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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-031839- -00008-0000

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Act. 444 RESPUESTAREQUE Folios: 23

Señor Director
DIRECCION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 379
Actuación : 444

Referencia : Expediente No. **09.031.839**
Asunto : Solicitud de patente para: **"INHIBIDORES DEL
COTRANSPORTADOR 2 DE SODIO Y GLUCOSA Y
MÉTODOS PARA SU USO"**
Solicitante : LEXICON PHARMACEUTICALS, INC.
Fecha de solicitud : Marzo 27 de 2009

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, me refiero al oficio No. **9200** notificado por fijación en lista el 1 de Junio de 2012.

2. Mediante oficio No. **9200** se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Las observaciones realizadas en el oficio son las siguientes:

2.1 Reivindicaciones

En el oficio técnico mencionado anteriormente, se ha considerado que las reivindicaciones no son concisas debido a que se reivindican sustituyentes que no se definen en la descripción.

2.3 Análisis de patentabilidad

2.3.1 Nivel inventivo

Para la evaluación de este requerimiento se han citado los documentos D1: US20060009400 y D2: WO2006073197. El Examinador afirma que una comparación elemento por elemento de la invención con respecto al estado de la técnica permite determinar que todos los elementos de las reivindicaciones 1 a 8, 10, 11 Y 38 a 40 se pueden obtener de una combinación de los documentos D1 y D2, afectando el nivel inventivo de dichas reivindicaciones.

3. Respuesta a las objeciones

De este modo y con el objeto de atender las objeciones arriba mencionadas, se desea presentar las siguientes modificaciones, aclaraciones y argumentos:

3.1 Modificación de una solicitud en trámite

De acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar un nuevo pliego reivindicatorio conformado por 19 reivindicaciones.

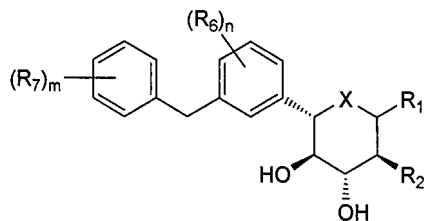
La reivindicación 1 se ha modificado de tal forma que se definen explícitamente los grupos A y B que se ilustraban en el anterior pliego. De esta forma, la reivindicación 1 es clara, ya que presenta un número razonable de alternativas que se encuentran sustentadas en la descripción.

En consecuencia de lo anterior, se considera que la objeción formulada en cuanto a la falta de claridad de las reivindicaciones ha sido superada.

3.2 Argumentos a favor del nivel inventivo de la presente solicitud

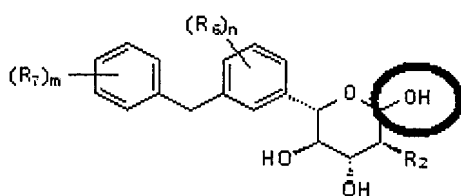
El examen de nivel inventivo se centra en las diferencias entre uno de los ejemplos de la solicitud y el contenido de los documentos D1 y D2. Con respecto a esto, es pertinente aclarar que el examen de nivel inventivo debe centrarse en la reivindicación objetada, no en los ejemplos específicos.

La nueva reivindicación 1 define un compuesto de acuerdo a la siguiente fórmula:

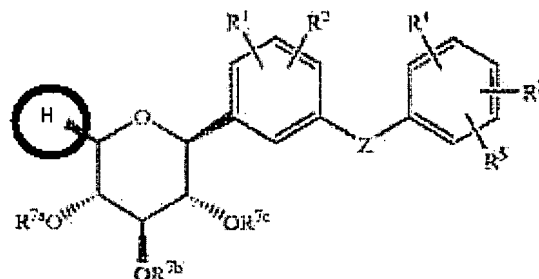


En donde x puede ser O, S, o NR₃. El documento D1 corresponde al caso en donde x es O. En este caso, R₁ puede ser OR_{1A}, SR_{1A}, SOR_{1A}, SO₂R_{1A} ó N(R_{1A})₂, y R_{1A} puede ser hidrógeno, alquilo, arilo, o heterociclo.

Puede notarse que la fórmula de D1, aunque es similar, tiene una diferencia fundamental, ya que en el lugar de R₁, se encuentra un grupo x, que puede ser un átomo de hidrógeno o un grupo alquilo. El grupo x mencionado en D1 puede ser comparable con el grupo R_{1A} de la presente solicitud, sin embargo, la fórmula de D1 no es comparable con la presente solicitud debido a que hace falta un componente esencial del grupo R₁ que puede ser O, S, SO, SO₂ o N conectando a dicho grupo con el ciclo. A continuación se ilustra con un ejemplo lo anterior:



Modalidad de la reivindicación 1

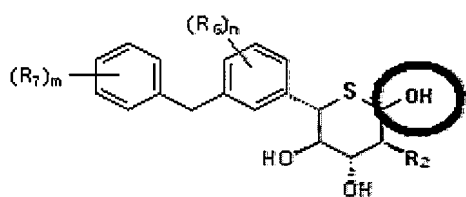


Modalidad de D1

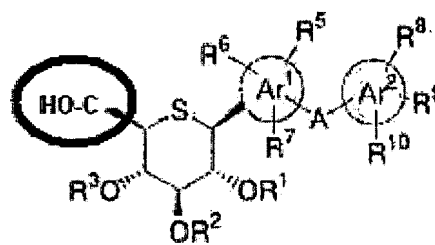
A pesar de que las composiciones arriba ilustradas son tan solo una modalidad de muchas posibles, revelan una diferencia que se mantiene en todos los casos, independientemente de la modalidad o ejemplo escogido de la reivindicación 1 o de D1. Lo anterior, debido a que bajo cualquier modalidad para el grupo x de D1, en este caso el átomo H, será equivalente al grupo R_{1A}, en este caso también el átomo H. Sin embargo, la reivindicación

1 requiere que dicho grupo se conecte al ciclo mediante el otro componente de R_1 , en este caso O, característica que no se enseña ni se sugiere en el documento D1.

El documento D2 por su parte corresponde al caso en donde x es S, en donde R_1 puede ser hidrógeno, OR_{1A} , SR_{1A} , SOR_{1A} , ó SO_2R_{1A} y R_{1A} puede ser hidrógeno, alquilo, arilo, ó heterociclo. La composición del documento D2 tiene, sin embargo, en el grupo correspondiente a R_1 , una diferencia esencial, ya que el grupo OR^4 de D2 se conecta al ciclo mediante un átomo de carbono. A continuación se ilustra de nuevo una posible modalidad de la reivindicación 1 comparada con una posible modalidad de D2:



Modalidad de la reivindicación 1



Modalidad de D2

A pesar de que las composiciones arriba ilustradas son tan solo una modalidad de muchas posibles, ponen de presente una diferencia que permanece en todos los casos, independientemente de la modalidad o ejemplo escogido de la reivindicación 1 o de D2. Lo anterior, debido a que cualquier posibilidad para el grupo OR^4 de D2, en este caso OH, será equivalente al grupo R_1 , en este caso también OH. Sin embargo, el documento D2 especifica que dicho grupo debe unirse al ciclo mediante un átomo de carbono, posibilidad que no se contempla en la reivindicación 1.

Puede notarse entonces que tanto el documento D1 como el documento D2 enseñan, en la posición que corresponde a R_1 en la reivindicación 1, un derivado del metileno, o un átomo de hidrógeno en su defecto, pero nada diferente a estas dos posibilidades. Por el contrario, la reivindicación 1 de la presente solicitud requiere, en dicha posición, un grupo seleccionado entre OR_{1A} , SR_{1A} , SOR_{1A} , SO_2R_{1A} ó $N(R_{1A})_2$.

