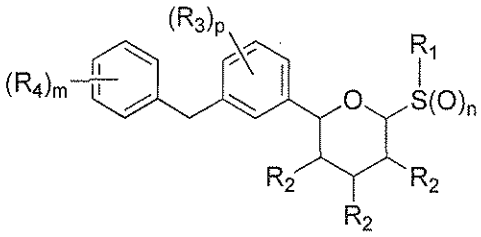
In one aspect, there is provided a compound of the formula:



or a pharmaceutically acceptable salt, dimer or trimer thereof, wherein:

R_1 is hydrogen or optionally substituted C_{1-10}-alkyl, C_{1-5}-cycloalkyl, or 5-membered heterocycle, which optional substitution is with one or more R_{1A};

each R_{1A} is independently amino, ester, amide, thiol, carboxylic acid, cyano, halo, hydroxyl, or optionally substituted C_{1-4}-alkoxy, C_{1-5}-cycloalkyl, or 5-membered heterocycle, which optional substitution is with one or more R_{1B};

each R_{1B} is independently C_{1-4}-alkyl, halo, or hydroxyl;

n is 0, 1, or 2;

each R_2 is independently F or OR_{2A}, wherein each R_{2A} is independently hydrogen, C_{1-4}-alkyl, or acyl;

each R_3 is independently halo, hydroxyl, or optionally substituted C_{1-10}-alkyl or C_{1-10}-alkoxy, which optional substitution is with one or more R_{3A};

each R_{3A} is independently amino, ester, amide, thiol, carboxylic acid, cyano, halo, hydroxyl, or optionally substituted C_{1-4}-alkoxy, C_{1-5}-cycloalkyl, or 5-membered heterocycle, which optional substitution is with one or more R_{3B};

each R_{3B} is independently C_{1-4}-alkyl, amino, cyano, halo, or hydroxyl;

p is 0, 1, or 2;

each R_4 is independently R_{4A}, $-N(R_{4A})(R_{4B})$, $-OR_{4A}$, $-SR_{4A}$, $-S(O)R_{4A}$, or $-S(O)_2R_{4A}$;

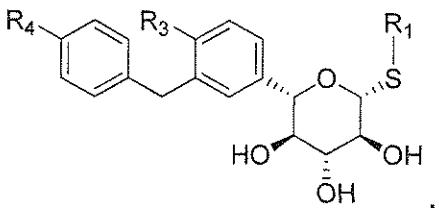
R_{4A} is $-C_{1-10}$-alkyl-$N(R_{4C})_2$, $-C_{1-10}$-alkyl-$N(R_{4C})C(O)R_{4C}$, $-C_{1-10}$-alkyl-$C(O)N(R_{4C})_2$, $-C_{1-10}$-alkyl-$C(O)N(R_{4C})$-C_{0-6}-alkyl-$C(O)R_{4C}$, $-C_{1-10}$-alkyl-$C(O)N(R_{4C})$-C_{0-6}-alkyl-$C(O)N(R_{4C})_2$, $-C_{1-10}$-alkyl-$N(R_{4C})C(O)$-C_{0-6}-alkyl-$N(R_{4C})_2$, or $-C_{1-10}$-alkyl-$N(R_{4C})C(O)$-C_{0-6}-alkyl-$N(R_{4C})C(O)R_{4C}$~~is optionally substituted C_{4-20}-alkyl or 4-20 membered heteroalkyl, which optional substitution is with one or more R_{4C}, and which is optionally attached to another R_{4A} moiety to provide a dimer or trimer~~;

R_{4B} is hydrogen or R_{4A};

each R_{4C} is independently amino, amido, azo, carbonyl, carboxyl, cyano, formyl, guanidino, halo, hydroxyl, imido, imino, isothiocyanate, nitrile, nitro, nitroso, nitroxy, oxo, sulfanyl, sulfinyl, sulfonyl, thial, thiocyanate, thione, thiourea, urea, or X_1, X_1-L_1-X_2, or X_1-L_1-X_2-L_2-X_3, wherein each of X_1, X_2 and X_3 is independently optionally substituted C_{1-4}-alkyl, C_{1-6}-cycloalkyl, 5- or 6-membered heterocycle, or aryl, which optional substitution is with one or more R_{4D}, and each of L_1 and L_2 is independently optionally substituted C_{1-6}-alkyl or 1-10-membered heteroalkyl, which optional substitution is with one or more of R_{4E};

each R_{4D} is independently R_{4E} or C_{1-6}-alkyl optionally substituted with one or more of R_{4E};

Some are of the formula:



This disclosure is further directed to pharmaceutical compositions comprising the compounds disclosed herein and methods of their use to treat and/or manage cardiovascular diseases and disorders, metabolic diseases and disorders, bowel diseases and disorders, and certain types of cancer.

