~~We c~~Claims:

1. Use of ~~An~~ an aldose reductase inhibitor ~~for use~~ in the manufacture of a medicament for the treatment of a genetic and/or metabolic disorder that alters sorbitol metabolism or causes over production of sorbitol~~, such as SDH deficiency~~.

2. The ~~aldose reductase inhibitor~~use of claim 1, wherein the treatment decreases sorbitol accumulation.

3. The ~~aldose reductase inhibitor~~ use ~~of~~ claim 1 or 2, wherein the disorder is a genetic disorder that alters metabolism of sorbitol or causes over-production of sorbitol.

4. The use of any one of claims 1-3, wherein the disorder is sorbitol dehydrogenase deficiency.

~~4~~5. The ~~aldose reductase inhibitor~~ use of any one of claims 1~~-4 or 2~~, wherein the disorder is genetic sorbitol dehydrogenase ~~SDH~~ deficiency.

~~5~~6. The ~~aldose reductase inhibitor~~ use of any one of claims 1-~~4~~5, wherein the disorder includes clinical features or complications selected from the group consisting of cataracts, neuropathy, retinopathy, cardiomyopathy, nephropathy, microvascular complications, atherosclerosis and other cardiovascular complications, albuminuria, and diabetes.

~~6~~7. ~~An~~ The ~~aldose reductase inhibitor~~ use of any one of claims 1-~~5~~6, wherein the disorder is hereditary neuropathy.

~~7~~8. The ~~aldose reductase inhibitor~~ use of claim ~~6~~7, wherein the hereditary neuropathy ~~as~~ is associated with sorbitol dehydrogenase ~~SDH~~ deficiency.

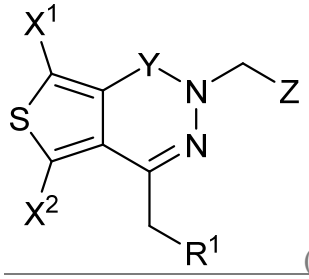
~~8~~9. The ~~aldose reductase inhibitor~~ use of claim ~~6~~ 7 or ~~7~~8, wherein the hereditary neuropathy is Charcot–Marie–Tooth disease (CMT).

10. The use of claim 9, wherein the CMT disease is CMT neuropathy type 1 (CMT-1).

911. The ~~aldose reductase inhibitor~~ use of claim ~~6-9or 7~~, wherein the CMT disease is CMT neuropathy type 2 (CMT-2).

~~10~~12. The ~~aldose reductase inhibitor~~ use of any one of claims 1-~~9~~7, wherein the disorder~~CMT-2~~ is distal hereditary motor neuronopathy (dHMN).

~~11~~13. The ~~aldose reductase inhibitor~~use of any one of claims 1-~~10~~12, wherein the aldose reductase inhibitor is a compound of ~~any one of~~ Formula~~s~~ (III)~~-(VI)~~



(III),

or a salt thereof, wherein

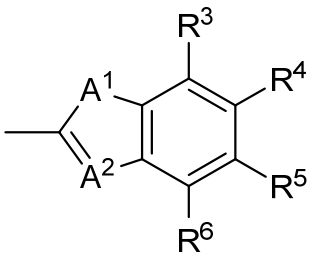
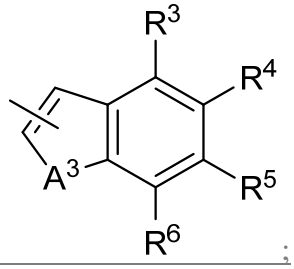
R^1 is CO_2R^2;

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

X^1 is hydrogen or halogen;

X^2 is hydrogen 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;

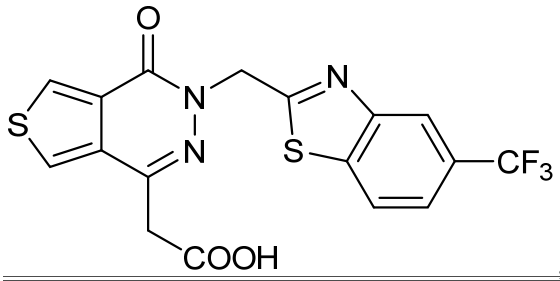
A^2 is N or CH;

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.

