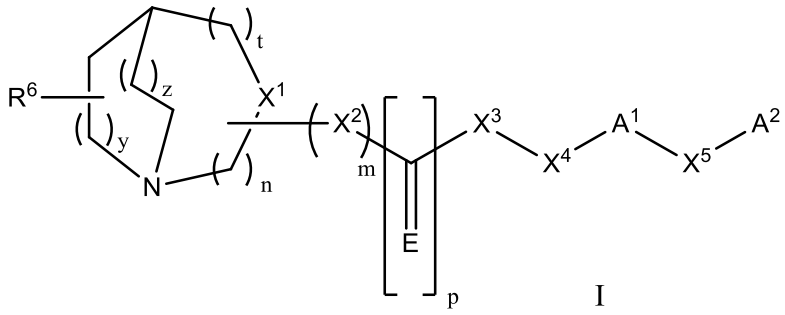
Claims

1. A compound for use in treating a disease or disorder mediated by glucosylceramide synthase (GCS) or a disease or disorder in which GCS is implicated in a subject, wherein the compound is 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 0;

p is 1;

t is 0, 1 or 2;

y is 1 or 2;

z is 0, 1 or 2;

E is O;

X^1 is N;

X^3 is a direct bond, O, -NH, or -NR^3;

X^4 is a direct bond, CR^4R^5, or CH_2-CR^4R^5;

X^5 is a direct bond, O, (C_1-C_6)alkyl, -R^7-(C_6-C_{12})aryl, (C_6-C_{12})aryl -R^7-, -R^7-(C_2-C_9)heteroaryl, or (C_2-C_9)heteroaryl-R^7-, wherein R^7 is a direct bond, O, (C_1-C_6)alkyl, (C_1-C_6)alkyloxy, or -O-(C_1-C_6)alkyl;

R^3 is-H, (C_1-C_6)alkyl optionally substituted by one or more substituents selected from the group consisting of halogen, (C_1-C_6)alkyl, (C_6-C_{12})aryl, (C_2-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{12})aryl, halo(C_6-C_{12})aryl, and halo(C_2-C_9)heteroaryl;

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, halogen, -CN, (C_6-C_{12})aryl, (C_6-C_{12})aryloxy, (C_1-C_6)alkyloxy; or

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

A^1 is (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; and

A^2 is (C_3-C_{10})cycloalkyl, (C_6-C_{12})aryl or (C_2-C_9)heteroaryl or (C_2-C_9)heterocycloalkyl; wherein A^2 is optionally substituted with one or more substituents selected from the group consisting of: halo, (C_1-C_6)alkyl, (C_1-C_6)alkylenyl, amino, (C_1-C_6) alkylamino, (C_1-C_6)dialkylamino, (C_1-C_6)alkoxy, O(C_3-C_6 cycloalkyl), (C_3-C_6) cycloalkoxy, nitro, CN, OH, (C_1-C_6)alkyloxy, (C_3-C_6) cycloalkyl, (C_1-C_6) alkoxycarbonyl, (C_1-C_6) alkylcarbonyl, (C_1-C_6) haloalkyl, (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 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; 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;

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

with the proviso that when X^3 is O -NH, or NR^3; and X^4 is CR^4R^5 or CH_2-CR^4R^5; then A^2 must be 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 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; 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, 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.

2. The compound for use of claim 1, wherein n is 2, t is 0, y is 1, and z is 1.

3. The compound for use of claim 1 or claim 2, wherein A^1 is (C_2-C_9)heteroaryl, optionally wherein A^1 is thiophenyl, thiazolyl, isothiazolyl, furanyl, oxazolyl, isoxazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pymiridinyl, pyridazinyl, indolyl, benzothiazolyl, benzopyrazolyl, benzoimidazolyl, benzofuranyl, benzooxazolyl or benzoisoxazolyl.

4. The compound for use of any one of claims 1 to 3, wherein A^2 is (C_6-C_{12})aryl.

5. The compound for use according to any one of claims 1 to 4, wherein the disease or disorder is cancer, a metabolic disorder, or a neuropathic disease.

6. The compound for use of claim 5, wherein the neuropathic disease is Parkinson's disease.

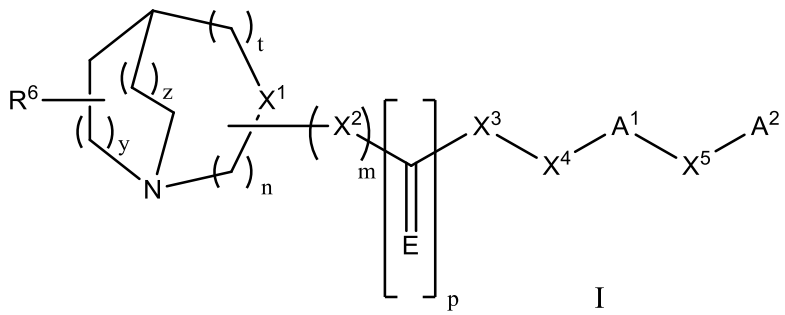
7. The compound for use of claim 5, wherein the metabolic disease is a lysosomal storage disease.