In one aspect, there is provided a pharmaceutical composition comprising a compound as disclosed herein and a pharmaceutically acceptable excipient or diluent.

~~In one aspect, there is provided~~Disclosed is use of a compound or composition as disclosed herein, in the manufacture of a medicament for treating or managing a cardiovascular or metabolic disease or disorder.

4. BRIEF DESCRIPTION OF THE FIGURES

Certain aspects of this invention may be understood with reference to the figures.

Figure 1A shows the effect of five compounds of the invention, administered at a dose of 1.0 mg/kg ("mpk") once daily for four days, on the blood glucose levels of 18 week-old male C57/Blk6 mice after being fed a glucose-containing meal six hours after the final dose. Areas under the curves for each animal in the experiment are shown in Figure 1B.

Figure 2 shows the compounds' effect on plasma tGLP-1, compared to vehicle, for each mouse.

Figure 3 shows the compounds' effect on the mice's cecal glucose.

Figure 4 shows the dose-dependent decrease in glucose excursion upon receiving a glucose challenge administered 15 hours after dosing a compound of the invention. The compound had been administered daily for 22 days to 12 week-old male KKay mice maintained on a 45% high fat diet.

Figure 5A shows the compound's effect on the mice's HbA1c levels after 26 days of dosing. Figure 5B shows the change in the mice's HbA1c levels between days 0 and 27.

Figure 6 shows the compound's effect on the mice's postprandial tGLP-1 after 29 days of dosing.

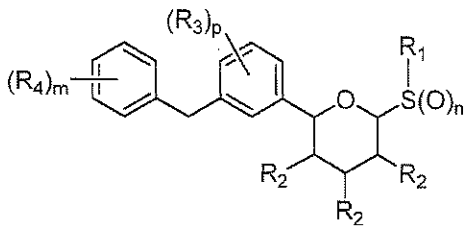
5. DETAILED DESCRIPTION

This invention is based on the discovery of novel and potent inhibitors of sodium glucose cotransporter 1 (SGLT1).

CLAIMS

What is claimed is:

1. A compound of the formula:



or a pharmaceutically acceptable salt, dimer or trimer thereof, wherein:

R_1 is hydrogen or optionally substituted C_{1-10}-alkyl, C_{1-5}-cycloalkyl, or 5-membered heterocycle, which optional substitution is with one or more R_{1A};

each R_{1A} is independently amino, ester, amide, thiol, carboxylic acid, cyano, halo, hydroxyl, or optionally substituted C_{1-4}-alkoxy, C_{1-5}-cycloalkyl, or 5-membered heterocycle, which optional substitution is with one or more R_{1B};

each R_{1B} is independently C_{1-4}-alkyl, halo, or hydroxyl;

n is 0, 1, or 2;

each R_2 is independently F or OR_{2A}, wherein each R_{2A} is independently hydrogen, C_{1-4}-alkyl, or acyl;

each R_3 is independently halo, hydroxyl, or optionally substituted C_{1-10}-alkyl or C_{1-10}-alkoxy, which optional substitution is with one or more R_{3A};

each R_{3A} is independently amino, ester, amide, thiol, carboxylic acid, cyano, halo, hydroxyl, or optionally substituted C_{1-4}-alkoxy, C_{1-5}-cycloalkyl, or 5-membered heterocycle, which optional substitution is with one or more R_{3B};

each R_{3B} is independently C_{1-4}-alkyl, amino, cyano, halo, or hydroxyl;

p is 0, 1, or 2;

each R_4 is independently R_{4A}, $-N(R_{4A})(R_{4B})$, $-OR_{4A}$, $-SR_{4A}$, $-S(O)R_{4A}$, or $-S(O)_2R_{4A}$;

R_{4A} is optionally substituted C_{4-20}-alkyl or 4-20-membered heteroalkyl, which optional substitution is with one or more R_{4C}, and which is optionally attached to another R_{4A} moiety to provide a dimer or trimer;

R_{4B} is hydrogen or R_{4A};

each R_{4C} is independently amino, amido, azo, carbonyl, carboxyl, cyano, formyl, guanidino, halo, hydroxyl, imido, imino, isothiocyanate, nitrile, nitro, nitroso, nitroxy, oxo, sulfanyl, sulfinyl, sulfonyl, thial, thiocyanate, thione, thiourea, urea, or X_1, X_1-L_1-X_2, or X_1-L_1-X_2-L_2-X_3, wherein each of X_1, X_2 and X_3 is independently optionally substituted C_{1-4}-alkyl, C_{1-6}-cycloalkyl, 5- or 6-membered heterocycle, or aryl, which optional substitution is with one or more R_{4D}, and each of

L_1 and L_2 is independently optionally substituted C_{1-6}-alkyl or 1-10-membered heteroalkyl, which optional substitution is with one or more of R_{4E};

each R_{4D} is independently R_{4E} or C_{1-6}-alkyl optionally substituted with one or more of R_{4E};

each R_{4E} is independently amino, amido, azo, carbonyl, carboxyl, cyano, formyl, guanidino, halo, hydroxyl, imido, imino, isothiocyanate, nitrile, nitro, nitroso, nitroxy, oxo, sulfanyl, sulfinyl, sulfonyl, thial, thiocyanate, thione, or urea; and

m is 1, 2 or 3.

