkyl optionally substituted by one to four halo;

A^1 is $(C_2$-$C_6)$alkynyl; $(C_3$-$C_{10})$cycloalkyl, $(C_6$-$C_{12})$aryl, $(C_2$-$C_9)$heteroaryl, or $(C_2$-$C_9)$heterocycloalkyl wherein A^1 is optionally substituted with one or more substituents selected from the group consisting of halo, $(C_1$-$C_6)$alkyl optionally substituted by one to

three halo; (C_1-C_6)alkenyl, amino, (C_1-C_6)alkylamino, (C_1-C_6)dialkylamino, (C_1-C_6)alkoxy, nitro, CN, -OH, (C_1-C_6)alkyloxy optionally substituted by one to three halo; (C_1-C_6)alkoxycarbonyl, and (C_1-C_6) alkylcarbonyl;

A^2 is (C_3-C_{10})cycloalkyl, (C_6-C_{12})aryl, (C_2-C_9)heteroaryl, or (C_2-C_9)heterocycloalkyl wherein A^2 is substituted with one or more substituents selected from the group consisting of (C_2-C_9)heterocycloalkyl, R^8R^9N-CO- wherein R^8 and R^9 are each independently selected from the group consisting of hydrogen and (C_1-C_6)alkyl or R^8 and R^9 can be taken together with the nitrogen to which they are attached to form a (C_2-C_9)heterocycloalkyl group optionally substituted by one to three halo groups, (C_1-C_6)alkylsulfonyl optionally substituted by one or two groups selected from (C_1-C_6)alkoxy and (C_3-C_{10})cycloalkyl;

(C_1-C_6)alkyl substituted by one to four substituents selected from the group consisting of hydroxy, cyano, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_2-C_9)heterocycloalkyl, (C_2-C_9)heteroaryl optionally substituted by (C_1-C_6)alkoxy; or (C_3-C_{10})cycloalkoxy optionally substituted by (C_1-C_6)alkoxy; and

(C_1-C_6)alkyloxy substituted by one to four substituents selected from the group consisting of hydroxy, cyano, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_2-C_9)heterocycloalkyl, (C_2-C_9)heteroaryl optionally substituted by (C_1-C_6)alkoxy; or (C_3-C_{10})cycloalkoxy optionally substituted by (C_1-C_6)alkoxy.

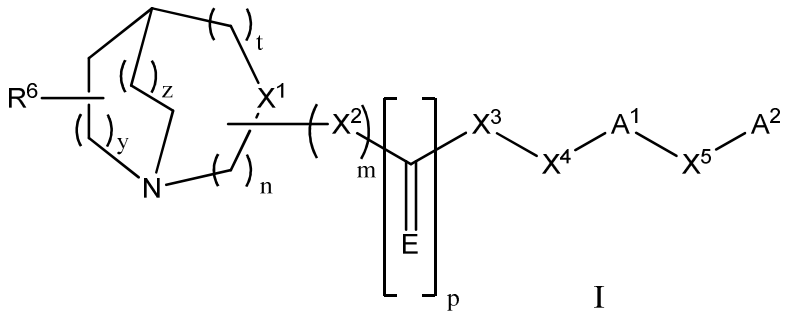
2. A compound according to claim 1, wherein n is 1; t is 0; y is 1 and z is 1.

3. A compound according to claim 1, wherein m is 1; E is O; X^2 is O and X^3 is NH.

4. A compound according to claim 1, wherein R^4 and R^5 are each (C_1-C_6)alkyl or taken together with the carbon to which they are attached to form a spiro (C_3-C_{10})cycloalkyl ring or a spiro (C_3-C_{10})cycloalkoxy ring.

