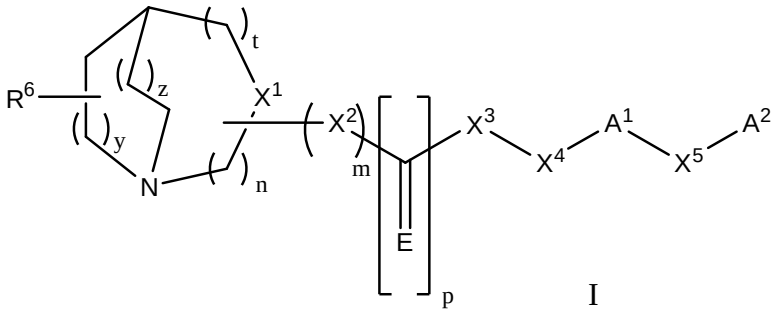
Claims

1. Use of a compound in the manufacture of a medicament for treating a subject diagnosed as having a lysosomal storage disease, wherein the compound is represented by the following structural formula,



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or a pharmaceutically acceptable salt thereof, wherein:

n is 1 or 2;

m is 0 or 1;

p is 1;

t is 0;

y is 1;

z is 0 or 1;

E is O;

$X^1$is CR^1 when m is 1 or N when m is 0;

X^2 is O, -NH, -CH_2-, or –NR^2 ;

X^3 is O, -NH, -CH_2-, - CH(C_1-C_6) alkyl, or –NR^3;

X^4 is CR^4R^5 or CH_2 CR^4R^5;

X^5 is a direct bond, O, or (C_1-C_6)alkyloxy;

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

R^2 and R^3 are each independently -H, or optionally when X^2 is –NR^2 and X^3 is –NR^3, R^2 and R^3 may be taken together with the nitrogen atoms to which they are attached form a non-aromatic heterocyclic ring;

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, -CN or (C_1-C_6)alkyl;

A^1 is (C_6-C_{12})aryl, (C_2-C_9)heteroaryl or benzo(C_2-C_9)heterocycloalkyl optionally substituted with one or more substituents selected from the group consisting of halo**,** (C_1-C_6)alkyl; (C_1-C_6)alkenyl, and (C_1-C_6)alkoxy;

A^2 is H, (C_3-C_{10})cycloalkyl, (C_6-C_{12})aryl, or (C_2-C_9)heteroaryl, 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; CN, and (C_1-C_6)alkyloxy optionally substituted by one to three halo;

with the proviso that when n is 1; t is 0; y is 1; z is 1; X^2 is NH; E is O; X^3 is NH; A^2 is H and X^5 is a direct bond; A^1 is not unsubstituted phenyl, halophenyl or isopropenyl phenyl;

with the proviso that when n is 1; t is 0; y is 1; z is 1; X^2 is O; E is O; X^3 is NH; A^1 is (C_6-C_{12})aryl and X^5 is a direct bond; A^2 is H and R^4 is H then R^5 is not cyclohexyl; and

with the proviso that when n is 1; t is 0; y is 1; z is 1; X^2 is NH; E is O; X^3 is CH_2; R^4 and R^5 are both hydrogen; A^2 is H and X^5 is a direct bond; then A^1 is not unsubstituted phenyl.

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

3. The use according to claim 1, wherein m is 1 and X^1 is CR^1.

4. The use according to claim 1, wherein m is 0 and X^1 is N.

5. The use according to claim 1, wherein m is 1; E is O; X^2 is O and X^3 is NH.

6. The use according to claim 1, wherein R^4 and R^5 are each methyl.

7. The use according to claim 1, wherein A^1 is (C_6-C_{12})aryl.

8. The use according to claim 1, wherein A^1 is (C_2-C_9)heteroaryl.

9. The use according to claim 8, wherein A^1 is thiophene, thiazole, isothiazole, furane, oxazole, isoxazole, pyrrole, imidazole, pyrazole, triazole, pyridine, pymiridine, pyridazine, indole, benzothiazole, benzopyrazole, benzoimidazole, benzofuran, benzooxazole or benzoisoxazole.