14. The use of claim 13, wherein the aldose reductase inhibitor is selected from the group consisting of



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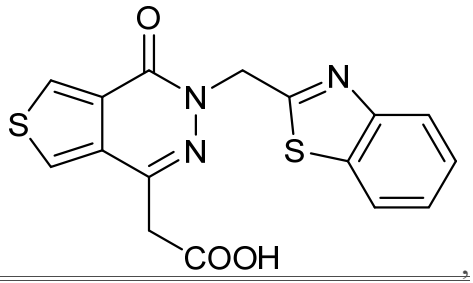

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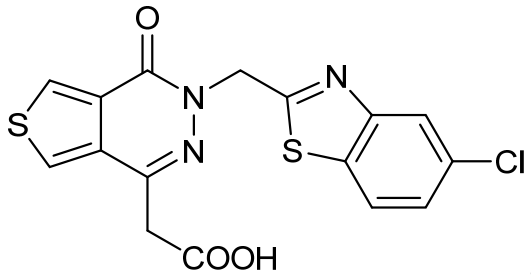

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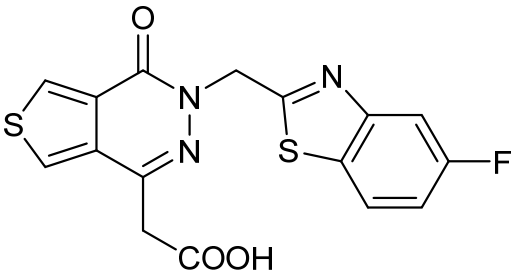
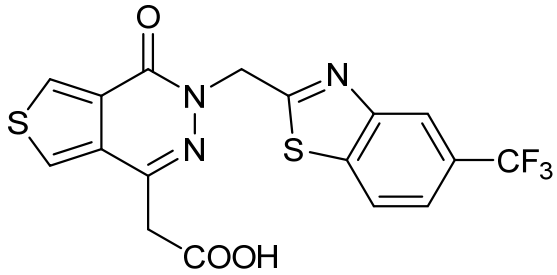


, and salts thereof.

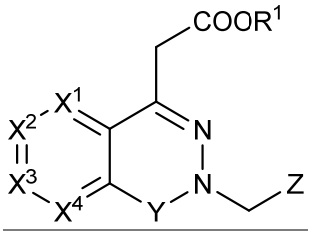
15. The use of any one of claims 1-14, wherein the aldose reductase inhibitor is Compound B:



or a salt thereof.

~~12~~16. The ~~aldose reductase inhibitor~~ use of any one of claims 1-~~10~~12, wherein the aldose reductase inhibitor is ~~a~~ zopolrestat or a salt thereof, or epalrestat or a salt thereof.

~~13~~17. The ~~aldose reductase inhibitor~~ use of any one of claims 1-~~10~~12, wherein the aldose reductase inhibitor is a compound of Formula (~~I~~):



or a salt thereof, wherein

R^1 is H, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, or (C_1-C_6)-aminoalkyl;

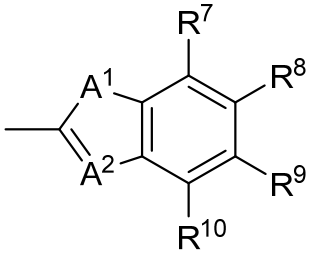
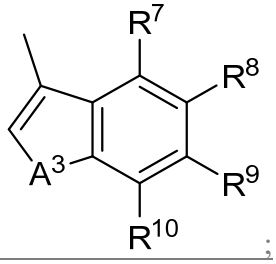
X^1 is N or CR^3;

X^2 is N or CR^4;

X^3 is N or CR^5;

X^4 is N or CR^6; with the proviso that two or three of X^1, X^2, X^3, or X^4 are N;

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^{11}, O, S, or CH_2;

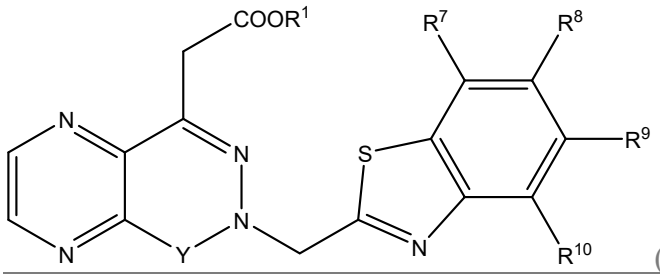
A^2 is N or CH;

A^3 is NR^{11}, O, or S;

R^3 through R^{10} 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; or two of R^3 through R^6 or two of R^7 through R^{10} taken together are (C_1-C_4)-alkylenedioxy; and

R^{11} is hydrogen, C_1-C_4 alkyl, or C(O)O-(C_1-C_4)-alkyl.