5. A compound according to claim 1, wherein X^4 is CR^4R^5 wherein R^4 and R^5 are each independently methyl.

6. A compound represented by the following structural formula,



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or a pharmaceutically acceptable salt thereof, wherein:

n is 1, 2 or 3;

m is 1;

p is 1;

t is 0 or 1;

y is 1;

z is 0 or 1;

E is O;

X^1 is CR^1;

X^2 is O;

X^3 is -NH or $–NR^3$;

X^4 is a direct bond;

X^5 is a direct bond or O;

R^1 is H, or (C_1-C_6)alkyl;

R^3 is -H or (C_1-C_6)alkyl;

R^4 and R^5 are independently selected from H, (C_1-C_6)alkyl, or taken together with the carbon to which they are attached to form a spiro (C_3-C_{10})cycloalkyl ring or spiro (C_3-C_{10})cycloalkoxy ring;

R^6 is -H, or (C_1-C_6)alkyl optionally substituted by one to four halo;

A^1 is (C_6-C_{12})aryl, or (C_2-C_9)heteroaryl selected from isothiazole, furan, oxazole, isoxazole, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrimidine, pyridazine, indole, benzothiazole, benzoisoxazole, benzopyrazole, benzoimidazole, benzofuran, and benzooxazole, wherein A^1 is optionally substituted with one or more substituents selected from the group consisting of halo, (C_1-C_6)alkyl optionally substituted by one to three

halo; (C_1-C_6)alkenyl, amino, (C_1-C_6)alkylamino, (C_1-C_6)dialkylamino, (C_1-C_6)alkoxy, nitro, CN, -OH, (C_1-C_6)alkyloxy optionally substituted by one to three halo; (C_1-C_6)alkoxycarbonyl, and (C_1-C_6) alkylcarbonyl; and

A^2 is (C_6-C_{12})aryl or (C_2-C_9)heteroaryl; wherein A^2 is substituted with one or more substituents selected from the group consisting of:

halo, (C_1-C_6)alkylenyl, (C_1-C_6) alkylamino, (C_1-C_6)dialkylamino, O(C_3-C_6 cycloalkyl), (C_3-C_6) cycloalkoxy, (C_3-C_6) cycloalkyl, (C_1-C_6) alkoxycarbonyl, (C_1-C_6) alkylcarbonyl, (C_2-C_9)heterocycloalkyl;

R^8R^9N-CO-, wherein R^8 and R^9 are each independently selected from the group consisting of hydrogen and (C_1-C_6)alkyl or R^8 and R^9 can be taken together with the nitrogen to which they are attached to form a (C_2-C_9)heterocycloalkyl or (C_2-C_9)heterocycloalkyl group optionally substituted by one to three halo groups, (C_1-C_6)alkylsulfonyl optionally substituted by one or two groups selected from (C_1-C_6)alkoxy and (C_3-C_{10})cycloalkyl;

(C_1-C_6)alkyl substituted by one to four substituents selected from the group consisting of hydroxy, cyano, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_2-C_9)heterocycloalkyl, and (C_2-C_9)heteroaryl optionally substituted by (C_1-C_6)alkoxy; and (C_3-C_{10})cycloalkoxy optionally substituted by (C_1-C_6)alkoxy; and

(C_1-C_6)alkyloxy substituted by one to four substituents selected from the group consisting of halo, hydroxy, cyano, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_2-C_9)heterocycloalkyl, and (C_2-C_9)heteroaryl optionally substituted by (C_1-C_6)alkoxy; or (C_3-C_{10})cycloalkoxy optionally substituted by (C_1-C_6)alkoxy.

7. A compound according to claim 6, wherein n is 1; t is 0; y is 1 and z is 1.

8. A compound according to claim 6, wherein m is 1; E is O; X^2 is O and X^3 is NH.

9. A compound according to claim 6, wherein A^1 is (C_2-C_9)heteroaryl selected from isothiazole, furan, oxazole, isoxazole, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrimidine, pyridazine, indole, benzothiazole, benzoisoxazole, benzopyrazole, benzoimidazole, benzofuran, and benzooxazole.

10. A compound according to claim 9, wherein A^1 is benzooxazole.

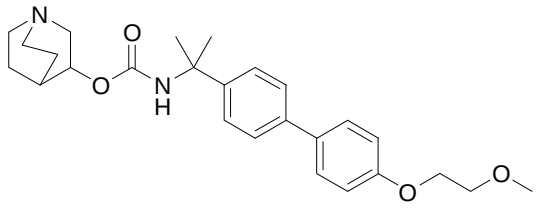
11. A compound according to claim 1 or claim 6, wherein R^6 is H.

12. A compound according to claim 1 or claim 6, where R^1 is hydrogen or methyl.

13. A compound according to claim 1 or claim 6, wherein X^5 is a direct bond.

14. A compound according to claim 1 or claim 6, wherein A^2 is $(C_6\text{-}C_{12})$aryl.

15. A compound represented by the formula



or a pharmaceutically acceptable salt thereof.