10. The use according to claim 1, wherein R^6 is H.

11. The use according to claim 1, wherein X^5 is a direct bond.

12. The use according to claim 1, wherein A^2 is (C_6-C_{12})aryl.

13. The use according to claim 1, wherein A^2 is (C_2-C_9)heteroaryl.

14. The use according to claim 1, where R^1 is hydrogen or methyl.

15. The use according to claim 1, wherein X^1 is CR^1; m is 1; X^2 is O; X^3 is NH; R^1 is H; R^4 and R^5 are each independently methyl; R^6 is a hydrogen or methyl; A^1 is (C_2-C_9)heteroaryl; X^5 is a direct bond, or O and A^2 is (C_6-C_{12})aryl.

16. The use of a compound as defined in any one of claims 1 to 15 in the manufacture of a medicament for treating 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, a neuropathic disease, or a disease in which excessive glycolipid synthesis occurs selected from atherosclerosis, polycystic kidney disease, and renal hypertrophy.

17. The use according to claim 16, wherein the neuropathic disease is Alzheimers disease or Parkinsons disease.

18. The use according to claim 1, wherein the lysosomal storage disease results from a defect in the glycosphingolipid pathway.

19. The use according to claim 18, 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.

20. The use according to claim 19, wherein the lysosomal storage disease is Fabry.

21. The use according to claim 19, wherein the lysosomal storage disease is Gaucher type 2 or type 3.

22. The use according to any one of claims 1 to 21, wherein said medicament is for use in combination with a lysosomal enzyme.

23. The use according to claim 22, 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.

24. The use according to claim 23, wherein the lysosomal enzyme is alpha-galactosidase A.

25. The use according to claim 23, wherein the lysosomal enzyme is glucocerebrosidase.

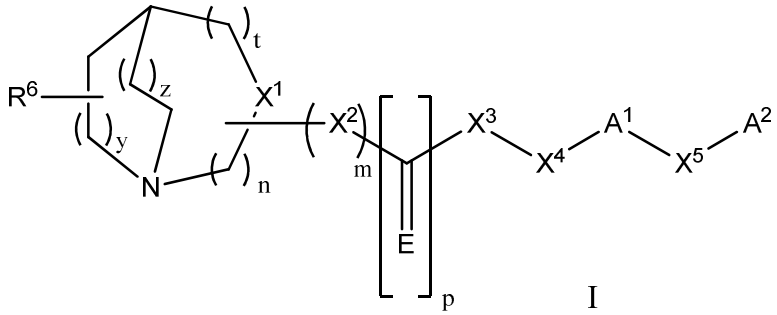
26. The use according to claim 22, wherein the subject has elevated levels of a lysosomal substrate prior to treatment.

27. The use according to claim 26, wherein the substrate is selected from the group consisting of globotriaosylceramide and lyso-globotriaosylceramide, and combinations thereof.

28. The use of a compound as defined in any one of claims 1 to 15 in the manufacture of a medicament for reducing glucosylceramide synthase (GCS) activity in a subject diagnosed as having a lysosomal storage disease, wherein the medicament is for use either alone or in combination with a lysosomal enzyme.

29. The use of a compound as defined in any one of claims 1 to 15 in the manufacture of a medicament for reducing accumulation of a GCS-derived material in a subject diagnosed as having a lysosomal storage disease, wherein the medicament is for use either alone or in combination with a lysosomal enzyme.

30. A compound represented by the following structural formula,



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or a pharmaceutically acceptable salt thereof,

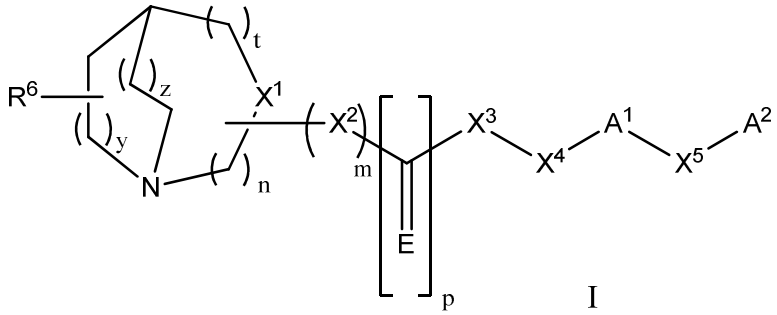
wherein n; m; p; t; y; z; E; X^1; X^2; X^3; X^4; X^5; R^1; R^2; R^3; R^6; A^1; and A^2 are as defined in claim 1,

and wherein R^4 and R^5 are independently selected from $(C_1\text{-}C_6)$alkyl,

with the proviso that when n is 1; t is 0; y is 1; z is 1; X^2 is NH; E is O; X^3 is NH; A^2 is H and X^5 is a direct bond; A^1 is not unsubstituted phenyl, halophenyl or isopropenyl phenyl.