8. The compound for use of claim 7, 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.

9. The compound for use of any one of claims 1 to 8, wherein the compound is to be administered at a dosage of from 0.5 mg/kg to 300 mg/kg, preferably from about 5 mg/kg to about 60 mg/kg (e.g., 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg and 60 mg/kg) by intraperitoneal, oral or equivalent administration from one to five times daily, particularly wherein the compound is to be administered in an oral dose of from about 1 mg/kg/day to about 100 mg/kg/day, e.g., 1 mg/kg/day, 5 mg/kg/day, 10 mg/kg/day, 15 mg/kg/day, 20 mg/kg/day, 15 mg/kg/day, 30 mg/kg/day, 35 mg/kg/day, 40 mg/kg/day, 45 mg/kg/day, 50 mg/kg/day, 55 mg/kg/day or 60 mg/kg/day, 65 mg/kg/day, 70 mg/kg/day, 75 mg/kg/day, 80 mg/kg/day, 85 mg/kg/day, 90 mg/kg/day, 95 mg/kg/day or 100 mg/kg/day.

10. The compound for use of any one of claims 1 to 9, wherein the compound is to be administered at a dose of from about 10 mg/day to about 500 mg/day (e.g. 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 110 mg/day, 120 mg/day, 130 mg/day, 140 mg/day, 150 mg/day, 160 mg/day, 170 mg/day, 180 mg/day, 190 mg/day, 200 mg/day, 210 mg/day, 220 mg/day, 230 mg/day, 240 mg/day, 250 mg/day, 260 mg/day, 270 mg/day, 280 mg/day, 290 mg/day, 300 mg/day), preferably wherein the compound is to be administered as an oral dose in the range from about 50 mg to about 100 mg, wherein the dose is to be administered twice daily.

11. A compound represented by the following structural formula,



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or a pharmaceutically acceptable salt thereof, wherein:

n is 2;

m is 0;

p is 1;

t is 0;

y is 1;

z is 1;

E is O;

X^1 is N;

X^3 is a direct bond O, -NH or $–NR^3$;

X^4 is a direct bond, CR^4R^5, or CH_2-CR^4R^5;

X^5 is a direct bond, O, (C_1-C_6)alkyl, -R^7-(C_6-C_{12})aryl, (C_6-C_{12})aryl -R^7-, -R^7-(C_2-C_9)heteroaryl, or (C_2-C_9)heteroaryl-R^7-, wherein R^7 is a direct bond, O, (C_1-C_6)alkyl, (C_1-C_6)alkyloxy, or -O-(C_1-C_6)alkyl;

R^3 is -H, (C_1-C_6)alkyl optionally substituted by one or more substituents selected from the group consisting of halogen, (C_1-C_6)alkyl, (C_6-C_{12})aryl, (C_2-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{12})aryl, halo(C_6-C_{12})aryl, and halo(C_2-C_9)heteroaryl;

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, halogen, -CN, (C_6-C_{12})aryl, (C_6-C_{12})aryloxy, (C_1-C_6)alkyloxy; or (C_1-C_6)alkyl optionally substituted by one to four halo or (C_1-C_6)alkyl;

A^1 is (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; wherein when A^1 is (C_2-C_9)heteroaryl it is selected from thiazolyl, isothiazolyl, isoxazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pymiridinyl, pyridazinyl, indolyl, benzothiazolyl, benzopyrazolyl, benzoimidazolyl, or benzoisoxazolyl;

wherein when A^1 is (C_2-C_9)heterocycloalkyl it is selected from pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydropyranyl, pyranyl, thiopyranyl, aziridinyl, azetidinyl, oxiranyl, methylenedioxyl, chromenyl, barbituryl, isoxazolidinyl, 1,3-oxazolidin-3-yl, isothiazolidinyl, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-

1-yl, piperidinyl, thiomorpholinyl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazinyl, morpholinyl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, tetrahydroazepinyl, piperazinyl, piperizin-2-onyl, piperizin-3-onyl, chromanyl, 2-pyrrolinyl, 3-pyrrolinyl, imidazolidinyl, 2-imidazolidinyl, 1,4-dioxanyl, 8-azabicyclo[3.2.1]octanyl, 3-azabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, octahydro-2H-pyrido[1,2-a]pyrazinyl, 3-azabicyclo[4.1.0]heptanyl, 3-azabicyclo[3.1.0]hexanyl 2-azaspiro[4.4]nonanyl, 7-oxa-1-aza-spiro[4.4]nonanyl, 7-azabicyclo[2.2.2]heptanyl, and octahydro-1H-indolyl; and

A^2 is (C_3-C_{10})cycloalkyl, (C_6-C_{12})aryl, (C_2-C_9)heteroaryl, (C_2-C_9)heterocycloalkyl; 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 with the proviso that the sum of n + t + y + z is not greater than 6;

with the proviso that when X^4 is CR^4R^5 or CH_2-CR^4R^5; then A^2 must be 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 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; 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, 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.

12. The compound according to claim 11, wherein X^3 is a direct bond.

13. The compound according to claim 11, wherein X^4 is a direct bond.

14. The compound according to claim 11, wherein X^3 and X^4 are each independently a direct bond.

15. The compound according to claim 11, wherein R^6 is H.

16. The compound according to claim 11, wherein A^2 is (C_6-C_{12})aryl.

17. A pharmaceutical composition comprising a compound according to any one of claims 11 to 16, and at least one pharmaceutically acceptable carrier.