Para aclarar la importancia de esta diferencia, se hace referencia al artículo de Handlon et al, incluido en los anexos, en donde se explica que todos los inhibidores de SGLT2

potencialmente útiles en el estado de la técnica comprenden, en la posición que corresponde a R_1 de la presente solicitud, CH_2OH o un derivado acetato del mismo. Esto corresponde con las enseñanzas de D1 y D2, y no es inesperado, ya que para inhibir un transportador de glucosa tiene sentido usar un antagonista que comprenda un grupo que se asemeje a la glucosa. Así, el estado del arte en general, a la fecha de prioridad de la presente solicitud, contiene enseñanzas contrarias a incluir un compuesto diferente a un derivado de metileno en la posición anteriormente mencionada (ver figuras 1 a 3 de Handlon et al).

De esta forma, se puede notar que ninguna posible combinación de los documentos D1 y D2 podría dar como resultado una composición que como acá reivindicada, contenga todas las características esenciales de la reivindicación 1. También se puede notar que la diferencia entre la composición reivindicada y el estado de la técnica no resulta obvia, debido a que el estado de la técnica en general contiene enseñanzas contrarias a lo especificado en la reivindicación 1.

Como consecuencia de lo anterior, es claro que la presente invención superó un prejuicio técnico en la medida que para la fecha de su prioridad en el estado del arte se consideraba que solo había una forma de lograr el resultado buscado y era incluyendo CH_2OH o un derivado acetato del mismo en la posición que corresponde a R_1 . Así entonces, queda demostrada la existencia de un indicio de nivel inventivo de la presente invención en los términos de la Guía de Patentes expedida el presente año por su Despacho, a saber:

“En las siguientes situaciones se considera que hay indicios de nivel inventivo:

- *Superación de un prejuicio técnico. Si la invención se realiza para eliminar dicho prejuicio, adoptando medios técnicos no utilizados anteriormente, es indicio a favor de la existencia de nivel inventivo”.*
(pág 74)

Teniendo en cuenta lo anterior, es claro que la nueva reivindicación independiente 1 es inventiva sobre el estado del arte citado. Consecuentemente, las reivindicaciones 2 a 17 son también inventivas en virtud de su dependencia de la reivindicación 1. Las reivindicaciones 18 y

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19 son también inventivas ya que definen una composición farmacéutica que comprende la composición de alguna de las reivindicaciones 1 a 17, que son inventivas.

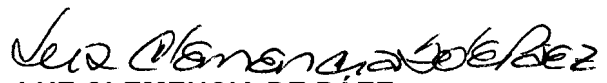
De acuerdo a todos los argumentos presentados, la presente solicitud cumple a cabalidad con los requerimientos exigidos en la Decisión 486 y las objeciones formuladas por el Examinador se ven superadas.

4. Puesto que se ha dado respuesta a todas las objeciones formuladas por el Examinador, se solicita atentamente proceder al otorgamiento de la solicitud de patente. En este sentido, respetuosamente recordamos al Examinador que la patente no podrá ser negada con base en objeciones diferentes a las expuestas en la acción oficial No. 9200, toda vez que al no haber sido trasladadas a mi representada, dicha decisión violaría tanto el tenor literal del artículo 45 de la Decisión 486 como el derecho constitucional al debido proceso. En este evento, y con base en el inciso 2 del artículo 45, respetuosamente solicitamos al Examinador expedir una nueva acción oficial que permita a mi representada contra argumentar las mismas o modificar la solicitud con el fin de cumplir los requisitos de patentabilidad.

5. Anexos

- Nuevo pliego reivindicatorio conformado por 19 reivindicaciones
- Artículo: "Sodium glucose co-transporter 2 (SLGT2) inhibitors as potential antidiabetic agents", Anthony L, Handlon.
- Formulario de modificaciones en solicitud pendiente
- Factura por concepto de nueve reivindicaciones adicionales a las primeras diez por \$270.000.

Señor Director,


LUZ CLEMENCIA DE PÁEZ

C.C. 35.456.344 de Usaquén

T.P.A. No. 23.555

COLO-17128-841-009-4
SML\LLG\ID-224447\WPC17128
No. M-2012-224447\SML

**Industria y Comercio**
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación

DIRECCIÓN DE NUEVAS CREACIONES
MODIFICACIONES Y/O CORRECCIONES**1. Identificación del Trámite**

- ☐ Error material ☒ Modificación a una Solicitud en trámite
- ☒ Patente de Invención
- ☐ Patente de Modelo de Utilidad
- ☐ Registro de Diseño Industrial
- ☐ Esquema de Trazado de Circuitos Integrados

2. Datos del solicitantePersona Natural ☐Persona Jurídica ☒**LEXICON PHARMACEUTICALS, INC.**

Nombre o denominación / Nombre o razón social completa

Nombre representante legal

Tipo de empresa Micro ☐ Pequeña ☐ Mediana ☐ Otra ☐Documento de identificación: ☐ C.C. ☐ C.E. ☐ NIT ☐ Otro Número _____

Nacionalidad/País de constitución	Dirección y domicilio del titular	Ciudad
Estados Unidos de América	8800 Technology Forest Place, The Woodlands, Texas 77381	The Woodlands
Dirección electrónica		No. Fax
clientes@cavelier.com		2 11 86 50
		Número telefónico
		3 47 36 11

- ☐ Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del apoderado:Apellidos y Nombre
De Páez Luz ClemenciaDocumento de identificación
C.C. 35.456.344Tarjeta profesional
T.P.A. 23.555

Dirección y domicilio		Ciudad
Carrera 4ª No. 72 -35		Bogotá
Dirección electrónica		No. Fax
cavelier@cavelier.com		2 11 86 50
		Número telefónico
		3 47 36 11
En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación o protocolo de poder general		

4. Datos del trámite

Corrección:

Expediente No 09.031.839

Aparece

Debe ser

Modificación:**Modificación al capítulo reivindicatorio.**

Presento nuevo capítulo reivindicatorio compuesto por 19 reivindicaciones y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas.

Respetuosamente manifiesto que a pesar de eliminar materia del pliego reivindicatorio originalmente presentado, mi representada no renuncia a la protección que pueda obtener sobre dicha materia y se reserva el derecho de presentar una solicitud divisional que la contenga durante el trámite de la presente solicitud, beneficiándose de la fecha de prioridad inicialmente reivindicada.

**Modificación al capítulo descriptivo.****Modificación al resumen.****Modificación a los dibujos.****Modificación al solicitante.****5. Anexos**

Poder, si fuere el caso.



Documento que contiene las modificaciones o correcciones.



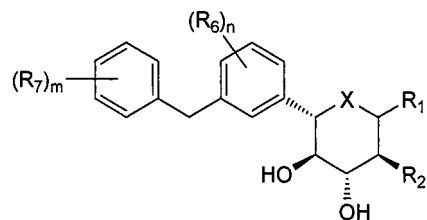
Comprobante de pago por 9 reivindicaciones adicionales después de la décima reivindicación por \$270.000.

6. Firma	
Nombre y apellidos	Firma
LUZ CLEMENCIA DE PAEZ	<i>LuZ Clemencia De PaeZ</i>
C.C. 35.456.344 DE Usaquén	Tarjeta Profesional 23.555 <i>TP #23555 OSJ</i>

SML\NCA\WPC17128\ID-224524

REIVINDICACIONES

1. Un compuesto de fórmula:



o una sal farmacéuticamente aceptable o solvato del mismo en donde:

X es O, S o NR₃;

cuando X es O, R₁ es OR_{1A}, SR_{1A}, SOR_{1A}, SO₂R_{1A} ó N(R_{1A})₂;

cuando X es S, R₁ es hidrógeno, OR_{1A}, SR_{1A}, SOR_{1A}, ó SO₂R_{1A};

cuando X es NR₃, R₁ es OR_{1A}, SR_{1A}, SOR_{1A}, SO₂R_{1A}, ó R_{1A};

cada R_{1A} es independientemente hidrógeno, alquilo, arilo, ó heterociclo;

R₂ es fluoro ó OR_{2A};

cada uno de R_{2A}, R_{2B}, y R_{2C} es independientemente hidrógeno, alquilo, C(O)alquilo, C(O)arilo, o arilo;