2. The compound of claim 1, wherein R_1 is optionally substituted C_{1-4}-alkyl.

3. The compound of claim 1, wherein n is 0.

4. The compound of claim 1, wherein R_2 is OR_{2A}.

5. The compound of claim 4, wherein at least one R_{2A} is hydrogen.

6. The compound of claim 1, wherein R_3 is optionally substituted C_{1-4}-alkyl.

7. The compound of claim 1, wherein R_3 is halo.

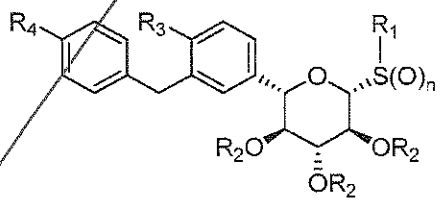
8. The compound of claim 1, wherein R_3 is optionally substituted C_{1-4}-alkoxy.

9. The compound of claim 1, wherein p is 1.

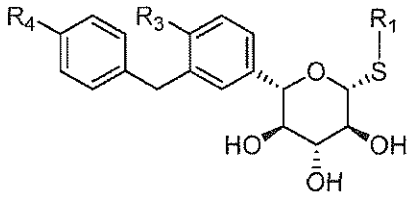
10. The compound of claim 1, wherein R_4 is R_{4A}.

11. The compound of claim 1, wherein R_4 is $-OR_{4A}$.

12. The compound of claim 1, which is of the formula:



13. The compound of claim 12, which is of the formula:



14. The compound of claim 13, wherein R_1 is C_{1-4}-alkyl.

15. The compound of claim 13, wherein R_3 is methyl.

16. The compound of claim 13, wherein R_4 is R_{4A}.

17. The compound of claim 13, wherein R_4 is $-OR_{4A}$.

18. The compound of claim 16 or 17, wherein R_{4A} is:

$-C_{1-10}$-alkyl-$N(R_{4C})_2$;

$-C_{1-10}$-alkyl-$N(R_{4C})C(O)R_{4C}$;

$-C_{1-10}$-alkyl-$C(O)N(R_{4C})_2$;

$-C_{1-10}$-alkyl-$C(O)N(R_{4C})$-C_{0-6}-alkyl-$C(O)R_{4C}$;

$-C_{1-10}$-alkyl-$C(O)N(R_{4C})$-C_{0-6}-alkyl-$C(O)N(R_{4C})_2$;

$-C_{1-10}$-alkyl-$N(R_{4C})C(O)$-C_{0-6}-alkyl-$N(R_{4C})_2$; or

$-C_{1-10}$-alkyl-$N(R_{4C})C(O)$-C_{0-6}-alkyl-$N(R_{4C})C(O)R_{4C}$.

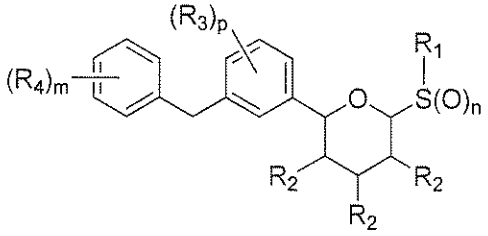
19. A pharmaceutical composition comprising a compound of any of the preceding claims and a pharmaceutically acceptable excipient or diluent.

20. Use of a compound or composition of any of the preceding claims, in the manufacture of a medicament for treating or managing a cardiovascular or metabolic disease or disorder.

CLAIMS

What is claimed is:

1. A compound of the formula:



or a pharmaceutically acceptable salt, dimer or trimer thereof, wherein:

