~~We c~~Claims:

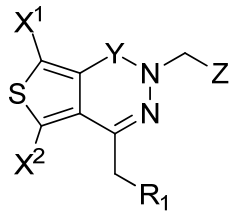
1. An aldose reductase inhibitor for use ~~method of~~ in treating PMM2-CDG~~, comprising administering a therapeutically effective amount of an aldose reductase inhibitor to a~~ in a subject ~~in need thereof~~.

2. An aldose reductase inhibitor for use in ~~method of~~ increasing PMM2 enzymatic activity in a subject with PMM2-CDG~~, comprising administering a therapeutically effective amount of an aldose reductase inhibitor to the subject~~.

3. Use of an aldose reductase inhibitor in the manufacture of a medicament for treating PMM2-CDG in a subject.

4. Use of an aldose reductase inhibitor in the manufacture of a medicament for increasing PMM2 enzymatic activity in a subject.

~~3~~5. The aldose reductase inhibitor or use ~~method~~ of any one of claims 1-~~2~~4, wherein the aldose reductase inhibitor is a compound of Formula (III):



(III),

~~-~~or a salt thereof

wherein,

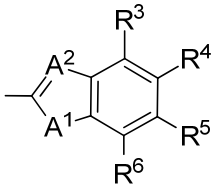
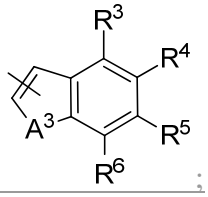
R^1 is CO_2R^2;

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 through 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.

6. The aldose reductase inhibitor or use of claim 5, wherein:

R^2 is H or $(C_1$-$C_6)$-alkyl;

Y is C=O;

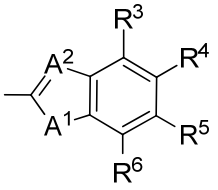
A^1 is NR^7, O, or S;

A^2 is N;

A^3 is O, or S; and

R^3 through R^6 are independently hydrogen, halogen, cyano, acyl, haloalkyl, haloalkoxy, haloalkylthio, $(C_1$-$C_4)$-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.

7. The aldose reductase inhibitor or use of claim 5 or 6, wherein Z is  or a salt thereof.

8. The aldose reductase inhibitor or use of any one of claims 5-7, wherein:

R^2 is H or $(C_1$-$C_6)$-alkyl;

X^1 is H;

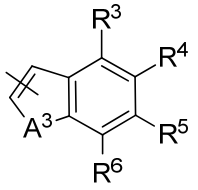
X^2 is H;

Y is C=O;

A^1 is S;

A^2 is N; and

R^3 through R^6 are independently hydrogen, halogen, or haloalkyl.

9. The aldose reductase inhibitor or use of claim 5 or 6, wherein Z is  or a pharmaceutically acceptable salt or solvate thereof.

10. The aldose reductase inhibitor or use of claim 9, wherein:

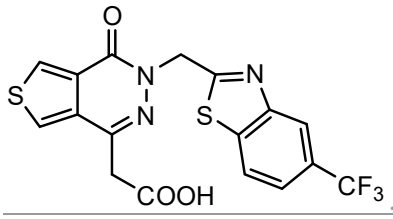
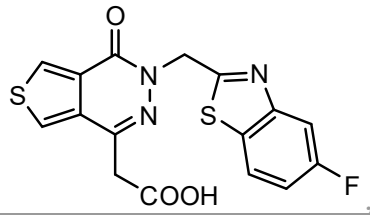
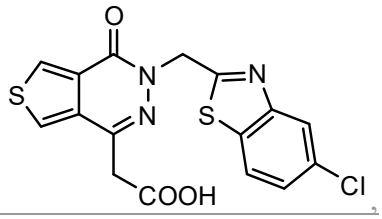
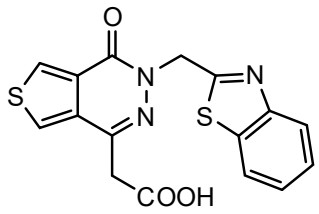
R^2 is hydrogen or (C_1-C_6)-alkyl;

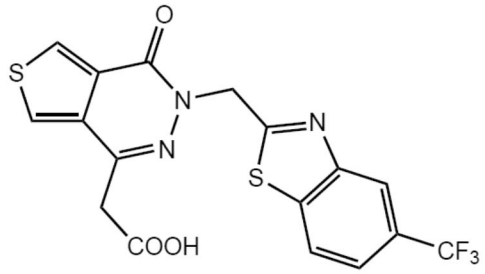
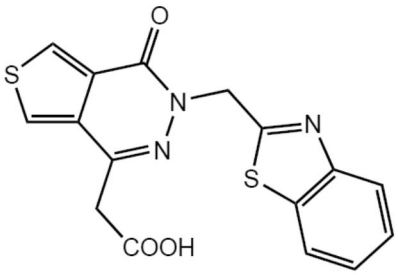
Y is C=O;

