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R<sup>4</sup> and R<sup>5</sup> are independently selected from H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, or taken together with the carbon to which they are attached to form a spiro (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl ring or spiro (C<sub>3</sub>-C<sub>10</sub>)cycloalkoxy ring;

25 (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted by one to four halo;

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three halo; (C<sub>1</sub>-C<sub>6</sub>)alkenyl, amino, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, (C<sub>1</sub>-C<sub>6</sub>)dialkylamino, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, nitro, CN, -OH, (C<sub>1</sub>-C<sub>6</sub>)alkyloxy optionally substituted by one to three halo; (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, and (C<sub>1</sub>-C<sub>6</sub>) alkylcarbonyl;

A<sup>2</sup> is (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>12</sub>)aryl, (C<sub>2</sub>-C<sub>9</sub>)heteroaryl, or (C<sub>2</sub>-

- 5 C<sub>9</sub>)heterocycloalkyl wherein A<sup>2</sup> is substituted with one or more substituents selected from the group consisting of (C<sub>2</sub>-C<sub>9</sub>)heterocycloalkyl, R<sup>8</sup>R<sup>9</sup>N-CO- wherein R<sup>8</sup> and R<sup>9</sup> are each independently selected from the group consisting of hydrogen and (C<sub>1</sub>-C<sub>6</sub>)alkyl or R<sup>8</sup> and R<sup>9</sup> can be taken together with the nitrogen to which they are attached to form a (C<sub>2</sub>-C<sub>9</sub>)heterocycloalkyl group optionally substituted by one to three halo groups, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl optionally substituted by one or two groups selected from (C<sub>1</sub>-C<sub>6</sub>)alkoxy and (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl;

- (C<sub>1</sub>-C<sub>6</sub>)alkyl substituted by one to four substituents selected from the group consisting of hydroxy, cyano, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>2</sub>-C<sub>9</sub>)heterocycloalkyl, (C<sub>2</sub>-C<sub>9</sub>)heteroaryl optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)alkoxy; or (C<sub>3</sub>-C<sub>10</sub>)cycloalkoxy optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)alkoxy; and

(C<sub>1</sub>-C<sub>6</sub>)alkyloxy substituted by one to four substituents selected from the group consisting of hydroxy, cyano, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>2</sub>-C<sub>9</sub>)heterocycloalkyl, (C<sub>2</sub>-C<sub>9</sub>)heteroaryl optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)alkoxy; or (C<sub>3</sub>-C<sub>10</sub>)cycloalkoxy optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)alkoxy.

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

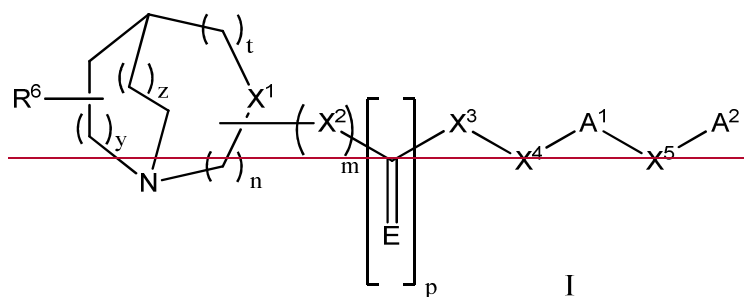
3. A compound according to claim 1, wherein m is 1; E is O; X<sup>2</sup> is O and X<sup>3</sup> is NH.

- 25 4. A compound according to claim 1, wherein R<sup>4</sup> and R<sup>5</sup> are each (C<sub>1</sub>-C<sub>6</sub>)alkyl or taken together with the carbon to which they are attached to form a spiro (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl ring or a spiro (C<sub>3</sub>-C<sub>10</sub>)cycloalkoxy ring.

