INHIBITORS OF SODIUM GLUCOSE COTRANSPORTER 1

1. FIELD OF THE INVENTION

This invention relates to compounds that can be used to inhibit sodium glucose cotransporter 1 (SLGT1), compositions comprising them, and methods of their use.

2. BACKGROUND

Type 2 diabetes mellitus is a chronic disease characterized by hyperglycemia caused by hepatic glucose production, a deficiency in insulin secretion, and/or peripheral insulin resistance. In recent years, considerable effort has been directed towards discovering ways of treating the disease. One relatively new approach is inhibition of the sodium glucose cotransporter (SLGT), which lowers blood glucose levels by removing glucose from the bloodstream.

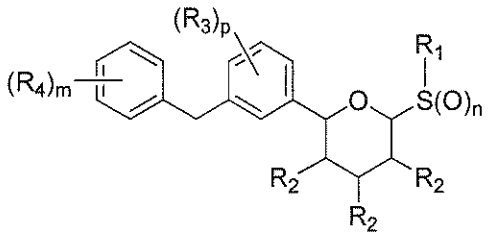
Under normal conditions, plasma glucose is filtered in the kidney glomerulus and in healthy individuals is almost completely reabsorbed. Obermeier, M., et al., Drug Metabolism Disposition 38(3):405-414, 406 (2010). That reabsorption is mediated by two sodium-dependent glucose cotransporters: SGLT1 and SGLT2. SGLT1 is expressed in the gut, heart, and kidney, while SGLT2 is expressed primarily in the proximal tubule of the nephron. *Id.* Although compounds that inhibit both transporters have been described, research has largely focused on discovering selective SGLT2 inhibitors. This is due, in part, to the discovery that a defective SGLT1 transporter in the gut is responsible for some glucose and galactose malabsorption disorders, and the belief that inhibition of SGLT1 would therefore be attended by unacceptable adverse effects. *Id.* Thus, most SGLT inhibitors currently in clinical trials, including dapagliflozin, canagliflozin, and empagliflozin, are selective SGLT2 inhibitors.

Recent clinical trial results do suggest, however, that inhibition of SGLT1 can provide benefits that extend beyond those provided merely by the inhibition of glucose reabsorption. See, e.g., U.S. patent application publication no. US-2011-0218159. In particular, it is believed that inhibition of SGLT1 can increase glucagon-like peptide-1 (GLP-1) levels. See, e.g., Moriya, R., *et al.*, Am J Physiol Endocrinol Metab 297: E1358–E1365 (2009). A number of well-known diabetes drugs, including sitagliptin, vildagliptin and saxagliptin, work by inhibiting dipeptidyl peptidase IV (DPP-4), which is the enzyme responsible for GLP-1 degradation.

3. SUMMARY ~~OF THE INVENTION~~

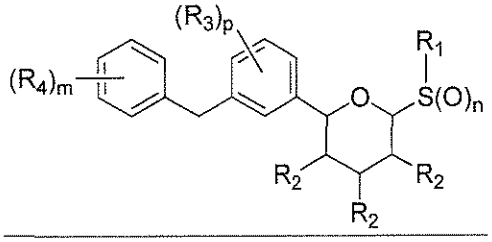
This ~~invention~~ disclosure is based on the discovery of novel and potent inhibitors of sodium glucose cotransporter 1 (SGLT1). Particular inhibitors are selective inhibitors of SGLT1. Particular inhibitors have low systemic exposure.

This ~~invention~~ disclosure is directed, in part, to compositions comprising and methods of using compounds of the formula:



and pharmaceutically acceptable salts, dimers or trimers 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.

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 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};

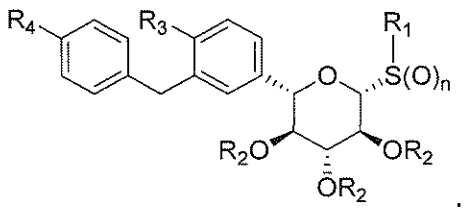
each R_{4C} is independently amino, amido, azo, carbonyl, carboxyl, cyano, formyl, guanidino, halo, hydroxyl, imido, imino, isothiocyanate, nitrile, nitro, nitroso, nitroxy, oxo, sulfanyl, sulfinyl, sulfonyl, thial, thiocyanate, thione, thiourea, urea, or X_1, X_1-L_1-X_2, or X_1-L_1-X_2-L_2-X_3, wherein 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};

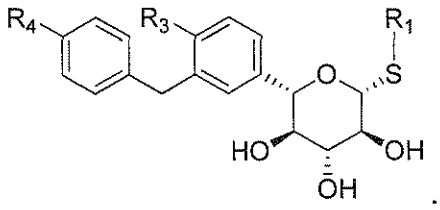
each R_{4E} is independently amino, amido, azo, carbonyl, carboxyl, cyano, formyl, guanidino, halo, hydroxyl, imido, imino, isothiocyanate, nitrile, nitro, nitroso, nitroxy, oxo, sulfanyl, sulfinyl, sulfonyl, thial, thiocyanate, thione, or urea; and

m is 1, 2 or 3.

Particular compounds are of the formula:



Some are of the formula:



This ~~invention~~ 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 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).

5.1. Definitions

Unless otherwise indicated, the term "alkyl" means a straight chain or branched hydrocarbon having from 1 to 20 (*e.g.*, 1 to 10 or 1 to 4) carbon atoms. Alkyl moieties having from 1 to 4 carbons are referred to as "lower alkyl." Examples of alkyl groups include, but are not

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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. ~~A method of treating or managing a disease or disorder, which comprises administering to a patient in need thereof a therapeutically effective amount~~Use of a compound or composition of any of the preceding claims, in the manufacture of a medicament for treating or managing ~~which disease or disorder is~~ a cardiovascular or metabolic disease or disorder.