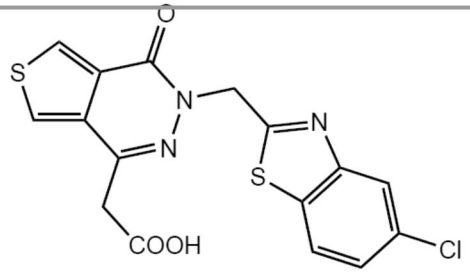
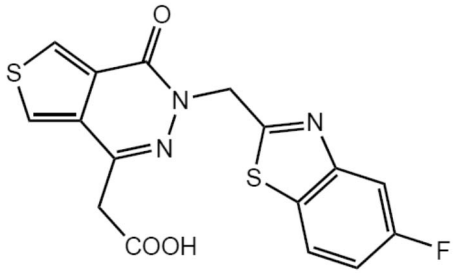
R^3 through R^6 are independently hydrogen, halogen, cyano, acyl, haloalkyl, haloalkoxy, haloalkylthio, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkylthio, (C_1-C_4)-alkylsulfinyl, or (C_1-C_4)-alkylsulfonyl; and

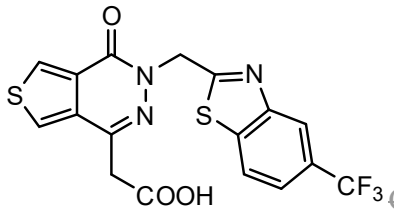
R^7 is hydrogen, C_1-C_4 alkyl, or C(O)O-(C_1-C_4)-alkyl.

411. The ~~method~~ aldose reductase inhibitor or use of any one of claims ~~3~~1-8, wherein the aldose reductase inhibitor is selected from the ~~following or salts thereof~~group consisting of:

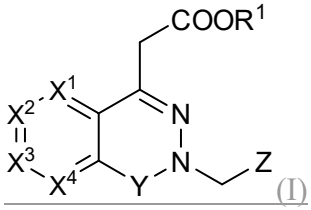




, and salts thereof


,

,


and

.

5~~1~~2. The ~~method~~ aldose reductase inhibitor or use of any one of claims 1-8 or 11~~4~~, wherein the aldose reductase inhibitor is  ~~Compound B~~ or a salt thereof.

13. The aldose reductase inhibitor or use of any one of claims 1-4, wherein the aldose reductase inhibitor is a compound of Formula (I):



(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;

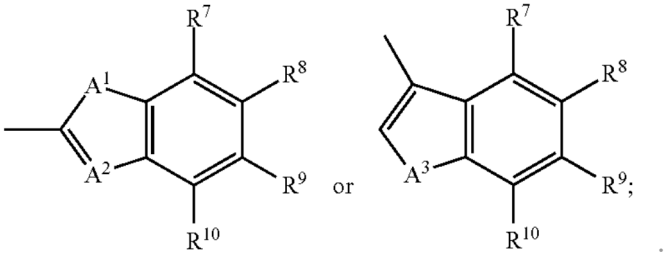
X^1 is N or CR^3;

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 

;

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.

14. The aldose reductase inhibitor or use of claim 13, wherein:

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

X^1 and X^4 are N;

X^2 is CR^4;

X^3 is CR^5;

Y is C═O;

A^1 is NR^{11}, O, or S;

A^2 is N;

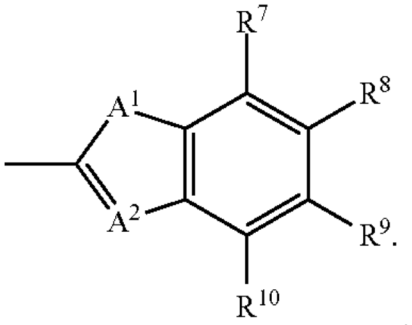
A^3 is O, or S; and

R^3 through R^{10} are each independently hydrogen, halogen, cyano, acyl, haloalkyl, haloalkoxy, haloalkylthio, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxy, $(C_1$-$C_4)$-alkylthio, $(C_1$-$C_4)$-alkylsulfinyl, or $(C_1$-$C_4)$-alkylsulfonyl; and

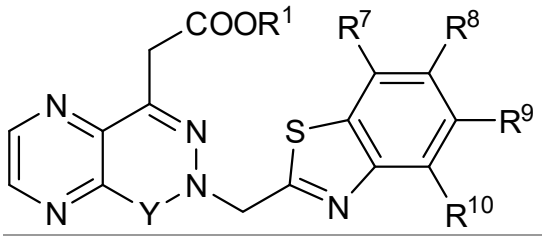
R^{11} is hydrogen, C_1-C_4 alkyl, or C(O)O-$(C_1$-$C_4)$-alkyl.