18. The use of any one of claims 1-12 or 17, wherein the aldose reductase inhibitor is a compound of Formula (II):



(II)

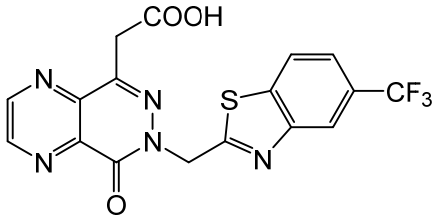
or a salt thereof, wherein

R^1 is H, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, or (C_1-C_6)-aminoalkyl;

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

R^7 through R^{10} 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; or two of R^7 through R^{10} taken together are (C_1-C_4)-alkylenedioxy.

~~14~~19. The ~~aldose reductase inhibitor~~use of ~~claim~~ claim 17 or 18~~13~~, wherein the aldose reductase inhibitor is selected from the ~~following or salts thereof~~ group consisting of



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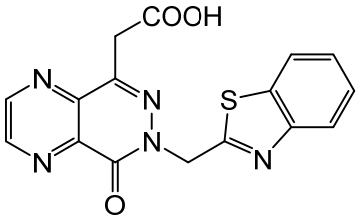

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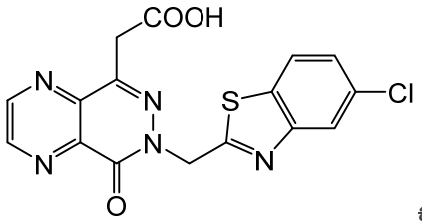
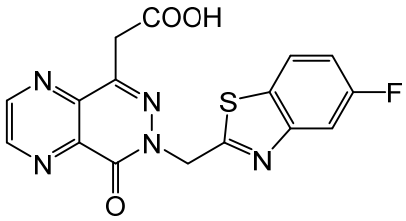
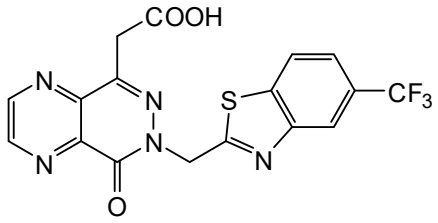


~~and,~~



, and salts thereof.

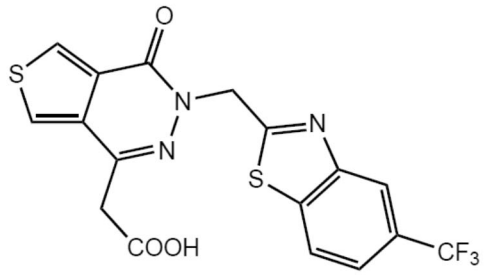
20. The use of any one of claims 1-12 or 17-19, wherein the aldose reductase inhibitor is Compound A



or a salt thereof.

~~15. The aldose reductase inhibitor of any one of claims 1-10, wherein the aldose reductase inhibitor is a compound of Formula (III).~~

~~16. The aldose reductase inhibitor of claim 15, wherein the aldose reductase inhibitor is selected from the following or salts thereof~~



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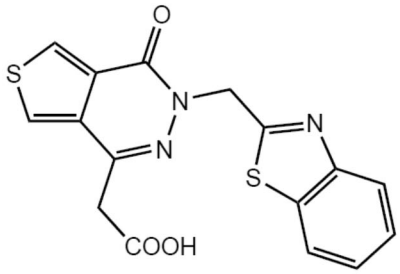

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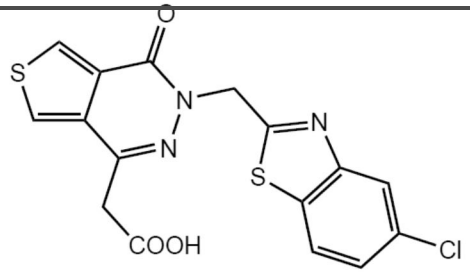