R₃ es hidrógeno, C(O)R_{3A}, CO₂R_{3A}, CON(R_{3B})₂, alquilo, arilo, o heterociclo;

cada R_{3A} es independientemente alquilo o arilo;

cada R_{3B} es independientemente hidrógeno, alquilo o arilo;

cada R₆ es independientemente hidrógeno, hidroxilo, halógeno, amino, ciano, nitro, C≡CR_{6A}, OR_{6A}, SR_{6A}, SOR_{6A}, SO₂R_{6A}, C(O)R_{6A}, CO₂R_{6A}, CO₂H, CON(R_{6A})(R_{6A}), CONH(R_{6A}), CONH₂, NHC(O)R_{6A}, NH₂SO₂R_{6A}, alquilo, arilo, o heterociclo;

cada R_{6A} es independientemente alquilo, arilo, o heterociclo;

cada R₇ es independientemente hidrógeno, hidroxilo, halógeno, amino, ciano, nitro, C≡CR_{7A}, OR_{7A}, SR_{7A}, SOR_{7A}, SO₂R_{7A}, C(O)R_{7A}, CO₂R_{7A}, CO₂H, CON(R_{7A})(R_{7A}), CONH(R_{7A}), CONH₂, NHC(O)R_{7A}, NH₂SO₂R_{7A}, alquilo, arilo, o heterociclo;

cada R_{7A} es independientemente alquilo, arilo, o heterociclo;

m está entre 1 y 3;

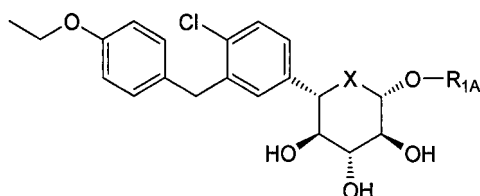
n está entre 1 y 3;

“alquilo” significa una cadena lineal, ramificada y/o hidrocarbano cíclico teniendo desde 1 hasta 20 átomos de carbono; y

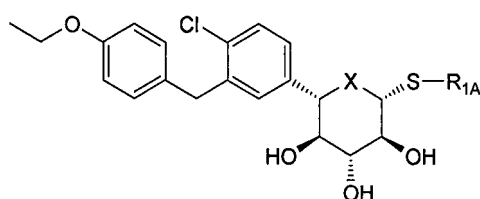
“arilo” significa un anillo aromático o un sistema de anillos aromáticos o parcialmente aromáticos compuesto por átomos de carbono e hidrógeno.

2. El compuesto de la reivindicación 1, en donde R₁ es OR_{1A}.

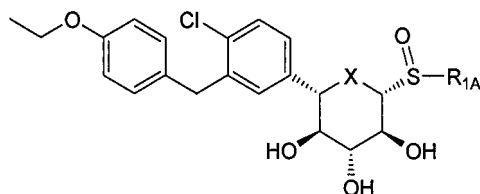
3. El compuesto de la reivindicación 1, en donde R_1 es SR_{1A} .
4. El compuesto de la reivindicación 1, en donde R_1 es SOR_{1A} .
5. El compuesto de la reivindicación 1, en donde R_1 es SO_2R_{1A} .
6. El compuesto de la reivindicación 1, en donde R_1 es hidrógeno ó R_{1A} .
7. El compuesto de cualquiera de las reivindicaciones 2 a 6, en donde R_{1A} o por lo menos un R_{1A} es hidrógeno o alquilo que tiene 1 a 4 átomos de carbono.
8. El compuesto de la reivindicación 1, en donde R_6 es hidrógeno, hidroxilo, halógeno, OR_{6A} o alquilo que tiene 1 a 4 átomos de carbono.
9. El compuesto de la reivindicación 3, en donde R_7 es hidrógeno, $C\equiv CR_{7A}$, OR_{7A} o alquilo que tiene 1 a 4 átomos de carbono.
10. El compuesto de la reivindicación 1 de acuerdo a la fórmula:



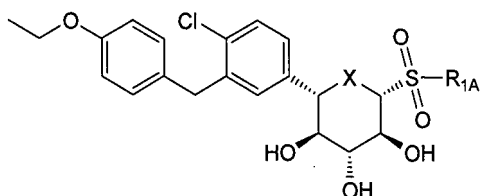
11. El compuesto de la reivindicación 2 de acuerdo a la fórmula:



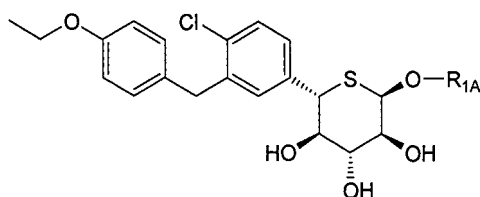
12. El compuesto de la reivindicación 1 de acuerdo a la fórmula:



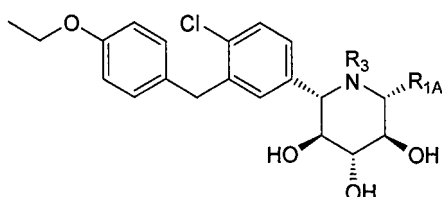
13. El compuesto de la reivindicación 1 de acuerdo a la fórmula:



14. El compuesto de la reivindicación 1 de acuerdo a la fórmula:



o a la fórmula:



15. El compuesto de cualquiera de las reivindicaciones 10 a 13, en donde X es O.

16. El compuesto de cualquiera de las reivindicaciones 10 a 15, en donde R_{1A} es hidrógeno, metilo o etilo.

17. El compuesto de la reivindicación 1, el cual es (2S,3R,4R,5S,6R)-2-[4-cloro-3-(4-etoxi-bencil)-fenil]-6-metilsulfanil-tetrahidro-piran-3,4,5-triol o una sal farmacéuticamente aceptable del mismo.

18. Una composición farmacéutica que comprende un compuesto de acuerdo a cualquiera de las reivindicaciones 1 a 17 y un diluyente o excipiente farmacéuticamente aceptable.

19. La composición farmacéutica de la reivindicación 18 que comprende (2S,3R,4R,5S,6R)-2-[4-cloro-3-(4-etoxi-bencil)-fenil]-6-metilsulfanil-tetrahidro-piran-3,4,5-triol o una sal farmacéuticamente aceptable del mismo y un diluyente o excipiente farmacéuticamente aceptable.

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Expert Opinion

1. Introduction
2. Published patents and applications
3. Expert opinion

Monthly Focus: Cardiovascular, Renal, Endocrine & Metabolic

Sodium glucose co-transporter 2 (SGLT2) inhibitors as potential antidiabetic agents

Anthony L Handlon

Metabolic and Viral Center of Excellence for Drug Discovery, GlaxoSmithKline, PO Box 13398, Research Triangle Park, North Carolina 27709-3398, USA

Sodium glucose co-transporter 2 (SGLT2) plays a key role in maintaining glucose equilibrium in the human body. SGLT2 is a kidney transporter that reabsorbs glucose from the renal filtrate and prevents the loss of glucose in the urine. Competitive inhibitors of SGLT2 cause the renal excretion of glucose. This observation has led to the hypothesis that SGLT2 inhibitors could be effective agents in the normalisation of high blood glucose levels that are associated with diseases such as Type 1 and Type 2 diabetes. With this goal in mind, a number of pharmaceutical companies have launched medicinal chemistry programmes directed towards the discovery of novel SGLT2 inhibitors. Several organisations have described potent and selective SGLT2 inhibitors that belong to a class of structurally-related aromatic C-, N- and O- β -D-glucopyranoside analogues of the natural product phlorizin. This review will highlight some of the advances that have been made in the discovery of SGLT2 inhibitors and discuss their potential as effective treatments for Type 2 diabetes and other diseases.