15. The aldose reductase inhibitor or use of claim 13 or 14, wherein R^3 through R^{10} are each independently hydrogen, halogen, or haloalkyl.

16. The aldose reductase inhibitor or use of any one of claims 14-15, wherein Z is



~~6~~17. The aldose reductase inhibitor or use ~~method~~ of any one of claims 1-~~2~~4 or 14-16, wherein the aldose reductase inhibitor is a compound of Formula (II):



(II),

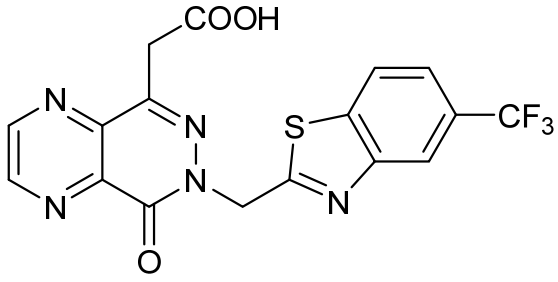
or a salt thereof, wherein:

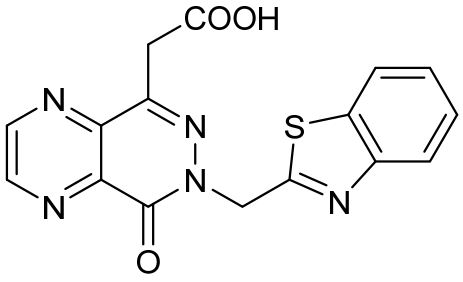
R^1 is H, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-hydroxyalkyl, or $(C_1$-$C_6)$-aminoalkyl;

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

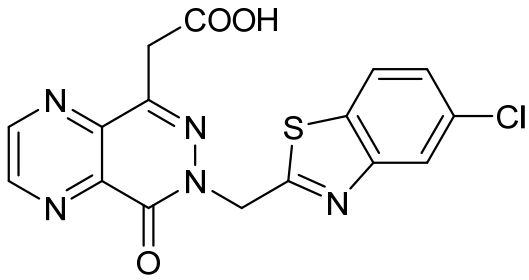
R^7 through R^{10} are independently hydrogen, halogen, cyano, acyl, haloalkyl, haloalkoxy, haloalkylthio, trifluoroacetyl, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkylthio, (C_1-C_4)-alkylsulfinyl, or (C_1-C_4)-alkylsulfonyl; or two of R^7 through R^{10} taken together are (C_1-C_4)-alkylenedioxy~~or salt thereof~~.

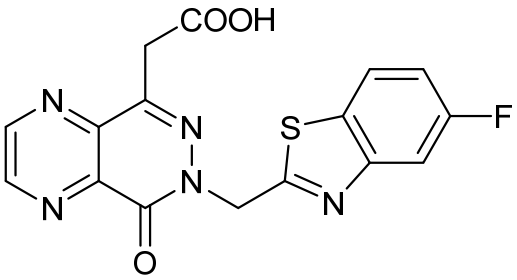
~~7~~18. The aldose reductase inhibitor or use ~~method~~ of any one of claims ~~6~~14-17, wherein the aldose reductase inhibitor is selected from the ~~following or salts thereof~~group consisting of:



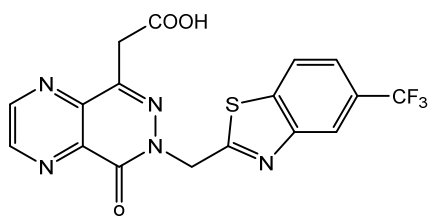
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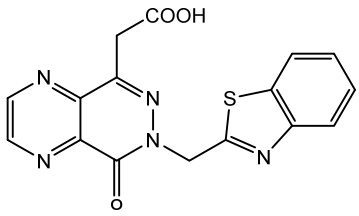
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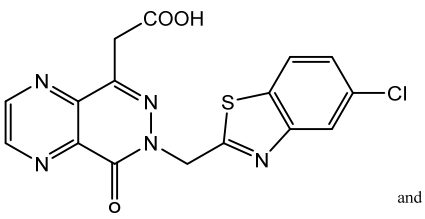


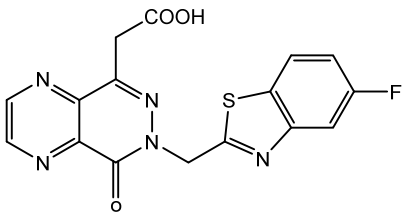
,


and salts thereof

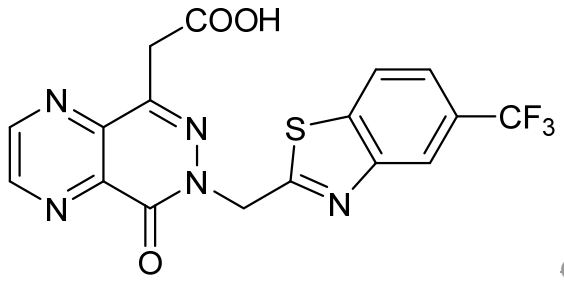






and


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~~8~~19. The aldose reductase inhibitor or use ~~method~~ of any one of claims ~~7~~14-18, wherein the aldose reductase inhibitor is  ~~Compound A~~ or a salt thereof.

