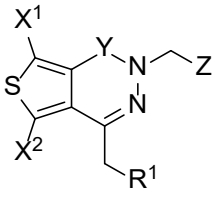
CLAIMS

1. Use of an aldose reductase inhibitor in the manufacture of a medicament for treating galactosemia or preventing complications of galactosemia, wherein the aldose reductase inhibitor is a compound of Formula (III) or pharmaceutically acceptable salt thereof:



(III)

wherein,

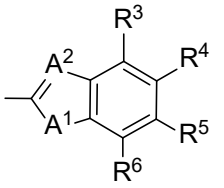
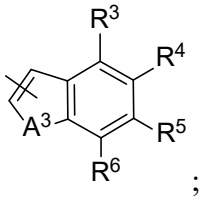
R^1 is CO_2R^2;

R^2 is H, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, or (C_1-C_6)-aminoalkyl;

X^1 is H or halogen;

X^2 is H or halogen;

Y is a bond, C=O, C=S, C=NH, or C=N(C_1-C_4)-alkyl;

Z is  or  ;

A^1 is NR^7, O, S, or CH_2;

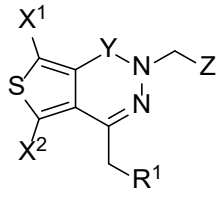
A^2 is N or CH;

A^3 is NR^7, O, or S;

R^3, R^4, R^5, and R^6 are independently hydrogen, halogen, cyano, acyl, haloalkyl, haloalkoxy, haloalkylthio, trifluoroacetyl, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkylthio, (C_1-C_4)-alkylsulfinyl, or (C_1-C_4)-alkylsulfonyl; and

R^7 is hydrogen, (C_1-C_4)-alkyl, or C(O)O-(C_1-C_4)-alkyl.

2. Use of an aldose reductase inhibitor in the manufacture of a medicament for reducing the amount or level of galactitol in a subject with galactosemia, wherein the aldose reductase inhibitor is a compound of Formula (III) or pharmaceutically acceptable salt thereof:


(III)

wherein,

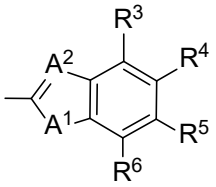
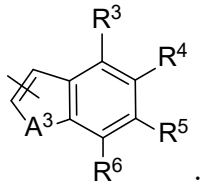
R^1 is CO_2R^2;

R^2 is H, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, or (C_1-C_6)-aminoalkyl;

X^1 is H or halogen;

X^2 is H or halogen;

Y is a bond, C=O, C=S, C=NH, or C=N(C_1-C_4)-alkyl;

Z is  or ;

A^1 is NR^7, O, S, or CH_2;

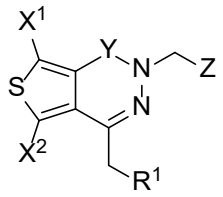
A^2 is N or CH;

A^3 is NR^7, O, or S;

R^3, R^4, R^5, and R^6 are independently hydrogen, halogen, cyano, acyl, haloalkyl, haloalkoxy, haloalkylthio, trifluoroacetyl, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkylthio, (C_1-C_4)-alkylsulfinyl, or (C_1-C_4)-alkylsulfonyl; and

R^7 is hydrogen, (C_1-C_4)-alkyl, or C(O)O-(C_1-C_4)-alkyl.

3. Use of an aldose reductase inhibitor in the manufacture of a medicament for treating cataracts in a subject in need thereof, wherein the subject in need thereof has galactosemia, wherein the aldose reductase inhibitor is a compound of Formula (III) or pharmaceutically acceptable salt thereof:


(III)

wherein,

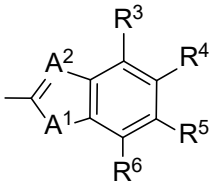
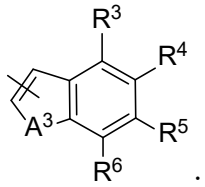
R^1 is CO_2R^2;

R^2 is H, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, or (C_1-C_6)-aminoalkyl;

X^1 is H or halogen;

X^2 is H or halogen;

Y is a bond, C=O, C=S, C=NH, or C=N(C_1-C_4)-alkyl;

Z is  or ;

A^1 is NR^7, O, S, or CH_2;

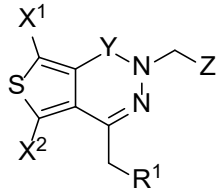
A^2 is N or CH;

A^3 is NR^7, O, or S;

R^3, R^4, R^5, and R^6 are independently hydrogen, halogen, cyano, acyl, haloalkyl, haloalkoxy, haloalkylthio, trifluoroacetyl, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkylthio, (C_1-C_4)-alkylsulfinyl, or (C_1-C_4)-alkylsulfonyl; and

R^7 is hydrogen, (C_1-C_4)-alkyl, or C(O)O-(C_1-C_4)-alkyl.

