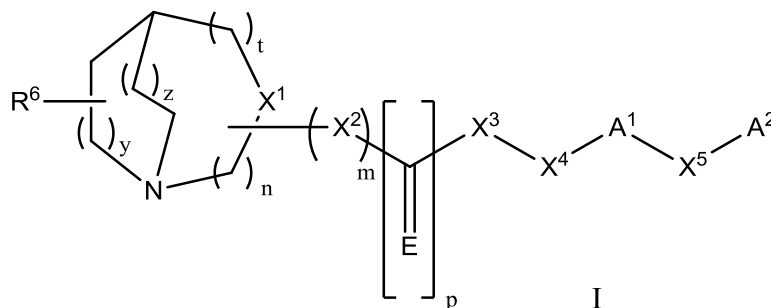


Claims

1. A compound represented by the following structural formula,



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

n is 1, 2 or 3;

m is 0 or 1;

p is 0 or 1;

t is 0, 1 or 2;

y is 1 or 2;

z is 0, 1 or 2;

E is S, O, NH, NOH, NNO₂, NCN, NR, NOR or NSO₂R;

X¹ is CR¹ when m is 1 or N when m is 0;

X² is O, -NH, -CH₂-, SO₂, NH-SO₂;CH(C₁-C₆) alkyl or -NR²;

X³ is O, -NH, -CH₂-, CO, -CH(C₁-C₆) alkyl, SO₂NH, -CO-NH- or -NR³;

X⁴ is CR⁴R⁵, CH₂ CR⁴R⁵ or CH₂-(C₁-C₆) alkyl-CR⁴R⁵;

X⁵ is a direct bond, O, S, SO₂, CR⁴R⁵; (C₁-C₆)alkyl, (C₁-C₆)alkyloxy, (C₁-C₆)alkenyl, or (C₁-C₆)alkenyloxy;

R is (C₆-C₁₂)aryl, (C₂-C₉)heteroaryl, (C₁-C₆)alkyl, or (C₂-C₉)heteroaryl(C₁-C₆)alkyl;

R¹ is H, CN, (C₁-C₆)alkylcarbonyl, or (C₁-C₆)alkyl;

R² and R³ are each independently -H, (C₁-C₆)alkyl optionally substituted by one or more substituents selected from the group consisting of halogen, (C₁-C₆)alkyl, (C₆-C₁₂)aryl, (C₂-C₉)heteroaryl, (C₁-C₆)alkyl(C₆-C₁₂)aryl, halo(C₆-C₁₂)aryl, and halo(C₂-C₉)heteroaryl, or optionally when X² is -NR² and X³ is -NR³, R² and R³ may be taken together with the nitrogen atoms to which they are attached form a non-aromatic heterocyclic ring optionally substituted by with one or more substituents selected from halogen, (C₁-C₆)alkyl, (C₆-C₁₂)aryl, (C₂-C₉)heteroaryl, (C₁-C₆)alkyl(C₆-C₁₂)aryl, halo(C₆-C₁₂)aryl, and

halo(C₂-C₉)heteroaryl;

R⁴ and R⁵ are independently selected from H, (C₁-C₆)alkyl, or taken together with the carbon to which they are attached to form a spiro (C₃-C₁₀)cycloalkyl ring or spiro (C₃-C₁₀)cycloalkoxy ring;

R⁶ is -H, halogen, -CN, (C₆-C₁₂)aryl, (C₆-C₁₂)aryloxy, (C₁-C₆)alkyloxy, or (C₁-C₆)alkyl optionally substituted by one to four halo or (C₁-C₆)alkyl;

A¹ is (C₂-C₆)alkynyl; (C₃-C₁₀)cycloalkyl, (C₆-C₁₂)aryl, (C₂-C₉)heteroaryl, (C₂-C₉)heterocycloalkyl or benzo(C₂-C₉)heterocycloalkyl optionally substituted with one or more substituents selected from the group consisting of halo, (C₁-C₆)alkyl optionally substituted by one to three halo; (C₁-C₆)alkenyl, amino, (C₁-C₆)alkylamino, (C₁-C₆)dialkylamino, (C₁-C₆)alkoxy, nitro, CN, -OH, (C₁-C₆)alkyloxy optionally substituted by one to three halo; (C₁-C₆)alkoxycarbonyl, and (C₁-C₆) alkylcarbonyl;