31. The compound of claim 30, wherein R^4 and R^5 are each methyl.

32. A compound represented by the following structural formula,



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or a pharmaceutically acceptable salt thereof,

wherein n; m; p; t; y; z; E; X^1; X^2; X^3; X^4; X^5; R^1; R^2; R^3; R^6; and A^1 are as defined in claim 1,

wherein R^4 and R^5 are taken together with the carbon to which they are attached to form a (C_3-C_{10})cycloalkyl ring or (C_3-C_{10})cycloalkoxy ring; and

wherein A^2 is (C_3-C_{10})cycloalkyl, (C_6-C_{12})aryl, (C_2-C_9)heteroaryl, (C_2-C_9) heterocycloalkyl or benzo(C_2-C_9)heterocycloalkyl 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)alkylenyl, amino, (C_1-C_6) alkylamino, (C_1-C_6)dialkylamino, (C_1-C_6)alkoxy, O(C3-C6 cycloalkyl), (C_3-C_6) cycloalkoxy, nitro, CN, OH, (C_1-C_6)alkyloxy optionally substituted by one to three halo; (C_3-C_6) cycloalkyl, (C_1-C_6) alkoxycarbonyl, (C_1-C_6) alkylcarbonyl, (C_1-C_6) haloalkyl.

33. The compound of claim 30 or claim 32, wherein n is 1; t is 0; y is 1 and z is 1.

34. The compound of claim 30 or claim 32, wherein m is 1 and X^1 is CR^1.

35. The compound of claim 30 or claim 32, wherein m is 1; E is O; X^2 is O and X^3 is NH.

36. The compound of claim 30 or claim 32, wherein A^1 is (C_2-C_9) heteroaryl.

37. The compound of claim 36, wherein A^1 is thiophene, thiazole, isothiazole, furane, oxazole, isoxazole, pyrrole, imidazole, pyrazole, triazole, pyridine, pymiridine, pyridazine, indole, benzothiazole, benzoisoxazole, benzopyrazole, benzoimidazole, benzofuran, benzooxazole or benzoisoxazole.

38. A pharmaceutical composition comprising a compound according to any one of claims 30 to 37 and at least one pharmaceutically acceptable carrier.

39. A compound according to any one of claims 30 to 37 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, a neuropathic disease, or a disease in which excessive glycolipid synthesis occurs selected from atherosclerosis, polycystic kidney disease, and renal hypertrophy.

40. A compound for use according to claim 39, wherein the neuropathic disease is Alzheimers disease or Parkinsons disease.

41. A compound according to any one of claims 30 to 37 for use in the treatment of a subject diagnosed as having a lysosomal storage disease.

42. A compound according to claim 41, wherein the lysosomal storage disease results from a defect in the glycosphingolipid pathway.

43. A compound for use according to claim 42, 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.

44. A compound for use according to claim 43, wherein the lysosomal storage disease is Fabry.

45. A compound for use according to claim 43, wherein the lysosomal storage disease is Gaucher type 2 or type 3.

46. A compound for use according to any one of claims 39 to 45, wherein said compound is for use in combination with a lysosomal enzyme.

47. A compound for use according to claim 46, 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.

48. A compound for use according to claim 47, wherein the lysosomal enzyme is alpha-galactosidase A.

49. A compound for use according to claim 47, wherein the lysosomal enzyme is glucocerebrosidase.

50. A compound for use according to claim 46, wherein the subject has elevated levels of a lysosomal substrate prior to treatment.

51. A compound for use according to claim 50, wherein the subject undergoing treatment has lower combined amounts of the lysosomal substrate in the urine and plasma than a subject treated with either the lysosomal enzyme or compound alone.

52. A compound for use according to claim 51, wherein the substrate is selected from the group consisting of globotriaosylceramide and lyso-globotriaosylceramide, and combinations thereof.

53. A compound as defined in any one of claims 30 to 37 for use in the reduction of glucosylceramide synthase (GCS) activity in a subject diagnosed as having a lysosomal storage disease, wherein the compound is for use either alone or in combination with a lysosomal enzyme.

54. A compound as defined in any one of claims 30 to 37 for use in the reduction of accumulation of a GCS-derived material in a subject diagnosed as having a lysosomal storage disease, wherein the compound is for use either alone or in combination with a lysosomal enzyme.