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

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~~6. A compound represented by the following structural formula;~~



or a pharmaceutically acceptable salt thereof, wherein:

5  $n$  is 1, 2 or 3;

$m$  is 1;

$p$  is 1;

$t$  is 0 or 1;

$y$  is 1;

10  $z$  is 0 or 1;

$E$  is O;

$X^1$  is  $CR^1$ ;

$X^2$  is O;

$X^3$  is  $NH$  or  $NR^3$ ;

15  $X^4$  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;

20  $R^4$  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,

25 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<sub>1</sub>-C<sub>6</sub>)alkenyl, amino, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, (C<sub>1</sub>-C<sub>6</sub>)dialkylamino, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, nitro, CN, OH, (C<sub>1</sub>-C<sub>6</sub>)alkyloxy optionally substituted by one to three halo; (C<sub>1</sub>-C<sub>6</sub>)alkoxycarbonyl, and (C<sub>1</sub>-C<sub>6</sub>) alkylcarbonyl; and

5 ~~———— A<sup>2</sup> is (C<sub>6</sub>-C<sub>12</sub>)aryl or (C<sub>2</sub>-C<sub>9</sub>)heteroaryl; wherein A<sup>2</sup> is substituted with one or more substituents selected from the group consisting of:~~

~~halo, (C<sub>1</sub>-C<sub>6</sub>)alkylenyl, (C<sub>1</sub>-C<sub>6</sub>) alkylamino, (C<sub>1</sub>-C<sub>6</sub>)dialkylamino, O(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), (C<sub>3</sub>-C<sub>6</sub>) cycloalkoxy, (C<sub>3</sub>-C<sub>6</sub>) cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>) alkoxycarbonyl, (C<sub>1</sub>-C<sub>6</sub>) alkylcarbonyl, (C<sub>2</sub>-C<sub>9</sub>)heterocycloalkyl;~~

10 ~~R<sup>8</sup>R<sup>9</sup>N-CO-, wherein R<sup>8</sup> and R<sup>9</sup> are each independently selected from the group consisting of hydrogen and (C<sub>1</sub>-C<sub>6</sub>)alkyl or R<sup>8</sup> and R<sup>9</sup> can be taken together with the nitrogen to which they are attached to form a (C<sub>2</sub>-C<sub>9</sub>)heterocycloalkyl or (C<sub>2</sub>-C<sub>9</sub>)heterocycloalkyl group optionally substituted by one to three halo groups, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl optionally substituted by one or two groups selected from (C<sub>1</sub>-C<sub>6</sub>)alkoxy and (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl;~~

15 ~~(C<sub>1</sub>-C<sub>6</sub>)alkyl substituted by one to four substituents selected from the group consisting of hydroxy, cyano, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>2</sub>-C<sub>9</sub>)heterocycloalkyl, and (C<sub>2</sub>-C<sub>9</sub>)heteroaryl optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)alkoxy; and (C<sub>3</sub>-C<sub>10</sub>)cycloalkoxy optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)alkoxy; and~~

20 ~~(C<sub>1</sub>-C<sub>6</sub>)alkyloxy substituted by one to four substituents selected from the group consisting of halo, hydroxy, cyano, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>2</sub>-C<sub>9</sub>)heterocycloalkyl, and (C<sub>2</sub>-C<sub>9</sub>)heteroaryl optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)alkoxy; or (C<sub>3</sub>-C<sub>10</sub>)cycloalkoxy optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)alkoxy.~~

25 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<sup>2</sup> is O and X<sup>3</sup> is NH.

9. — A compound according to claim 6, wherein A<sup>1</sup> is (C<sub>2</sub>-C<sub>9</sub>)heteroaryl selected from  
30 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<sup>1</sup> is benzooxazole.

~~146.~~ A compound according to claim 1-~~or claim 6~~, wherein R<sup>6</sup> is H.

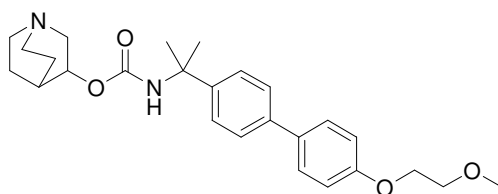
~~147.~~ A compound according to claim 1-~~or claim 6~~, where R<sup>1</sup> is hydrogen or methyl.