Keywords: C-glycoside, phlorizin, sodium glucose co-transporter (SGLT), SGLT2, T-1095, Type 2 diabetes

Expert Opin. Ther. Patents (2005) 15(11):1531-1540

1. Introduction

1.1 Inhibitors of sodium glucose co-transport

Substances that cause the renal excretion of glucose have been known for a long time. Phlorizin (1; Figure 1) is a natural product that was first isolated from fruit tree bark in 1835 [1]. At high doses, this phenol glycoside was known to cause 'phlorizin diabetes,' that is, phlorizin-induced glucosuria. Although it was recognised in the early 20th century that phlorizin was affecting kidney function, the mechanism of action of phlorizin at the molecular level was not understood until after the expression cloning and subsequent characterisation of SGLT2 in the early 1990s [2,3]. SGLT2 is located in the brush border membrane of the proximal convoluted tubule of the nephron and is responsible for the reabsorption of glucose from the glomerular filtrate. SGLT2 has the capacity to transport glucose across the membrane against a concentration gradient, a process that is thermodynamically favourable because sodium is simultaneously transported down its concentration gradient. Inhibition of SGLT2 with compounds such as phlorizin prevents the reabsorption of glucose from the renal filtrate and leads to the rapid appearance of glucose in the urine.

1.2 The SLC5 gene family

SGLT2 is a member of a larger group of sodium substrate co-transporters, the SLC5 gene family, of which there are 11 members in the human genome [4]. SGLT1 is a sodium glucose/galactose co-transporter with 59% sequence identity to SGLT2 [5]

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Sodium glucose co-transporter 2 (SGLT2) inhibitors as potential antidiabetic agents

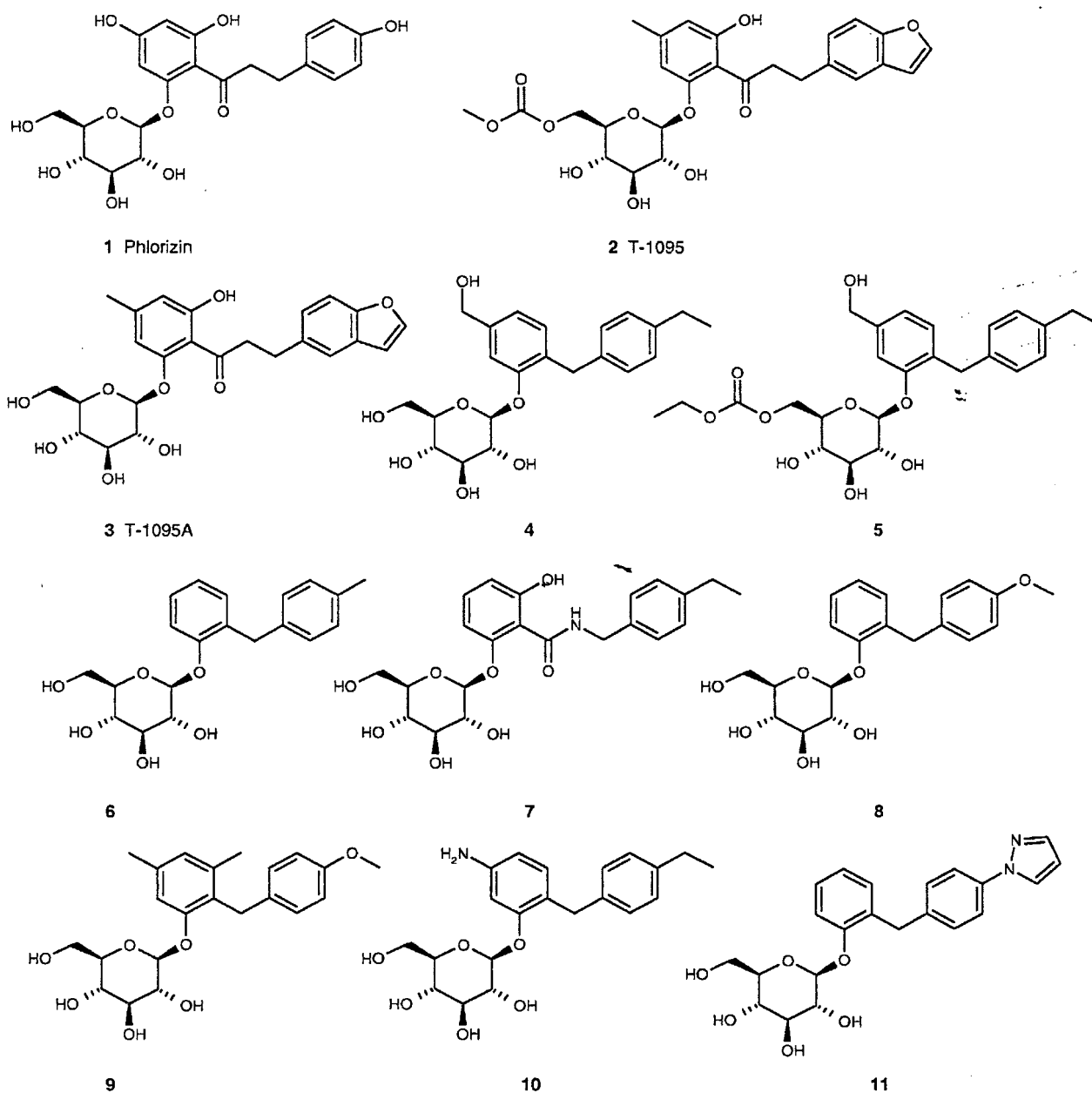


Figure 1. Phenyl O-glycosides.

and is primarily expressed in the small intestine, but is also present in the kidney. It is a low capacity/high affinity transporter and, as such, is thought to account for only a small proportion of renal glucose reabsorption. SGLT1 is found in the human heart where it may be involved in cardiac glucose transport [6] and has also been localised in cerebral blood vessels of rat and pig where it is thought to transport glucose

across the blood-brain barrier [7]. Because of its putative role in the transport of glucose across cell membranes in the heart and brain, it has been assumed that inhibition of SGLT1 in these tissues would be undesirable. Other members of the SLC5 family include SGLT3, which shares 70% sequence identity with SGLT1. SGLT3 is a glucose-sensing sodium channel located in the small intestine and is co-localised with

cholinergic neurons in the enteric nervous system where it may be involved in sensing glucose and stimulating intestinal motility, although its exact physiological role is still a matter of investigation [8]. It is unclear what the effects of SGLT3 crossreactivity by SGLT2 inhibitors would be. Recently, scientists from Kissei Pharmaceutical Co. have cloned and characterised human SGLT4. It was reported that SGLT4 is primarily located in the small intestine and kidney and that its substrates include D-glucose, D-mannose and D-fructose [9]. However, not all of the members of the SLC5 family transport glucose. For example, SLC5A3 is a sodium myo-inositol co-transporter, and SLC5A5 is a sodium iodide co-transporter.

1.3 SGLT2 inhibitors in the treatment of Type 2 diabetes

Type 2 diabetes is characterised by insulin resistance and β -cell dysfunction that results in hyperglycaemia. If untreated, hyperglycaemia damages many tissues in the body, including the retina, kidney and nerve tissue. Chronically high plasma glucose concentrations also inhibit wound healing. Type 2 diabetes leads to a host of medical complications, such as heart disease, blindness, kidney failure, stroke and lower limb infections and gangrene. Most pernicious of all is that high glucose levels aggravate insulin resistance, impair β -cell function and contribute to β -cell apoptosis [10]. Because the β -cells are responsible for the synthesis and release of insulin, the loss of β -cell function exacerbates hyperglycaemia, resulting in a vicious cycle that culminates in the abject destruction of the β -cells [11,12]. Therefore, it is of critical importance to identify patients with insulin resistance and hyperglycaemia and to return their plasma glucose to normal levels.

In recent years much attention has been given to SGLT2 as a molecular target to directly induce glucose excretion and to safely normalise plasma glucose in the treatment of Type 2 diabetes. This review will highlight some of the advances that have been made in the discovery of SGLT2 inhibitors and discuss their potential as effective treatments for Type 2 diabetes. The following review is not intended as an examination regarding ownership of any particular intellectual property right. Rather, as will be appreciated by the reader, this review is intended to provide an exemplar summary of the information contained in published patent literature. For other perspectives on SGLT2 there are several excellent review articles that have appeared recently [4,5,13-15].