A² is H, (C₃-C₁₀)cycloalkyl, (C₆-C₁₂)aryl, (C₂-C₉)heteroaryl, (C₂-C₉)heterocycloalkyl or benzo(C₂-C₉)heterocycloalkyl optionally substituted with one or more substituents selected from the group consisting of halo, (C₁-C₆)alkyl optionally substituted by one to three halo; (C₁-C₆)alkylenyl, amino, (C₁-C₆)alkylamino, (C₁-C₆)dialkylamino, (C₁-C₆)alkoxy, O(C₃-C₆ cycloalkyl), (C₃-C₆) cycloalkoxy, nitro, CN, OH, (C₁-C₆)alkyloxy optionally substituted by one to three halo; (C₃-C₆) cycloalkyl, (C₁-C₆) alkoxycarbonyl, (C₁-C₆) alkylcarbonyl, and (C₁-C₆) haloalkyl;

with the proviso that the sum of n + t + y + z is not greater than 6;

with the proviso that when p is 0; X² is NH-SO₂ and X³ is NH;

with the proviso that when n is 1; t is 0; y is 1; z is 1; X² is NH; E is O; X³ is NH; A² is H and X⁵ is a direct bond; A¹ 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; X² is O; E is O; X³ is NH; A¹ is (C₆-C₁₂)aryl and X⁵ is a direct bond; A² is H and R⁴ is H then R⁵ is not cyclohexyl; and

with the proviso that when n is 1; t is 0; y is 1; z is 1; X² is NH; E is O; X³ is CH₂; R⁴ and R⁵ are both hydrogen; A² is H and X⁵ is a direct bond; then A¹ is not unsubstituted phenyl.

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 and X¹ is CR¹.
4. A compound according to claim 1, wherein m is 0 and X¹ is N.
5. A compound according to claim 1, wherein m is 1; E is O; X² is O and X³ is NH.
6. A compound according to claim 1, wherein R⁴ and R⁵ are each (C₁-C₆)alkyl or taken together with the carbon to which they are attached to form a spiro (C₃-C₁₀)cyclo- alkyl ring or a spiro (C₃-C₁₀)cycloalkoxy ring.

7. A compound according to claim 6, wherein R⁴ and R⁵ are each methyl.
8. A compound according to claim 1, wherein A¹ is (C₂-C₆)alkynyl or (C₆-C₁₂)aryl.
9. A compound according to claim 1, wherein A¹ is (C₂-C₉)heteroaryl.
10. A compound according to claim 9, wherein A¹ is thiophene, thiazole, isothiazole, furane, oxazole, isoxazole, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrimidine, pyridazine, indole, benzothiazole, benzopyrazole, benzoimidazole, benzofuran, benzooxazole or benzoisoxazole.
11. A compound according to claim 1, wherein A¹ is (C₂-C₉)heterocycloalkyl.
12. A compound according to claim 1, wherein R⁶ is H.
13. A compound according to claim 1, wherein X⁵ is a direct bond.
14. A compound according to claim 1, wherein A² is (C₆-C₁₂)aryl.
15. A compound according to claim 1, wherein A² is (C₂-C₉)heteroaryl.
16. A compound according to claim 1, where R¹ is hydrogen or methyl.
17. A compound according to claim 1, wherein n is 1; 2 or 3; t is 0, 1 or 2; y is 1; z is 0, 1 or 2; X¹ is CR¹; m is 1; p is 1; E is O; X² is O; X³ is NH; R¹ is H; R⁴ and R⁵ are each independently methyl; R⁶ is a hydrogen or methyl; A¹ is (C₂-C₉)heteroaryl; X⁵ is a direct bond, O or CR⁴R⁵ and A² is (C₆-C₁₂)aryl.
18. A pharmaceutical composition comprising a compound according to claim 1 and at least one pharmaceutically acceptable carrier.
19. The compound according to claim 1, wherein said compound is used in the treatment of a disease or disorder mediated by glucosylceramide synthase (GCS) or a disease or disorder in which GCS is implicated.
20. The compound of claim 19, 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.

21. The compound of claim 20, wherein the neuropathic disease is Alzheimers disease or Parkinsons disease.

22. The compound according to claim 1, wherein said compound is used in the treatment of a subject diagnosed as having a lysosomal storage disease.

23. The compound of claim 22, wherein the lysosomal storage disease results from a defect in the glycosphingolipid pathway.

24. The compound of claim 23, 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.

25. The compound of claim 24, wherein the lysosomal storage disease is Fabry.

26. The compound of claim 24, wherein the lysosomal storage disease is Gaucher type 2 or type 3.

27. The compound of any one of claims 22 to 26, wherein said compound is used in combination with a lysosomal enzyme.

28. The compound of claim 27, 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.

29. The compound of claim 28, wherein the lysosomal enzyme is alpha-galactosidase A.

30. The compound of claim 28, wherein the lysosomal enzyme is glucocerebrosidase.

31. The compound of claim 27, wherein prior to treatment the subject undergoing treatment has elevated levels of a lysosomal substrate.

32. The compound of claim 31, 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.

33. The compound of claim 32, wherein the substrate is selected from the group consisting of globotriaosylceramide and lyso-globotriaosylceramide, and combinations thereof.

34. The compound according to claim 1, wherein said compound is used in the reduction of glucosylceramide synthase (GCS) activity in a subject diagnosed as having a lysosomal storage disease, wherein the compound is used either alone or in combination with a lysosomal enzyme.

35. The compound according to claim 1, wherein said compound is used in the reduction of accumulation of a GCS-derived material in a subject diagnosed as having a lysosomal storage disease, wherein the compound is used either alone or in combination with a lysosomal enzyme.