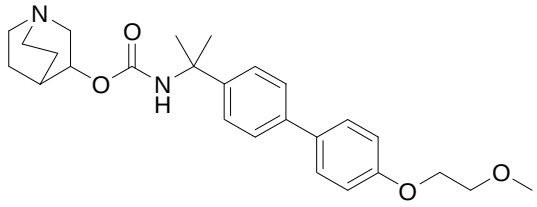
16. A pharmaceutical composition comprising a compound according to any one of claims 1 to 15 and at least one pharmaceutically acceptable carrier.

17. A compound according to any one of claims 1 to 15 or a pharmaceutical composition according to claim 16 for use in therapy.

18. A compound according to any one of claims 1 to 15 or a pharmaceutical composition according to claim 16 for use in the treatment of a disease or disorder mediated by glucosylceramide synthase (GCS) or a disease or disorder in which GCS is implicated, wherein the disease or disorder is cancer, a metabolic disorder, or a neuropathic disease, or a disease in which excessive glycolipid synthesis occurs selected from atherosclerosis, polycystic kidney disease, and renal hypertrophy.

19. A compound or pharmaceutical composition for use according to claim 18, wherein the disease or disorder is a neuropathic disease selected from Alzheimer's disease and Parkinson's disease.

20. A compound or pharmaceutical composition for use according to claim 18, wherein the compound is represented by the following structural formula,



or a pharmaceutically acceptable salt thereof.

21. A compound according to any one of claims 1 to 15 or a pharmaceutical composition according to claim 16 for use in the treatment of a lysosomal storage disease.

22. The compound or pharmaceutical composition for use of claim 21, wherein the lysosomal storage disease is selected from the group consisting of Gaucher, Fabry, G_{M1}-gangliosidosis, G_{M2} Activator deficiency, Tay-Sachs and Sandhoff.

23. The compound or pharmaceutical composition for use of claim 22, wherein the lysosomal storage disease is Fabry.

24. The compound or pharmaceutical composition for use of claim 22, wherein the lysosomal storage disease is Gaucher type 2 or Gaucher type 3.

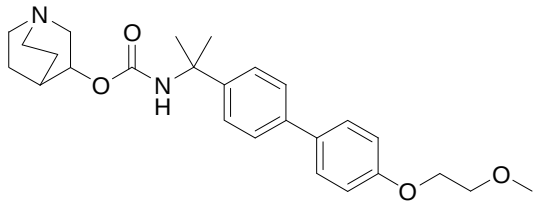
25. The compound or pharmaceutical composition for use of claim 21, wherein the treatment comprises the step of administering to the subject a therapeutically effective amount of a lysosomal enzyme.

26. The compound or pharmaceutical composition for use of claim 25, wherein the lysosomal enzyme is selected from the group consisting of glucocerebrosidase, alpha-galactosidase A, Hexosaminidase A, Hexosaminidase B and G_{M1}-ganglioside-β-galactosidase.

27. The compound or pharmaceutical composition for use of claim 25, wherein the lysosomal enzyme is alpha-galactosidase A.

28. The compound or pharmaceutical composition for use of claim 25, wherein the lysosomal enzyme is glucocerebrosidase.

29. The compound or pharmaceutical composition for use of claim 21, wherein the compound is represented by the following structural formula,



or a pharmaceutically acceptable salt thereof.

30. A compound for use in the treatment, amelioration or prevention of a renal cystic disease selected from acquired renal cystic disease (ARCD), dialysis-associated cystic disease, autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease (ARPKD), congenital multi cystic kidney (CMK), multi cystic dysplastic kidney, end-stage renal disease (ESRD), medullary sponge kidney (MSK), nephronophthisis-medullary cystic kidney disease complex (NMCD), nephronophthisis-uremic medullary cystic disease complex, juvenile nephronophthisis, medullary cystic disease, renal cell carcinoma (RCC), tuberous sclerosis (TS), and von Hippel-Lindau syndrome (VHLS), wherein said compound is (S)-Quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate, or Quinuclidin-3-yl (2-(4'-fluoro-[1,1'-biphenyl]-3-yl)propan-2-yl)carbamate, or wherein said compound is a compound as claimed in any one of claims 1 to 15.