1.4 T-1095, a case study

Although phlorizin (1; Figure 1), has proven to be a useful pharmacological tool that helped to elucidate the role of SGLT2 in glucose homeostasis, it is not practical as a drug because it has poor oral bio-availability. Tanabe Seiyaku has discovered an analogue of phlorizin, T-1095 (2), a methyl carbonate prodrug that is readily absorbed. After oral dosing, T-1095 is rapidly converted to an active metabolite, T-1095A (3), which has an IC_{50} value of 50 nM for human SGLT2 and is moderately selective against human SGLT1 (IC_{50} = 200 nM) [16].

In a number of publications, Tanabe Seiyaku and researchers at the University of Tokyo have demonstrated that T-1095 causes glucosuria and lowers blood glucose levels in animal models of diabetes [14,15]. For example, after a single oral dose to Zucker diabetic fatty (ZDF) rats, T-1095 significantly lowered blood glucose levels in a dose-dependent manner. When dosed chronically as a 0.1% admixture in food over a period of 4 weeks, T-1095 normalised blood glucose to levels that were seen with lean ZDF controls. T-1095 was also found to ameliorate impaired insulin sensitivity in streptozotocin (STZ)-induced diabetic rats as evidenced by a normalisation of the glucose infusion rate and glucose utilisation rate during a hyperinsulinaemic euglycaemic clamp study [14]. In STZ-induced diabetic rats, T-1095 caused significant and dose-dependent lowering of plasma glucose in liquid meal tolerance tests [16]. When T-1095 was given orally at 30 mg/kg 15 min prior to the meal, the peak blood glucose level that resulted was roughly equivalent to non-diabetic animals. The effects of T-1095 were also investigated in KK-A γ mice, an animal that is genetically obese, insulin resistant, and diabetic. In a 28 day study it was found that T-1095, dosed 0.1 wt% in food, led to a 60% decrease in blood glucose concentrations to levels that equalled non-diabetic controls. Furthermore, there was a significant decrease in plasma triglycerides, insulin concentration and glycosylated haemoglobin (HbA $_{1c}$). The authors of this study conclude that long-term normalisation of plasma glucose levels by T-1095 suppresses glucotoxicity and insulin resistance [16].

In a separate examination of the longer term effects of T-1095 on β -cell function, it was found that among spontaneously diabetic Goto-Kakizaki (GK) rats, insulin secretion was significantly improved versus untreated GK rats after 8 weeks of treatment [17]. This result further strengthens support for the hypothesis that lowering blood glucose via the induction of renal glucose disposal can at least partially restore normal β -cell function that had been compromised by hyperglycaemia. Recently, it has been demonstrated in GK rats that extended treatment with T-1095 over a 32 week period led to a dose-dependent decrease in blood glucose and HbA $_{1c}$ levels, and restoration of insulin sensitivity. In addition, it was found that nerve damage resulting from hyperglycaemia could be prevented with long-term treatment by T-1095 [17].

2. Published patents and applications

2.1 Carbocyclic O-glycosides

The first SGLT2 inhibitor was the natural product phlorizin (1) and all subsequent SGLT2 inhibitors have been glycosides derived from its structure. Compound screening has not yielded SGLT2 inhibitors that are not carbohydrate-derived. The first subset of SGLT2 inhibitors to be explored was the β -D-glucosides in which the aglycone moiety was an aromatic carbocycle. Tanabe Seiyaku's early patent applications in the SGLT arena published in 1995, and T-1095 (2) was disclosed in 1998 [10]. In 2001, Kissei Pharmaceutical Co. publicly

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disclosed *O*-glucoside (4), which inhibited the uptake of methyl α -D-glucopyranoside into COS-7 cells that overexpressed human SGLT2 with an IC_{50} value of 8.1 nM [102]. In rats, compound 4 at 1 mg/kg i.v. caused urinary glucose disposal at the rate of 238.9 mg glucose per 200 g body weight over 24 h. Subsequently Kissei reported that ethyl carbonate (5) had an oral bioavailability of 43% and that it caused urinary glucose excretion at the rate of 195 mg/24 h/200 g body weight when given orally to Sprague–Dawley (SD) rats at a dose of 10 mg/kg [103]. Also in 2001, Bristol-Myers Squibb described phenyl glucoside (6) [104] and benzamide (7) [105] as SGLT2 inhibitors, but provided no supporting biological data. In 2002 Kissei disclosed compound 8, which had an IC_{50} value of 350 nM against human SGLT2 that was overexpressed in COS-7 cells [106]. Later in the same year, Kissei described compounds 9 and 10, which inhibited human SGLT2 with IC_{50} values of 290 and 10 nM, respectively [107]. When given intravenously at 10 mg/kg, *O*-glucoside (9) induced glucosuria at 288 mg/24 h/200 g body weight in male SD rats. Kissei further elaborated this series by investigating heterocyclic substituents on the benzyl ring, and in early 2003 described compound 11. This pyrazole-substituted glucoside resulted in a significant increase in potency to an IC_{50} value of 0.1 nM for inhibiting the uptake of methyl α -D-glucopyranoside in CHO-K1 cells transfected with human SGLT2 [108].

2.2 Heterocyclic *O*-glycosides

The next structural type to be exploited was aromatic *O*-glycosides in which the aglycone moiety was a heteroaromatic ring. In a series of patent applications that were published between 2001 and 2004, Kissei Pharmaceutical Co. disclosed a broad range of 3-*O*-pyrazole glucosides. For example, compound 12 (Figure 2) was described as inhibiting the uptake of α -methyl-glucoside in COS-7 cells expressing human SGLT2 with an IC_{50} value of 84 nM [109]. Kissei also described prodrugs; for example, compound 13 was reported to have an oral bioavailability of 27% in SD rats. At a 10 mg/kg oral dose, ethyl carbonate (13) led to the urinary excretion of glucose at the rate of 167.3 mg/24 h/200 g body weight [110]. In 2002, Kissei disclosed pyrazole *O*-glucosides 14 [111] and 15 [112], which inhibited human SGLT2 with IC_{50} values of 15 and 200 nM, respectively. In 2004, Kissei further elaborated this series and described compound 16 as an SGLT (specifically sodium myo-inositol transporter, [SMIT]) inhibitor with no supporting data [113]. Ajinomoto Co. described a series of novel pyrazole derivatives that inhibited sugar re-uptake in the kidney and caused glucose excretion in the urine. Oral dosing of compound 17 at 100 mg/kg caused 918 mg glucose excretion in the urine over a 24 h period [114]. Ajinomoto also reported that the methyl carbonate prodrugs had superior oral activity as compared to the parent molecules. In early 2003, Kyowa Hakko Kogyo Co. disclosed compound 18. The SGLT inhibitory effects were investigated using porcine proximal tubule epithelial LLC-PK1 cells. Compound 18 was

reported to have an IC_{50} value of 47 nM and showed a dose-dependent increase in urinary glucose excretion at doses of 0.3 and 1 mg/kg in rats [115]. Later in the same year, Bristol-Myers Squibb described a series of pyrazole *O*-glucosides, including compound 19 [116]. Recently, Boehringer Ingelheim International GmbH also disclosed a series of pyrazole *O*-glycosides [117].

In 2003, Kissei Pharmaceutical Co. detailed a series of pyridine *O*-glucosides, such as compound 20, which inhibited the re-uptake of methyl α -D-glucopyranoside by recombinant COS-7 cells that express human SGLT2 with an IC_{50} value of 41 nM [118]. In the following year, Kissei disclosed 2-pyridine-*O*-glucoside (21) with an enhanced potency of 3 nM against human SGLT2 [119]. Also in 2004, Fujisawa described a series of pyrimidinyl *O*-glucosides, including compound 22, which had an IC_{50} value of 0.82 μ M in an SGLT-2 *in vitro* assay and was > 120-fold selective over SGLT-1 [120].

In three patent applications in 2005, Janssen Pharm. NV and Tanabe Seiyaku Co. jointly disclosed a series of benzofused heterocyclic derivatives. The synthesis and biological activity of indazoles were outlined in an application that included example 23, which inhibited human SGLT2 (stably expressed in CHO-K1 cells) with an IC_{50} value of 460 nM [121]. Benzotriazoles were detailed in a concurrent application that included example 24, which was found to inhibit human SGLT2 with an IC_{50} value of 8 nM [122]. Janssen Pharm. NV and Tanabe Seiyaku Co. also exemplified several indole *O*-glucosides, including compound 25, which was described as inhibiting human SGLT2 with an IC_{50} value of 20 nM [123].