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~~148.~~ A compound according to claim 1-~~or claim 6~~, wherein X<sup>5</sup> is a direct bond.

~~149.~~ A compound according to claim 1-~~or claim 6~~, wherein A<sup>2</sup> is (C<sub>6</sub>-C<sub>12</sub>)aryl.

10 ~~1510.~~ A compound represented by the formula



or a pharmaceutically acceptable salt thereof.

~~1611.~~ A pharmaceutical composition comprising a compound according to any one of  
15 claims 1 to ~~1510~~ and at least one pharmaceutically acceptable carrier.

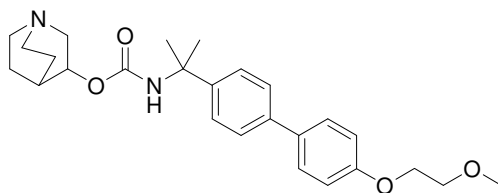
~~1712.~~ A compound according to any one of claims 1 to ~~1510~~ or a pharmaceutical  
composition according to claim ~~1611~~ for use in therapy.

20 ~~1813.~~ A compound according to any one of claims 1 to ~~1510~~ or a pharmaceutical  
composition according to claim ~~1611~~ 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  
25 from atherosclerosis, polycystic kidney disease, and renal hypertrophy.

~~1914.~~ A compound or pharmaceutical composition for use according to claim ~~1813~~,  
wherein the disease or disorder is a neuropathic disease selected from Alzheimer's  
disease and Parkinson's disease.

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~~20~~15. A compound or pharmaceutical composition for use according to claim ~~18~~13, wherein the compound is represented by the following structural formula,



or a pharmaceutically acceptable salt thereof.

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~~24~~16. A compound according to any one of claims 1 to ~~15~~10 or a pharmaceutical composition according to claim ~~16~~11 for use in the treatment of a lysosomal storage disease.

10 ~~22~~17. The compound or pharmaceutical composition for use of claim ~~24~~16, wherein the lysosomal storage disease is selected from the group consisting of Gaucher, Fabry, G<sub>M1</sub>-gangliosidosis, G<sub>M2</sub> Activator deficiency, Tay-Sachs and Sandhoff.

~~23~~18. The compound or pharmaceutical composition for use of claim ~~22~~17, wherein the  
15 lysosomal storage disease is Fabry.

~~24~~19. The compound or pharmaceutical composition for use of claim ~~22~~17, wherein the lysosomal storage disease is Gaucher type 2 or Gaucher type 3.

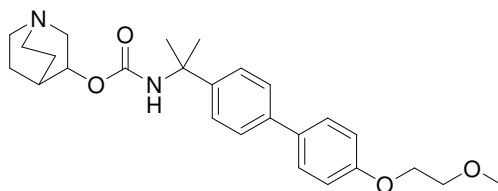
20 ~~25~~20. The compound or pharmaceutical composition for use of claim ~~24~~16, wherein the treatment comprises the step of administering to the subject a therapeutically effective amount of a lysosomal enzyme.

~~26~~21. The compound or pharmaceutical composition for use of claim ~~25~~20, wherein the  
25 lysosomal enzyme is selected from the group consisting of glucocerebrosidase, alpha-galactosidase A, Hexosaminidase A, Hexosaminidase B and G<sub>M1</sub>-ganglioside-β-galactosidase.

~~27~~22. The compound or pharmaceutical composition for use of claim ~~25~~20, wherein the  
30 lysosomal enzyme is alpha-galactosidase A.

~~28~~23. The compound or pharmaceutical composition for use of claim ~~25~~20, wherein the lysosomal enzyme is glucocerebrosidase.

~~29~~24. The compound or pharmaceutical composition for use of claim ~~24~~16, wherein the  
5 compound is represented by the following structural formula,



or a pharmaceutically acceptable salt thereof.

~~30~~25. A compound for use in the treatment, amelioration or prevention of a renal cystic  
10 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-  
15 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  
20 claimed in any one of claims 1 to ~~45~~10.