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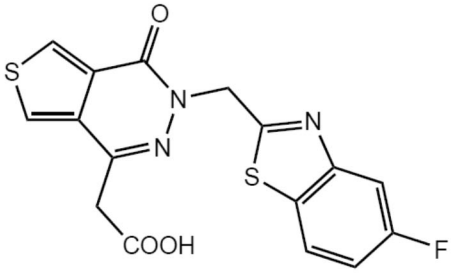

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~~17~~21. The ~~aldose reductase inhibitor~~ use of any one of claims 1-~~16~~20, wherein the ~~disease or~~ disorder is in a human.

~~18~~22. The ~~aldose reductase inhibitor~~ use of claim ~~17~~21, wherein the human has diabetes.

~~19~~23. The ~~aldose reductase inhibitor ethod~~ use of claim ~~18~~21 or 22, wherein the human has a complication of diabetes.

~~20. The aldose reductase inhibitor of any one of the preceding claims, wherein the aldose reductase inhibitor is Compound A or a salt thereof.~~

~~21. The aldose reductase inhibitor of any one of the preceding claims, wherein the aldose reductase inhibitor is Compound B or a salt thereof.~~

~~22. A method of treating a genetic and/or metabolic disorder that alters sorbitol metabolism or causes over production of sorbitol, such as SDH deficiency, in a subject, comprising administering a therapeutically effective amount of an aldose reductase inhibitor to a subject in need thereof.~~

~~23. The method of claim 22, wherein the effective amount of an aldose reductase inhibitor is sufficient to reduce sorbitol accumulation in the subject.~~

~~24. The methods of claim 22 or 23, wherein the genetic disorder is a disorder that alters metabolism of sorbitol or causes over-production of sorbitol.~~

~~25. The method of claim 22 or 23, wherein the disorder is genetic SDH deficiency.~~

~~26. The method of any one of claims 22-25, wherein the disorder includes clinical features or complications selected from the group consisting of cataracts, neuropathy, retinopathy, cardiomyopathy, nephropathy, microvascular complications, atherosclerosis and other cardiovascular complications, albuminuria, and diabetes.~~

~~27. A method of claim 22, wherein the disorder is hereditary neuropathy.~~

~~28. The method of claim 27, wherein the hereditary neuropathy is associated or caused by SDH deficiency.~~

~~29. The method of claim 27 or 28, wherein the hereditary neuropathy is Charcot-Marie-Tooth disease (CMT).~~

~~30. The method of claim 27 or 28, wherein the Charcot-Marie-Tooth neuropathy type 2 (CMT-2).~~

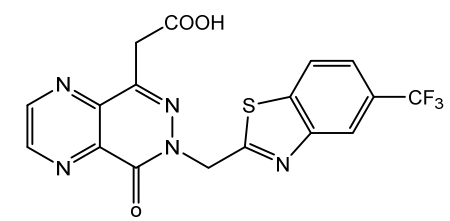
~~31. The method of claim 30, wherein the CMT-2 is distal hereditary motor neuronopathy (dHMN).~~

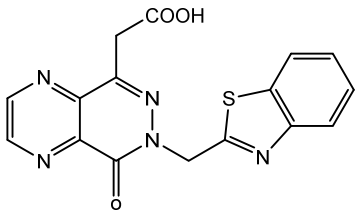
~~32. The method of any one of claims 22-31, wherein the aldose reductase inhibitor is a compound of any one of Formulas (I)-(VI) or salt thereof.~~

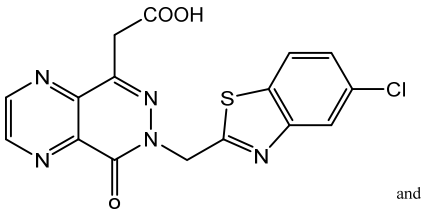
~~33. The method of any one of claims 22-31, wherein the aldose reductase inhibitor is a zopolrestat or salt thereof, or epalrestat or salt thereof.~~

~~34. The method of any one of claims 22-31, wherein the aldose reductase inhibitor is a compound of Formula (II) or salt thereof.~~