2.3 Carbocyclic *C*-glycosides

The next structural category to be considered is the carbon glycosides in which the bond between the glucose and the aglycone is a carbon–carbon bond. *C*-glycosides may possess attributes that would render them more suitable as medicinal compounds, such as the enhanced chemical stability of the glycosidic bond. Furthermore, *C*-glycosides are not substrates for glucosidases, thus rendering them more metabolically stable. In a 2001 patent disclosure, Kotobuki Pharm. Co. exemplified a number of *C*-glycosides structurally related to phlorizin, including analogue 26 (Figure 3). The efficacy of this compound was tested by dosing SD rats at 10 mg/kg i.p. b.i.d. Compound 26 caused urinary glucose excretion at the rate of 289 mg/24 h [124]. In a series of patent applications between 2001 and 2004, Bristol-Myers Squibb Co. disclosed a number of *C*-glycosides and compound 27 was exemplified among a number of closely related analogues [125]. In 2002, Bristol-Myers Squibb published a US patent application that described a single *C*-glycoside derivative (28) [126]. In 2004, Bristol-Myers Squibb outlined the methodology to prepare *C*-aryl glycosides in large quantities and described the preparation of compounds 27 and 28 in multi-kilogram scales, suggesting that one or both of these compounds may be advancing to clinical development [127].

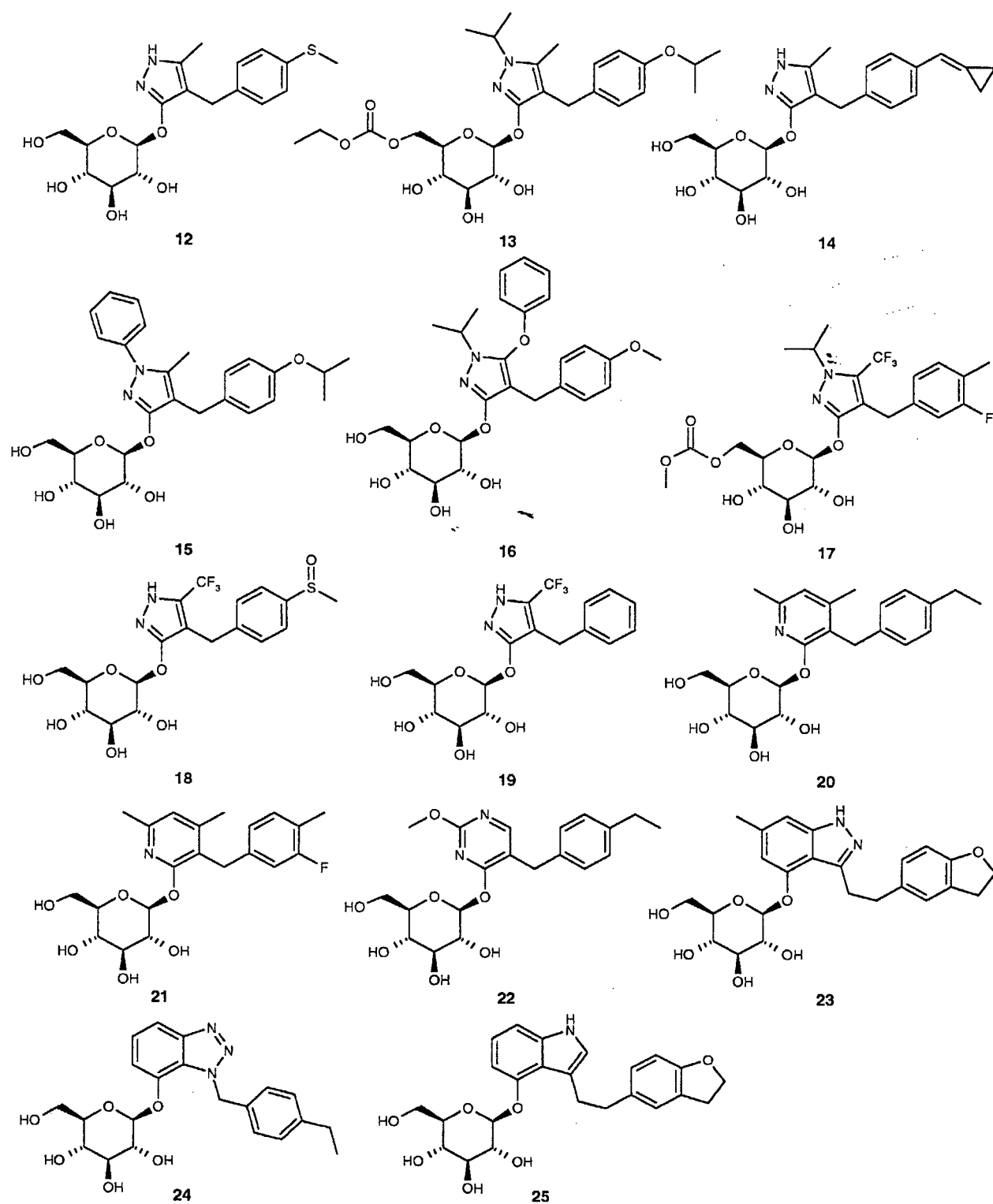


Figure 2. Heterocyclic O-glycosides.

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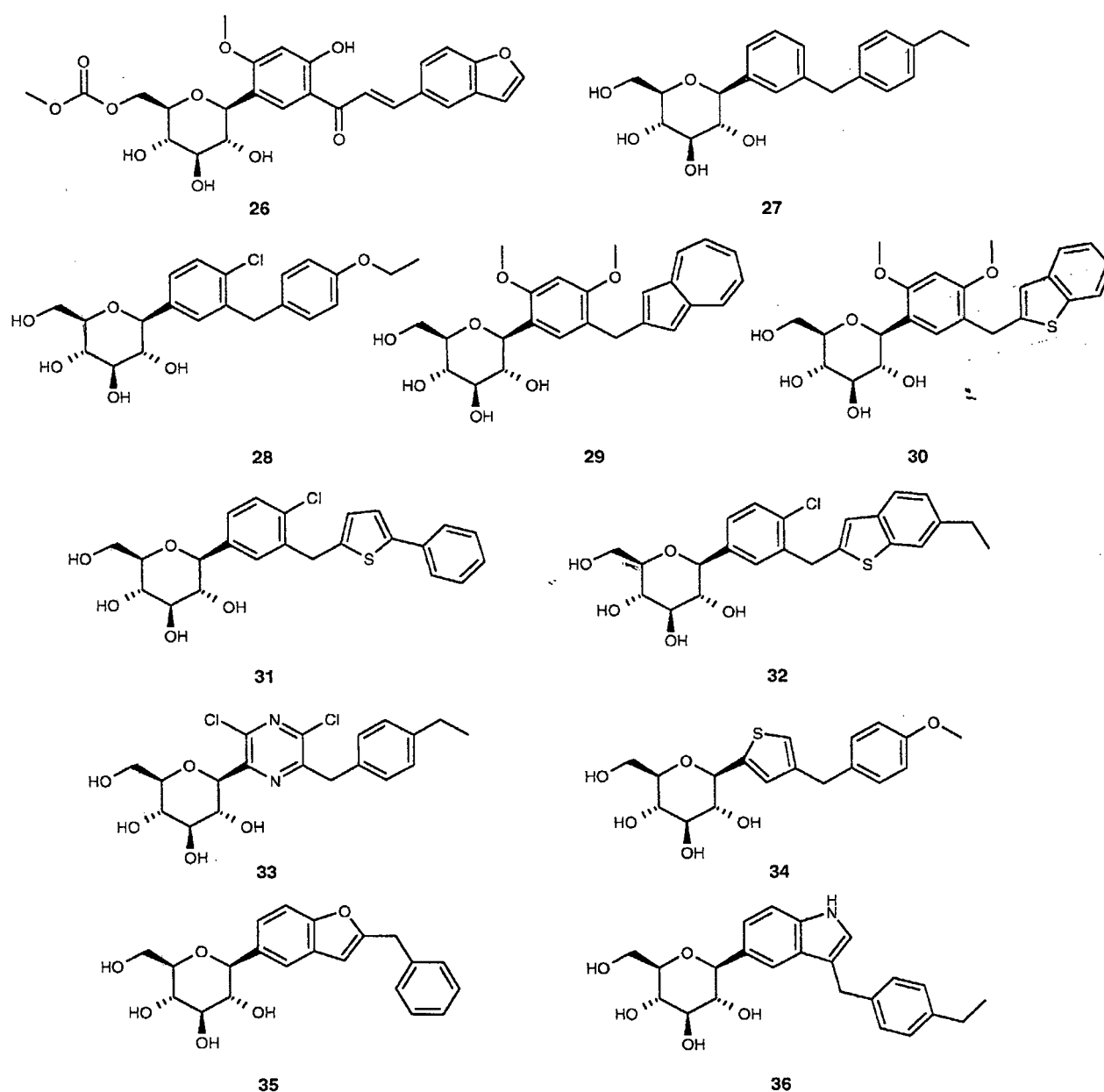