R_1 is hydrogen or optionally substituted C_{1-10}-alkyl, C_{1-5}-cycloalkyl, or 5-membered heterocycle, which optional substitution is with one or more R_{1A};

each R_{1A} is independently amino, ester, amide, thiol, carboxylic acid, cyano, halo, hydroxyl, or optionally substituted C_{1-4}-alkoxy, C_{1-5}-cycloalkyl, or 5-membered heterocycle, which optional substitution is with one or more R_{1B};

each R_{1B} is independently C_{1-4}-alkyl, halo, or hydroxyl;

n is 0, 1, or 2;

each R_2 is independently F or OR_{2A}, wherein each R_{2A} is independently hydrogen, C_{1-4}-alkyl, or acyl;

each R_3 is independently halo, hydroxyl, or optionally substituted C_{1-10}-alkyl or C_{1-10}-alkoxy, which optional substitution is with one or more R_{3A};

each R_{3A} is independently amino, ester, amide, thiol, carboxylic acid, cyano, halo, hydroxyl, or optionally substituted C_{1-4}-alkoxy, C_{1-5}-cycloalkyl, or 5-membered heterocycle, which optional substitution is with one or more R_{3B};

each R_{3B} is independently C_{1-4}-alkyl, amino, cyano, halo, or hydroxyl;

p is 0, 1, or 2;

each R_4 is independently R_{4A}, $-N(R_{4A})(R_{4B})$, $-OR_{4A}$, $-SR_{4A}$, $-S(O)R_{4A}$, or $-S(O)_2R_{4A}$;

R_{4A} is $-C_{1-10}$-alkyl-$N(R_{4C})_2$, $-C_{1-10}$-alkyl-$N(R_{4C})C(O)R_{4C}$, $-C_{1-10}$-alkyl-$C(O)N(R_{4C})_2$, $-C_{1-10}$-alkyl-$C(O)N(R_{4C})$-C_{0-6}-alkyl-$C(O)R_{4C}$, $-C_{1-10}$-alkyl-$C(O)N(R_{4C})$-C_{0-6}-alkyl-$C(O)N(R_{4C})_2$, $-C_{1-10}$-alkyl-$N(R_{4C})C(O)$-C_{0-6}-alkyl-$N(R_{4C})_2$, or $-C_{1-10}$-alkyl-$N(R_{4C})C(O)$-C_{0-6}-alkyl-$N(R_{4C})C(O)R_{4C}$;

R_{4B} is hydrogen or R_{4A};

each R_{4C} is independently amino, amido, azo, carbonyl, carboxyl, cyano, formyl, guanidino, halo, hydroxyl, imido, imino, isothiocyanate, nitrile, nitro, nitroso, nitroxy, oxo, sulfanyl, sulfinyl, sulfonyl, thial, thiocyanate, thione, thiourea, urea, or X_1, X_1-L_1-X_2, or X_1-L_1-X_2-L_2-X_3, wherein each of X_1, X_2 and X_3 is independently optionally substituted C_{1-4}-alkyl, C_{1-6}-cycloalkyl, 5- or 6-membered heterocycle, or aryl, which optional substitution is with one or more R_{4D}, and each of

L_1 and L_2 is independently optionally substituted C_{1-6}-alkyl or 1-10-membered heteroalkyl, which optional substitution is with one or more of R_{4E};

each R_{4D} is independently R_{4E} or C_{1-6}-alkyl optionally substituted with one or more of R_{4E};

each R_{4E} is independently amino, amido, azo, carbonyl, carboxyl, cyano, formyl, guanidino, halo, hydroxyl, imido, imino, isothiocyanate, nitrile, nitro, nitroso, nitroxy, oxo, sulfanyl, sulfinyl, sulfonyl, thial, thiocyanate, thione, or urea; and

m is 1, 2 or 3.

2. The compound of claim 1, wherein R_1 is optionally substituted C_{1-4}-alkyl.

3. The compound of claim 1, wherein n is 0.

4. The compound of claim 1, wherein R_2 is OR_{2A}.

5. The compound of claim 4, wherein at least one R_{2A} is hydrogen.

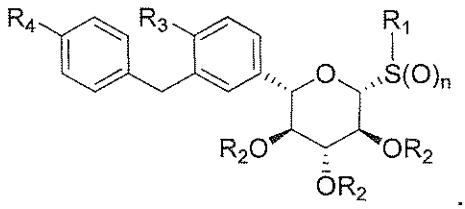
6. The compound of claim 1, wherein R_3 is optionally substituted C_{1-4}-alkyl.

7. The compound of claim 1, wherein R_3 is halo.

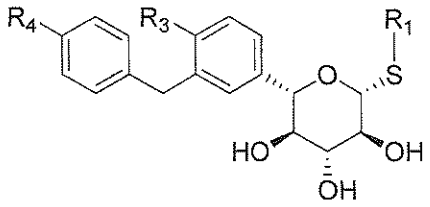
8. The compound of claim 1, wherein R_3 is optionally substituted C_{1-4}-alkoxy.

9. The compound of claim 1, wherein p is 1.

10. The compound of claim 1, which is of the formula:



11. The compound of claim 10, which is of the formula:



12. The compound of claim 11, wherein R_1 is C_{1-4}-alkyl.

13. The compound of claim 11, wherein R_3 is methyl.

14. A pharmaceutical composition comprising a compound of any of the preceding claims and a pharmaceutically acceptable excipient or diluent.