~~35. The method of claim 34, wherein the aldose reductase inhibitor is selected from the following or salts thereof~~







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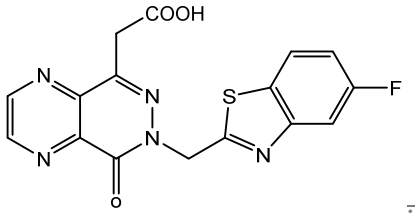
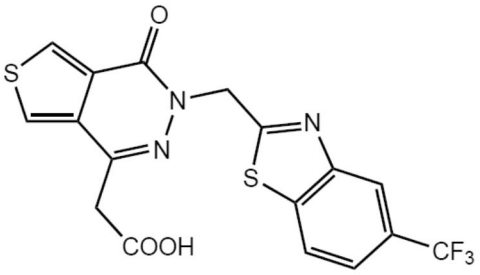


~~36. The method of any one of claims 22-31, wherein the aldose reductase inhibitor is a compound of Formula (III).~~

37. The method of claim 36, wherein the aldose reductase inhibitor is selected from the following or salts thereof



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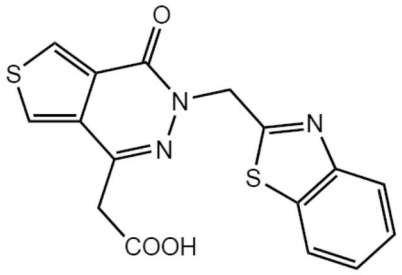

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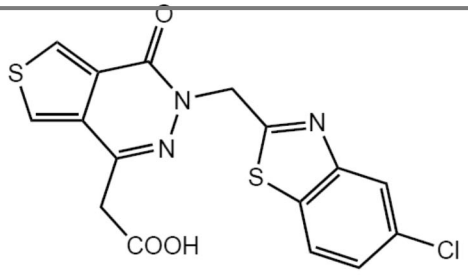

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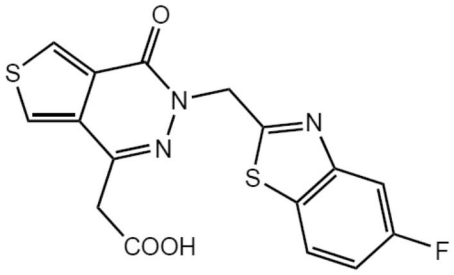

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38. The method of any one of claims 22-137, wherein the subject is a human.

39. The method of claim 38, wherein the subject in need thereof has diabetes.

40. The method of claim 39, wherein the subject in need thereof has a complication of diabetes.

41. The method of any one of claims 22-40, wherein the aldose reductase inhibitor is Compound A or a salt thereof.

42. The method of any one of claims 22-40, wherein the aldose reductase inhibitor is Compound B or a salt thereof.

43. Use of an aldose reductase inhibitor (ARI) for treating sorbitol dehydrogenase (SDH) deficiency.

~~44. Use of an aldose reductase inhibitor (ARI) for treating a genetic disorder that alters metabolism of sorbitol or cause over-production of sorbitol.~~

~~45. Use of an aldose reductase inhibitor (ARI) for treating hereditary neuropathy.~~

~~46. An aldose reductase inhibitor (ARI) for use in the manufacture of a medicament for treating sorbitol-dehydrogenase (SDH) deficiency.~~

~~47. An aldose reductase inhibitor (ARI) for use in the manufacture of a medicament for treating a genetic disorder that alters metabolism of sorbitol or cause over-production of sorbitol.~~

~~48. An aldose reductase inhibitor (ARI) for use in the manufacture of a medicament for treating hereditary neuropathy.~~

~~49. A pharmaceutical composition for treating sorbitol-dehydrogenase (SDH) deficiency comprising administering an aldose reductase inhibitor (ARI) as an active ingredient.~~

~~50. A pharmaceutical composition for treating a genetic disorder that alters metabolism of sorbitol or cause over-production of sorbitol comprising administering an aldose reductase inhibitor (ARI) as an active ingredient.~~

~~51. A pharmaceutical composition for treating hereditary neuropathy comprising administering an aldose reductase inhibitor (ARI) as an active ingredient.~~