Figure 3. Aryl C-glycosides.

Yamanouchi Pharmaceutical and Kotobuki Pharmaceutical described the synthesis and biological activity of a series of azulene derivatives. Example 29 inhibited the uptake of methyl- α -D-glucopyranoside in Chinese hamster ovary (CHO) cells stably expressing human SGLT2 with an IC_{50} value of 5.7 nM. This compound was dosed orally into KK-A γ mice at 3 mg/kg and led to a 45% decrease in blood glucose area beneath the blood glucose concentration versus time curve (AUC) over an

8 h period [128]. In a subsequent patent application, these two companies jointly disclosed a series of C-aryl glycosides in which the B ring included aromatic heterocycles, for example, compound 30. Benzo[thiophene] (30) inhibited human SGLT2 with an IC_{50} value of 3.8 nM and was found to lower plasma glucose AUC by 34% over an 8 h period in KK-A γ mice at an oral dose of 1 mg/kg [129]. In 2005, Tanabe Pharmaceutical Co. also described C-aryl glycosides in which ring B was an

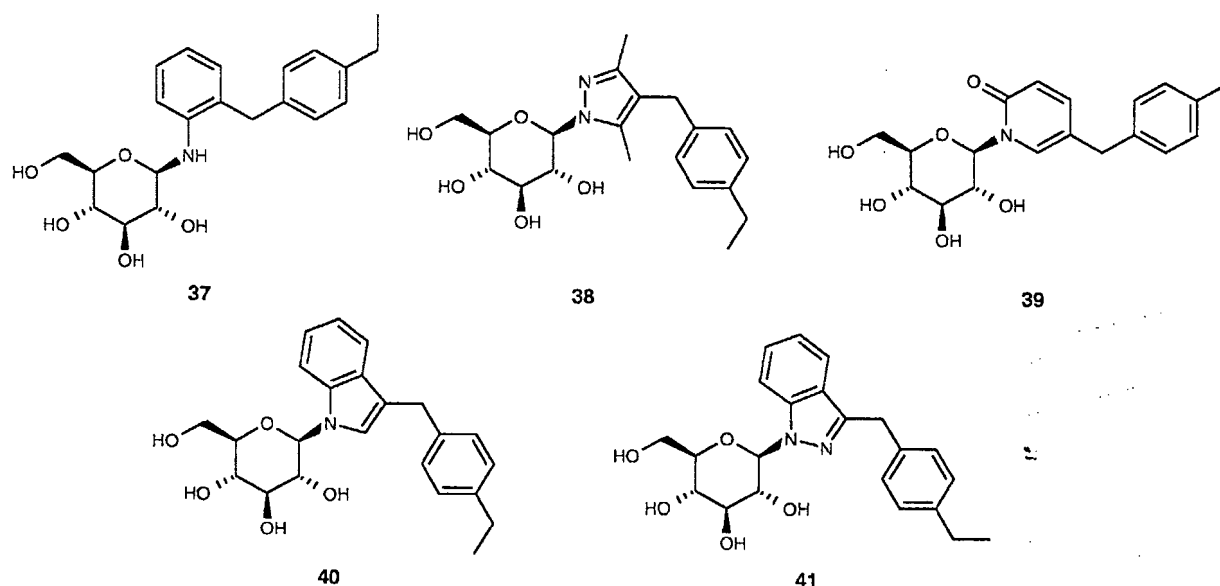


Figure 4. Aromatic N-glycosides.

aromatic heterocycle. This filing included a large number of thiophenes and benzothiophenes, including the most preferred examples 31 and 32 [130].

2.4 Heterocyclic C-glycosides

The next category to be considered is C-aryl glycosides in which the aromatic ring bonded to glucose is heterocyclic. In 2004, Yamanouchi Pharmaceutical disclosed a series of compounds that included pyrazine (33; Figure 3), which was reported to inhibit human SGLT2 with an IC_{50} value of 6.5 nM. They also exemplified other heterocyclic derivatives, such as thiophene 34 and benzofuran 35 [131]. In early 2005, Janssen Pharm. NV and Tanabe Seiyaku jointly disclosed 1*H*-indol-5-yl glycosides, such as compound 36, which was reported to inhibit human SGLT2 with an IC_{50} value of 132 nM and to be inactive against human SGLT1 [132].

2.5 N-glycosides

With the publication of two international patent applications in early 2005, Tanabe expanded the chemical space available to SGLT2 inhibitors by including N-glycosides. The first document describes aniline glycosides, such as example 37 (Figure 4), but provides no supporting biological data [133]. Within another application that was published concurrently, Tanabe exemplified a series of heterocyclic N-glycosides, including pyrazole 38, 2-pyridone 39, indole 40 and indazole 41, as well as a triazole and an indoline analogue [134].

2.6 O-glycosides with modified glucose moiety

So far, all of the SGLT2 inhibitors that have been described are aryl glycosides containing a glucose moiety. Because of the

relative uniformity of the glycosides in the SGLT2 patent literature, it has become increasingly difficult for potential drug inventors to find unexplored chemical space. In an effort to fully explore the structure-activity relationships (SARs) and to find novel SGLT2 inhibitors, alterations in the glucose ring have been investigated. In early 2004 Taisho Pharmaceutical disclosed a series of phenyl thioglycosides in which oxygen of the pyranose ring is replaced with sulfur. Compound 42 (Figure 5) was found to inhibit glucose transport with an IC_{50} value of 160 nM in a preparation of brush border membrane vesicles from rat kidney [135]. Later in the same year, the same company published a patent application that described the preparation of heterocyclic *O*-thioglycosides via Mitsunobu coupling between a heterocycle and an appropriately protected thio-D-glucopyranose derivative. They exemplified a number of pyrazoles (e.g., 43) together with a host of other heterocyclic derivatives, including pyridines, pyrazines and pyrimidines [136]. In a separate application that was published concurrently, Taisho described a series of heterocyclic aromatic thioglycosides, such as pyridine 44, which inhibited SGLT2 with an IC_{50} value of 140 nM, as well as a number of pyrazines, pyrimidines and pyridazines [137]. Aventis Pharma also investigated sugar-modified SGLT2 inhibitors. In 2004, Aventis disclosed a series of phenyl *O*-glycosides in which the 4'-OH on the pyranose ring is replaced with a fluorine atom. Compound 45 inhibited glucose transport in brush border membrane vesicles prepared from rat kidney with an IC_{50} value of 400 nM [138]. In an accompanying patent application, Aventis described the corresponding heteroaryl glycosides, such as thiophene derivative 46, with an IC_{50} value of 300 nM [139].