4. Use of an aldose reductase inhibitor in the manufacture of a medicament for treating or preventing cognitive or neurological deficiency associated with galactosemia, wherein the aldose reductase inhibitor is a compound of Formula (III) or pharmaceutically acceptable salt thereof:



(III)

wherein,

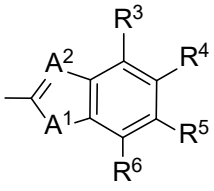
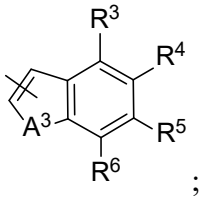
R^1 is CO_2R^2;

R^2 is H, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, or (C_1-C_6)-aminoalkyl;

X^1 is H or halogen;

X^2 is H or halogen;

Y is a bond, C=O, C=S, C=NH, or C=N(C_1-C_4)-alkyl;

Z is  or ;

A^1 is NR^7, O, S, or CH_2;

A^2 is N or CH;

A^3 is NR^7, O, or S;

R^3, R^4, R^5, and R^6 are independently hydrogen, halogen, cyano, acyl, haloalkyl, haloalkoxy, haloalkylthio, trifluoroacetyl, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkylthio, (C_1-C_4)-alkylsulfinyl, or (C_1-C_4)-alkylsulfonyl; and

R^7 is hydrogen, (C_1-C_4)-alkyl, or C(O)O-(C_1-C_4)-alkyl.

5. The use of claim 4, wherein the cognitive or neurological deficiency associated with galactosemia is speech dysfunction.

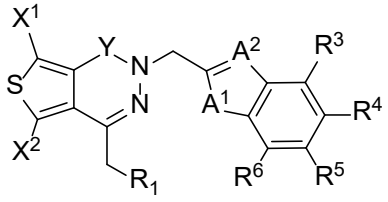
6. The use of claim 4, wherein the cognitive or neurological deficiency associated with galactosemia is motor ataxia.

7. The use of claim 4, wherein the cognitive or neurological deficiency associated with galactosemia is cognitive dysfunction.

8. The use of claim 4, wherein the cognitive or neurological deficiency associated with galactosemia is pseudomotor cerebrii.

9. The use of claim 4, wherein the cognitive or neurological deficiency associated with galactosemia is seizure.

10. The use of any one of the preceding claims, wherein the aldose reductase inhibitor is a compound of Formula (III-1) or pharmaceutically acceptable salt thereof:



(III-1)

wherein, R^1 is CO_2R^2;

R^2 is H;

X^1 is H;

X^2 is H;

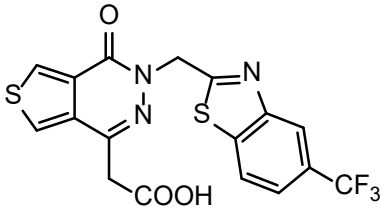
Y is C=O;

A^1 is S;

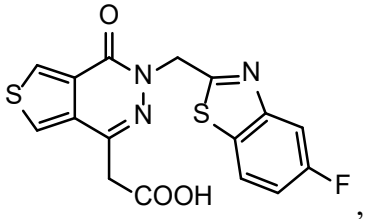
A^2 is N; and

R^3, R^4, R^5, and R^6 are independently hydrogen, halogen, or haloalkyl.

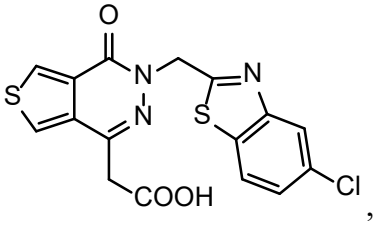
11. The use of any one of the preceding claims, wherein the aldose reductase inhibitor is selected from the group consisting of



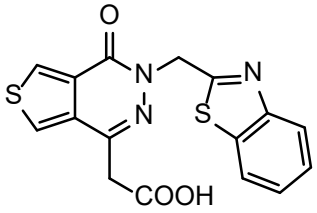
,



,



,



, and pharmaceutically acceptable salts thereof.

12. The use of any one of the preceding claims, wherein the galactosemia is in a human subject.

13. The use of any one of the preceding claims, wherein the galactosemia is manifested as increased alditol levels in blood, urine, or intraocular fluid.

14. The use of claim 13, wherein the alditol is galactitol, myoinositol, or sorbitol.

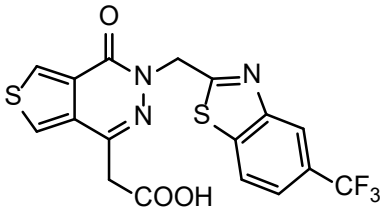
15. The use of any one of the preceding claims, wherein the galactosemia is manifested as increased liver cirrhosis, retinal disorder, macular edema, eye cataract, ovarian dysfunction, muscle or nerve dysfunction, retinopathy, neuropathy, impaired neural conduction, or mental retardation.

16. The use of any one of the preceding claims, wherein the galactosemia is Type I Galactosemia (GALT deficiency).

17. The use of any one of claims 1-15, wherein the galactosemia is Type II Galactosemia (GALK deficiency).

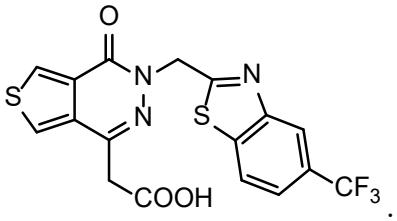
18. The use of any one of claims 1-15, wherein the galactosemia is Type III Galactosemia (GALE deficiency).

19. The use of any one of the preceding claims, wherein the aldose reductase inhibitor is Compound B:



, or pharmaceutically acceptable salt thereof.

20. The use of any one of the preceding claims, wherein the aldose reductase inhibitor is Compound B:



.