~~9. The method of any one of claims 1-2, wherein the aldose reductase inhibitor is a compound of any one of Formulas (I)-(VI) or salt thereof.~~

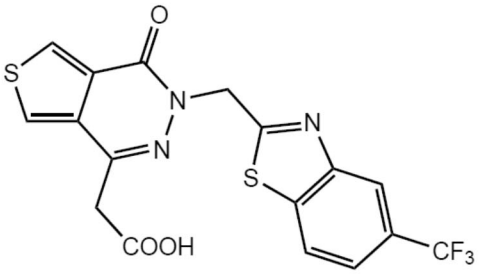
~~10~~20. The aldose reductase inhibitor or use ~~method~~ of any one of claims 1-~~9~~19, wherein the subject is a human.

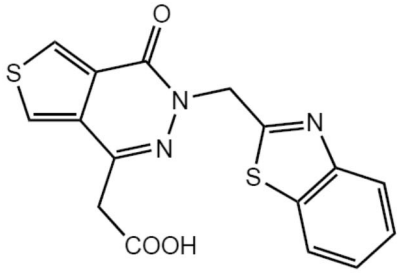
~~11. An aldose reductase inhibitor for use in the treatment of PMM2-CDG.~~

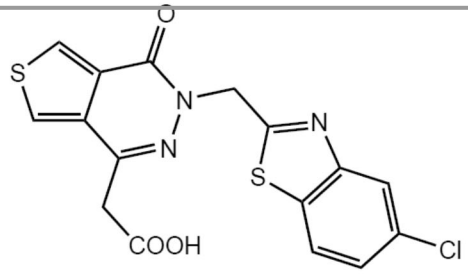
~~12. The use of claim 11, wherein treatment increases PMM2 enzymatic activity in a subject with PMM2-CDG.~~

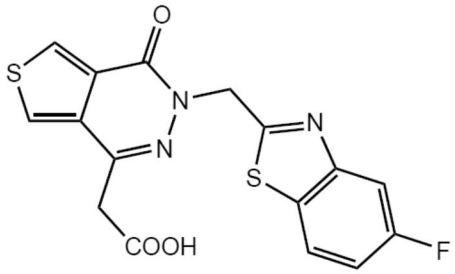
~~13. The use of any one of claims 11-12, wherein the aldose reductase inhibitor is a compound of Formula (III) or salt thereof.~~

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



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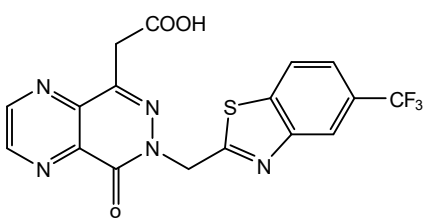
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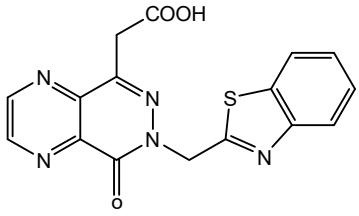
and


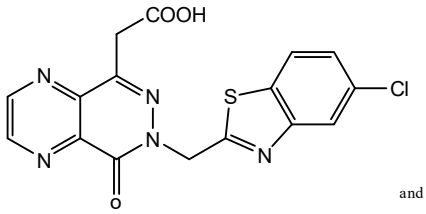
~~15. The use of any one of claims 11-14, wherein the aldose reductase inhibitor is Compound B or a salt thereof.~~

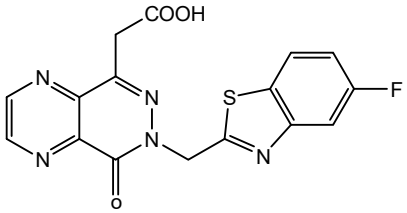
~~16. The use of any one of claims 11-12, wherein the aldose reductase inhibitor is a compound of Formula (II) or salt thereof.~~

~~17. The method of claim 16, wherein the aldose reductase inhibitor is selected from the following or salts thereof~~







and


~~18. The method of claim 17, wherein the aldose reductase inhibitor is Compound A or a salt thereof.~~

~~19. The method of any one of claims 11-12, wherein the aldose reductase inhibitor is a compound of any one of Formulas (I)-(VI) or salt thereof.~~