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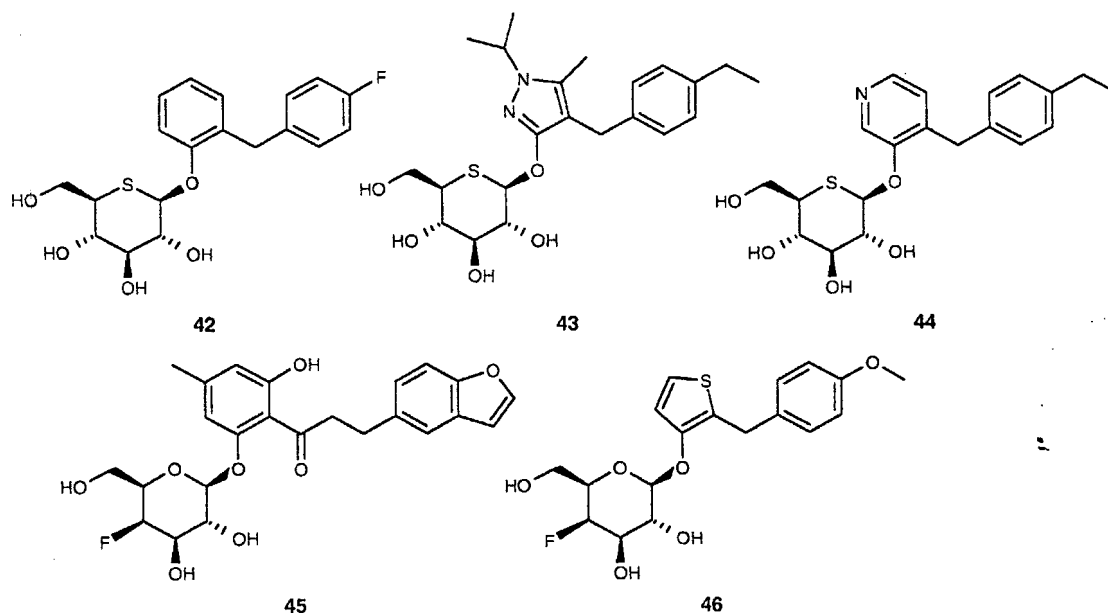


Figure 5. Aromatic O-glycosides with modified sugar rings.

3. Expert opinion

Type 2 diabetes has reached epidemic proportions in western industrialised nations. This disease, which used to be referred to as adult-onset diabetes, is now encountered in younger populations, even adolescents and children. Type 2 diabetes has become one of the most costly diseases because of its chronic nature and its frequent association with heart disease, stroke, kidney disease, blindness and lower limb amputations [20]. Type 2 diabetes is often seen as part of a broader affliction, termed metabolic syndrome, the diagnosis of which must include three or more of the following: high blood pressure, central obesity, high serum triglyceride levels, low serum high-density lipoprotein (HDL) cholesterol levels, and high fasting blood glucose levels. There are ~ 47 million people in the US with metabolic syndrome [202].

The aetiology of Type 2 diabetes is complex. An inappropriately high level of hepatic glucose production is thought to contribute to hyperglycaemia in the fasting state. Insulin resistance, which may involve genetic and environmental factors and seems to be associated with obesity, leads to hyperglycaemia after meals. Through a process whose molecular mechanism is the topic of active research, high plasma glucose impairs the β -cell [10,11]. The resulting inability of β -cells to synthesise and excrete adequate insulin exacerbates the hyperglycaemia leading to a chronic condition of elevated blood sugar and increased β -cell destruction via apoptosis [18-20]. By inducing renal excretion of glucose, SGLT2 inhibitors directly lower glucose levels and, thus, would be expected to interrupt the vicious cycle of β -cell destruction. An ideal SGLT2

inhibitor would lower fasting plasma glucose levels, restore insulin sensitivity and lead to β -cell recovery. Furthermore, a glucose lowering agent would prevent the ravaging effects of hyperglycaemia on other organs such as the eye, kidney and nervous system.

The patent literature is replete with descriptions of other potential therapeutic uses for SGLT2 inhibitors, such as the treatment of obesity, lipid disorders, atherosclerosis, cardiovascular disease, high blood pressure and metabolic syndrome, amongst others. Because SGLT2 inhibitors cause the net loss of calories from the body in the form of glucose, these compounds may have potential for the treatment of obesity. The kidney filters and reabsorbs ~ 180 g of glucose per day and the majority of this is transported by SGLT2 [5]. Because each gram of glucose equals 4 Kcal of energy, the inhibition of SGLT2 should lead to the excretion of a few hundred Kcals per day. Whether the loss of calories in the form of urinary glucose will lead to a compensatory increase in feeding is unclear. Nevertheless, treatment with an SGLT2 inhibitor would be expected to stimulate the utilisation of other fuel sources, such as triglycerides, in much the same way as a low carbohydrate diet does. Furthermore, decreasing the postprandial glucose load would be expected to lower the levels of insulin, a hormone that is thought to promote obesity by stimulating lipogenesis [21].

Are there any potential adverse effects of SGLT2 inhibitors? Compared to a healthy population, diabetic patients have greater frequency of urinary tract infection (UTI), and it has been speculated that stimulating glucose excretion may increase the chance of UTI. Diabetic patients have

greater amounts of bacterial flora in the urinary tract that is thought to be the result of incomplete voiding of the bladder, which allows the proliferation of bacteria [22]. However, it is not clear whether increasing glucose excretion will exacerbate UTI. In fact, a recent study analysing risk factors for UTI in diabetic women found that glucosuria did not increase the risk of developing UTI [23]. Based on this result, SGLT2 inhibitors would be unlikely to increase UTI. If anything, SGLT2 inhibitors that normalise blood glucose and ameliorate the symptoms of diabetes should decrease UTI risk.

Another consideration for patients taking SGLT2 inhibitors is that the increased osmolality of glucose-laden urine would be expected to lead to an increase in urine volume (polyuria), but the implications of this are considered an inconvenience rather than a matter of clinical concern. If urine output is increased, there is the chance for increasing renal excretion of solutes other than glucose, and it may be prudent to monitor plasma electrolytes to ensure that they remain in the normal zone.

There is abundant clinical evidence that diabetes, if left untreated, can lead to kidney damage and potentially renal failure. It has been suggested that SGLT2 inhibitors, by enhancing glucose excretion, may add to the burden on the kidneys. Whilst it is clear that patients with poorly managed diabetes spill glucose in the urine, it is not the case that kidney damage is due to renal excretion of glucose. Rather, the damage is thought to result from abnormally high concentrations of intracellular glucose (which produces advanced glycation end products, oxidative stress and inflammatory processes), and not from increased concentration of glucose outside of cells in the renal tubules [24]. SGLT2 inhibitors would be expected to prevent kidney damage, not cause it.

The most compelling evidence for the safety of SGLT2 inhibitors comes from individuals with a condition known as familial renal glucosuria. These individuals have inherited a defective form of SGLT2 that leads to the excretion of ≤ 100 g/day of glucose [25]. People with familial renal glucosuria have a somewhat increased urine volume and water intake, but they have normal kidney function, are not hypoglycaemic and have no pathology caused by the transporter defect. Based on this evidence, there is no reason to believe that inducing glucose excretion via SGLT2 inhibition should lead to adverse effects.

As confirmed by the amount of patenting activity amongst several pharmaceutical companies, there is an abundance of interest in the therapeutic use of SGLT2 inhibitors for the treatment of Type 2 diabetes and other conditions associated with metabolic syndrome. Aventis lists an SGLT2 inhibitor, AVE-2268, within its portfolio of metabolic targets that have reached Phase I/IIa clinical trials [203]. Given the plethora of potent SGLT2 inhibitors that have been disclosed in the patent literature, it is expected that additional companies will advance compounds to clinical development in the near future. With the continuing dedicated effort of medicinal and clinical researchers everywhere, it is hoped that SGLT2 inhibitors may lead the way to the discovery of safe and effective treatments for diabetes.

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9 50005-01-01 SOLICITUDES	1607 REIVINDICACION UNITARIA ADICIONAL A LAS 10 INICIALES	30.000.00	270.000.00
			\$270.000.00

SON: **DOSCIENTOS SETENTA MIL PESOS MONEDA CORRIENTE***

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Recibo de Caja Aplicado al Expediente No. _____

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